

Chapter 7: Decline of Renal Function in Normal Aging, Role of Oxidants/Inflammation: When Does It Begin: Is It Inevitable, Preventable, or Treatable?

Helen Vlassara,* Luigi Ferrucci,[†] James Post,[‡] and Gary Striker[§]

*Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, New York, New York; [†]Longitudinal Studies Section, Baltimore Longitudinal Study of Aging, Clinical Research Branch, National Institute on Aging, National Institutes of Health, Bethesda, Maryland; [‡]Department of Nephrology, Bronx Medical Center, Division of Nephrology, Mount Sinai School of Medicine, New York, New York; and [§]Division of Nephrology, Department of Medicine, and Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, New York, New York

This chapter will include two large longitudinal, observational studies of renal function changes in normal aging, a smaller cross-sectional and interventional study focusing on oxidants and inflammation, and a consideration of the causes of decreased function in aging in both animal models and aging normal humans. We chose to focus on oxidant stress (OS) and inflammation because they increase in aging and are thought to both underlie aging-related diseases, including decreased kidney function. Importantly, it is now possible to reduce OS and inflammation in both normal adults and patients with chronic kidney disease (CKD). Therefore, if OS and inflammation are critical in the pathogenesis of reduced renal function in aging, and progression in CKD, it is incumbent on the renal community to recognize/reduce their levels as a part of normal care or in the construction of clinical trials aimed at reducing CKD or cardiovascular disease (CVD). Finally, increased OS and inflammation may reduce the ability of the aging person to sustain metabolic or physical stress.

LONGITUDINAL, OBSERVATIONAL STUDIES OF RENAL FUNCTION IN ADULTS

The Baltimore Longitudinal Study of Aging

The Baltimore Longitudinal Study of Aging (BLSA), the first continuing scientific examination of human aging, was started in 1958 and has been an important source of information on the aging kidney.¹ In 1976, the BLSA confirmed the previously postulated progressive decline of renal function with aging, using age-adjusted standards for creatinine clearance (CrCl).² The BLSA data were

unique for two reasons: (1) both cross-sectional and longitudinal observations were used in the prediction and (2) only individuals considered healthy, based on strict, standard criteria, were selected for these analyses. Reports on the longitudinal studies only used data from BLSA participants followed for at least 10 yr and who had five or more serial measures. Overall, the longitudinal data analysis confirmed the cross-sectional observations, although the accelerated decline of kidney function with age was more accentuated and statistically significant. The estimated average annual change in CrCl was -0.26 ml/min per 1.73 m² in the age group 20 to 39 yr and became 1.51 ml/min per 1.73 m² after the age of 80 yr.³ A study of water restriction confirmed that older BLSA participants have impaired response of renal tubules to change in plasma osmolality associated with impaired sodium homeostasis, previously reported in smaller studies.³ Although these data are a widely cited reference for kidney aging, they have some intrinsic limitations. First, they were estimated from men only. Second, the number of very long-lived individuals (>85 yr of age) was quite small. Third, while BLSA participants were selected to be “healthy,” the diagnostic technology available at that time may have not detected subclinical cardiovascular and kidney disease. This is important because the distinction between aging-related renal changes and progressive renal insufficiency are associated with a different prognosis.

Correspondence: Helen Vlassara, MD, Division of Experimental Diabetes and Aging, Department of Geriatrics, Mount Sinai School of Medicine, 1 Gustave Levy Place, New York, NY 10029.

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Nevertheless, the findings of the BLSA remain the best description of the course of renal function with aging. Ongoing research in the BLSA has added studies of renal function in women and will consider genetic and environmental factors that affect renal function with aging. Perhaps one of the most important findings of the BLSA for future research was that kidney function varied between persons at all ages, and when declines with aging were noted, they occurred at substantially different rates. In some individuals with an accelerated decline in CrCl, the presence of undetected, subclinical diseases could not be excluded. Indeed, Rowe *et al.*³ showed that in restricting the analysis to individuals without diabetes or any degree of hypertension, the decline was much less accentuated. Perhaps more important for nephrologists is the fact that some BLSA participants showed periods of 5 yr or even 10 yr without a significant decline of renal function. Although the number of these individuals was small and few were older than 70 yr of age, they challenge the notion that the decline of kidney function with age is unavoidable and calls for further investigation (Figure 1).

Despite the reduction of CrCl in many adults with aging, serum creatinine remains relatively stable and, in observational studies of older individuals, is only slightly correlated with age. A change in body composition, especially the crude and relative decline of muscle mass, may partly explain this finding since skeletal muscle is the major source of creatinine production. Therefore, some suggest that information on lean body mass, such as those that can be gathered by dual-energy x-ray absorptometry (DEXA), could be used to modify the CrCl estimating equation. This was applied to a representative aging population in Italy, the InCHIANTI study, and used an estimating equation that included information on grip strength, a surrogate of muscle mass; however, the improvement in prediction was small and of questionable clinical value, and no other study that includes information on muscle mass/strength has been validated in large samples.

The InCHIANTI Study

Longitudinal data from this study addressed the question of whether measured and estimated CrCl in older individuals is a

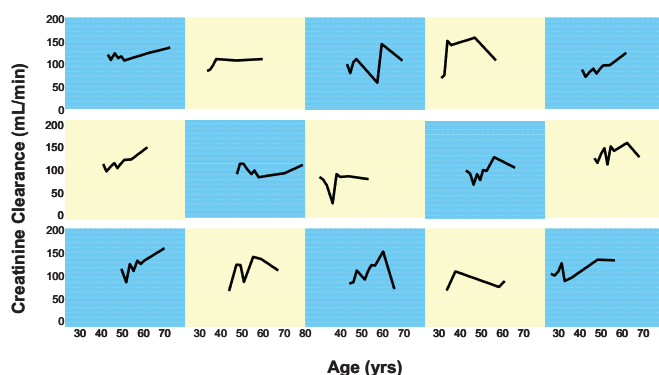


Figure 1. Representative subjects from the Baltimore Longitudinal Study of Aging, who did not show a significant decline in measured creatinine clearance values over a period of several years.

significant predictor of mortality⁴ (Figure 2). The 24-h creatinine clearance (CrCl)-, Cockcroft-Gault (C-G)-, and Modification of Diet in Renal Disease (MDRD)-derived equations (full and simplified) were calculated at enrollment (1998–2000), and all-cause mortality and cardiovascular mortality were prospectively ascertained by Cox regression over a 6-yr follow-up. Participants with CrCl 60 to 90 ml/min per 1.73 m² and CrCl <60 ml/min per 1.73 m² were, respectively, 1.70 (95% CI: 1.02 to 2.83) and 1.91 (95% CI: 1.11 to 3.29) times more likely to die over the follow-up compared with those with CrCl >90 ml/min per 1.73 m². Using the C-G equation, the group with values <60 ml/min per 1.73 m² had a significantly higher all-cause mortality compared with those with values >90 ml/min per 1.73 m² (HR: 2.59, 95% CI: 1.13 to 5.91). Interestingly, classification based on the MDRD formulae did not provide any significant prognostic information for mortality. A possible interpretation of these differences is that C-G includes information on chronological age, whereas the MDRD formulae do not directly include age. Although the data from the BLSA and InCHIANTI studies indirectly suggested that the age-associated decline of CrCl may have little effect on health and mortality in the absence of other disease, the presence of even small amounts of proteinuria (microalbuminuria) is associated with an increased risk of CVD.⁵

RENAL FUNCTION, INFLAMMATION, AND OS IN NORMAL AGING ADULTS: ROLE OF DIETARY ADVANCED GLYCATION ENDPRODUCTS

Advanced Glycation Endproducts

The pro-oxidants considered in this chapter are representatives of pro-oxidants in general and belong to a common class of compounds referred to as advanced glycation endproducts (AGEs). AGEs form spontaneously between sugars and the amino groups of proteins lipids and nucleic acids.⁶ They are highly reactive, generating reactive oxygen species (ROS) and inflammation responses both intracellularly and extracellularly. While it has generally been thought that AGEs are principally derived from cellular metabolism, it is now widely appreciated that a large part of the total oxidant burden derives from the diet in normal adults and in chronic diseases, such as CKD and diabetes.^{7–17}

Uptake, Detoxification, and Elimination of AGEs

AGEs react with cell surface receptors, which mediate opposite responses. One receptor (AGER1) lowers OS and inflammatory reactions,^{18–20} whereas another (RAGE) mediates increases in these parameters.^{9,21–23} Both receptors are driven by the ambient levels of ligand (AGEs) in normal, healthy subjects. Serum AGEs, often bound to small peptides, are filtered by the kidneys and AGEs. They can also be metabolized to inactive molecules and excreted in the renal tubules.

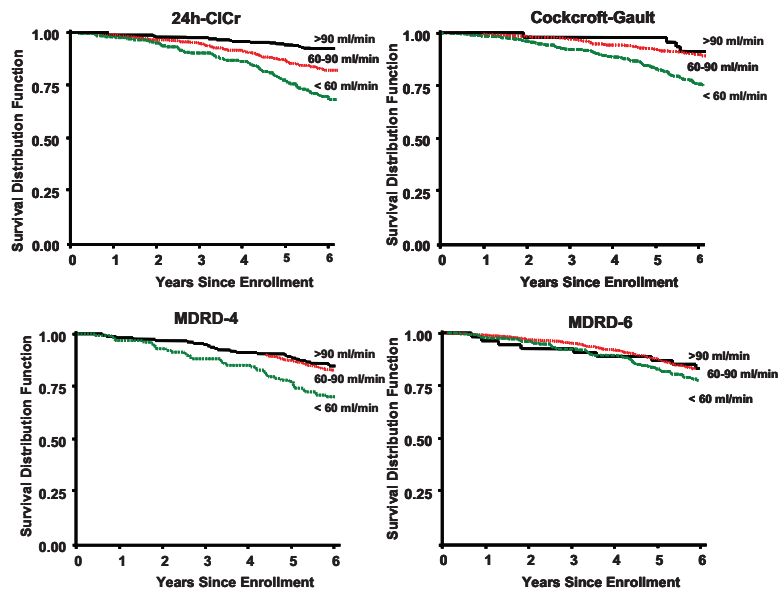


Figure 2. Comparisons of different methods of calculating GFR in the InCHIANTI study individuals with respect to predictions of survival. Note that there was considerable variation in the predictive value of the various equations, suggesting that additional factors may have to be considered in the aging population.

Oxidant Stress and Inflammation in Normal Adults From Early to Late Adulthood

Many studies have shown that oxidant stress and inflammation generally increase with aging; however, few have considered adults older than 75 yr old.^{2,24} When we studied a normal cohort residing in New York that included older adults, we found that there was considerable heterogeneity between individuals (Figure 3).¹⁴ Although, on average, there is an increase in oxidant stress and inflammation in aging, this was not a universal finding in the normal population. For instance, although there was an overall increase in carboxymethyl lysine (CML; Figure 3A) and methylglyoxal (MG; Figure 3B), there was a substantial number of older individuals who had normal levels (upper limit of normal for CML = 12 to 15 and MG = 1.0). There was an inverse correlation between CML levels and estimated GFR (eGFR; MDRD; Figure 3C), but, as with the BLSA, there was a number of normal adults that did not show

a decrease in eGFR with aging (Figure 3C, inset). Nonetheless, urinary excretion of AGEs was significantly lower in older adults, consistent with a lower intake.

SOURCES OF PRO-OXIDANTS IN ADULTS

Generally speaking, the amount of pro-oxidants in food increases when food is cooked at high heat and without water.^{25,26} We find that the way the food is cooked, rather than the composition of the diet, is the critical factor in the amount of oxidants in the food (Table 1). For instance, meat cooked with water (steamed or boiled) has a much lower AGE content than broiled meat. In addition, in food that is cooked in the presence of lipids at high temperature (as in fries), the amount of AGEs is markedly increased. Additional ways to reduce oxidant for-

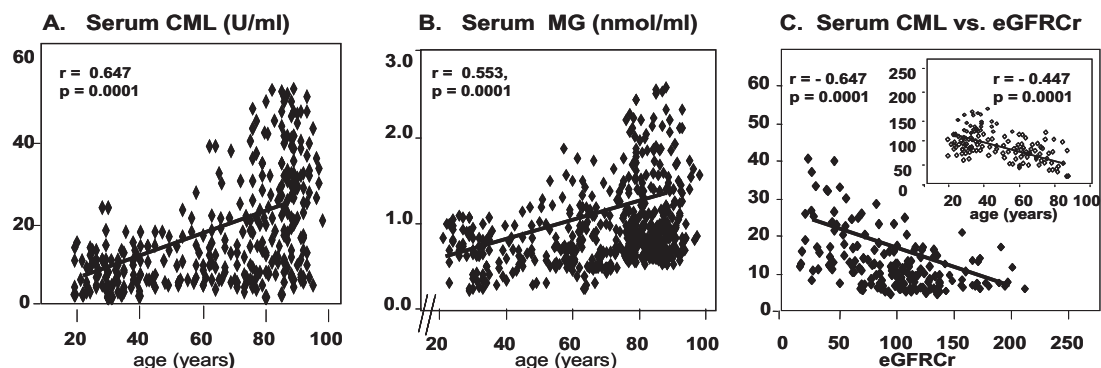


Figure 3. Data from a cross-section of subjects without obvious concurrent disease. (A) Serum carboxymethyllysine, (B) serum methylglyoxal, and (C) serum CML versus eGFR (inset, eGFR versus age). Note that the slope of the curves in A and B is largely driven by the large range in CML and MG levels in the aged. The eGFR values in the aged also show a large spread.

Table 1. Thermally modulated AGE content in common foods				
Regular Diet (U/mg)			Low AGE Diet	
Beef:	<u>broiled</u>	5367	→	<u>STEWED</u> 2000
Chicken:	<u>broiled</u>	5245	→	<u>STEWED</u> 1011
Salmon:	<u>broiled</u>	1348	→	<u>RAW</u> 502
Potato:	<u>fried</u>	1522	→	<u>STEAMED</u> 17

The levels of AGEs in most foods, not only red meats, depend largely on the method of cooking (see potato). Data are shown as CML-immunoreactivity, based on ELISA.

mation in foods include marinating with acidic substances (to-matoes, red wine, vinegar, lemon juice, etc.).

MODIFYING OXIDANT INTAKE

Studies in Normal Adults

Generally, the adult, healthy population maintains a constant level of oxidant intake at any given period of life, and this intake directly correlates with serum AGEs¹⁴(Figure 4A). Although this has not been extensively analyzed in the CKD population, many of the same principles are likely to apply. Namely, adults have constant habits for cooking and order foods cooked in similar ways in restaurants. Surprisingly, it appears that this behavior can be readily modified. We enrolled adults in the highest tertile of consumption of AGEs among normal subjects of all ages (Figure 4B), randomly divided them into two groups, and followed them for 4 mo.²⁷ One group maintained their normal cooking methods and food types. The second was provided with instructions on how to cook the food that they normally eat so that the formation of AGEs would be lowered. Two results were noted: first, there was a substantial reduction in the amount of AGEs consumed by the subjects who modified their food preparation methods. Second, this intervention was associated with an approximate decrease of 30 to 60% in the amount of circulating inflammatory

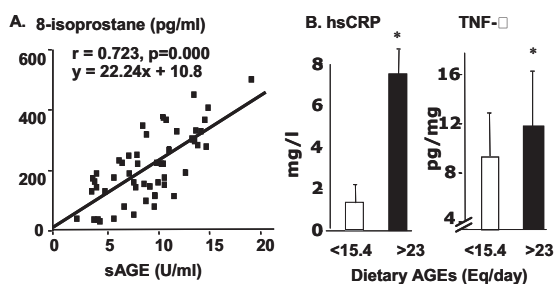


Figure 4. Correlations of serum levels of AGEs and levels of oxidants markers of inflammation. (A) Serum levels of AGEs directly correlate with markers of lipid oxidation (8-isoprostanes). (B) Those subjects who consumed lower levels of AGEs had lower serum levels of hsCRP and TNF α . hsCRP, high-sensitivity C-reactive protein; TNF, tumor necrosis factor; sAGE, serum advanced glycation factor.

mediators and oxidant stress (Figure 5A). Those who maintained their normal diet had a stable or a modest increase in OS and inflammation. However, the energy intake remained constant in the two groups. Importantly, this intervention was done in normal subjects at their own home, they continued to prepare their usual types of foods, and they did not require extensive supervision to maintain adherence to the recommended cooking methods. Since this intervention turned out to be practical and economical, it may be applicable to the general population. The length of time required to uncover

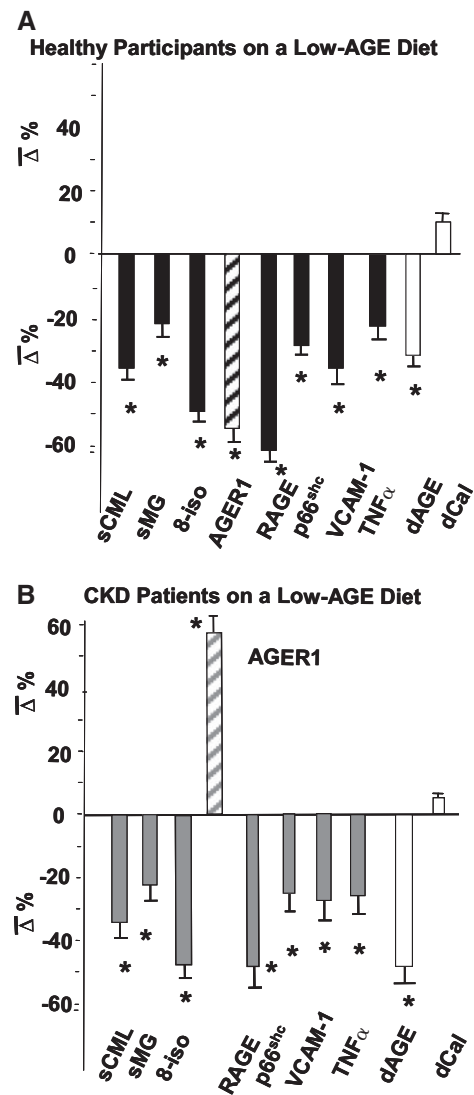


Figure 5. The influence of a reduction of the intake of AGEs on the blood levels of AGEs, measures of OS and inflammation, and AGE receptors. (A) After a 4-mo period on a low-AGE diet (~50% reduction), the levels of serum markers of OS, inflammation, and AGE receptors were all substantially reduced, whereas calorie intake remained essentially unchanged. (B) After a 4-wk period on a low-AGE diet, CKD 2–4 patients had a similar reduction of markers of OS and inflammation. Note that whereas RAGE levels were reduced by the dietary intervention, AGER1 levels returned to normal levels.

significant changes in OS and inflammation using this simple dietary maneuver was found to be much shorter (4 mo) than we had anticipated. In addition, both glucose and insulin levels, two indicators of the metabolic syndrome, were coordinately lowered in the normal subjects consuming a diet with lower AGEs content. It is important to note that the decrease in the AGEs content of the diet was, on average, only approximately 30 to 40%. This suggests that the normal diet often contains a sufficiently large amount of oxidants that the antioxidant systems are saturated. Importantly, a modest reduction in oxidant intake can reduce OS and inflammation in normal adults. Thus, the diet may underlie the high OS found in normal aging.

Modifying the Levels of Oxidants and Inflammation in Patients With CKD

Somewhat surprisingly, the high baseline levels of OS and inflammation in patients with CKD also responded to a similar reduction in dietary AGE intake.²⁷ A 4-wk low-AGE dietary diet was given to patients with stage 2 to 4 CKD [using food prepared by the general clinical research center (GCRC)]. Both OS and inflammation were reduced, paralleling the percent change reached in healthy adults (Figure 5B). This result suggests that the reduced excretion of oxidants in patients with CKD may be amenable to treatment without drugs and could be both practical and economical. It remains to be seen in larger longitudinal studies whether this reduction results in improved cardiac, renal, or central nervous system (CNS) outcomes in aging and chronic diseases.

FACTORS INFLUENCING THE REMOVAL OF PRO-OXIDANTS AND REDUCTION OF INFLAMMATION IN NORMAL AGING AND IN PATIENTS WITH CKD

As noted above, AGEs react with cell surface receptors that mediate opposite responses. AGER1 reduces both OS and inflammation, whereas RAGE promotes OS and inflammatory reactions. Both receptors are driven by the ambient levels of ligand (AGEs) in healthy subjects. Thus, the levels of both receptor types were decreased when the levels of oxidants in the diet were lowered (Figure 5A). While AGER1 levels have been shown to be decreased in patients with CKD,^{10,18,20,28} a reduction in the dietary load of oxidants resulted in restoration of AGER1 levels to near normal values in these patients (Figure 5B). This surprising result must be verified in larger studies, but it further supports the view that OS and inflammation may be amenable to reduction in CKD patients without drugs. The take-home message from these studies is that oxidants in the diet directly lead to increased serum levels of inflammatory mediators and OS, but this process can be interrupted by simply changing the methods of processing and/or cooking the usual foods consumed by adults. Importantly, the same outcomes may also be seen in CKD patients.

INFLAMMATION/OXIDANT STRESS IN PATIENTS WITH CKD AND NEUROLOGIC SYMPTOMS

It is well known that adults with elevated oxidant stress and/or inflammation have an increased risk of aging-related diseases: CVD, Alzheimer's disease (AD), atherosclerosis, stroke, CKD, and diabetes.^{29–33} The time at which the increased risk begins is not known, but the above data suggest that an increase in the risk factors can begin in young adulthood in the normal population. There has been increasing evidence for a kidney—cognition connection or a renocerebral syndrome. Moderate CKD defined as an eGFR of 30 to 59 ml/min per 1.73 m² has been associated with poor baseline cognitive function and an increased risk for cognitive decline in both elderly and young populations *versus* those with an eGFR \geq 60 ml/min per 1.73 m².^{34–36} The impaired cognition in patients with CKD seems to be related to the severity of renal disease and is more severe in those receiving hemodialysis.³⁶ In patients receiving outpatient hemodialysis, cognitive impairment, defined as mini mental state examination (MMSE) \leq 24, has a prevalence reported to range from 30 to 60%.^{37,38} Milder forms of cognitive impairment have also been reported in 34% of outpatient hemodialysis patients compared with age-, gender-, and comorbidity-matched controls.³⁹

Patients with CKD have a high prevalence of subclinical subcortical white matter damage on neuroimaging and a high incidence rate of stroke.^{40,41} These findings are likely related to a high burden of traditional and nontraditional vascular risk factors in these patients including hypertension, diabetes, hyperlipidemia, elevated oxidative stress, and elevated inflammatory state. Since positive outcomes in patients with advanced CKD and receiving HD require adherence to complex treatment regimens, identification of neurocognitive deficits that may be a prodrome to later vascular dementia may provide an opportunity to slow the progression of cognitive decline and provide a method to identify modifiable factors associated with early cognitive decline. The effect of antihypertensives, statins, ARB/ACE inhibitors, antioxidants, and modifiers of inflammation on the high prevalence of cognitive impairment and stroke in this population are potential areas of future research.

UPTAKE OF DIETARY AGEs IN HEALTHY ADULTS AND PATIENTS WITH EARLY DIABETIC NEPHROPATHY

Healthy adults exposed to diets with a low or high content of AGEs show rapid absorption of AGEs, resulting in a spike in serum levels, followed shortly thereafter by an increase in the content of AGEs in the urine (Figure 6A).¹⁴ Those fed a diet rich in AGEs had higher peak serum and urine AGE levels than those fed a low-AGE diet. However, the levels rapidly returned to baseline.

Two groups of patients with diabetes, with either micro- or macroalbuminuria and either a normal or only slightly re-

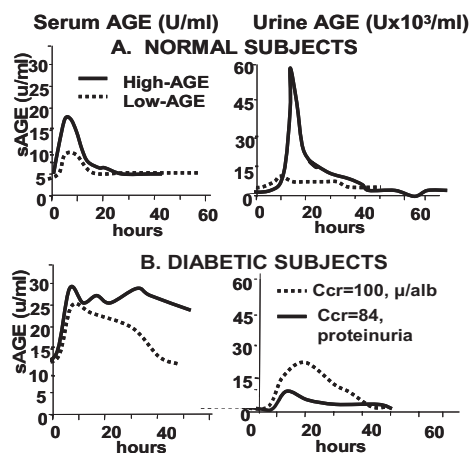


Figure 6. The levels of AGEs in the serum and urine of normal subjects and patients with CKD after eating a meal with either a low or high AGE content. (A) The levels of serum AGEs and urine rapidly rose in normal subjects, varying directly with the amount of AGEs in the diet. (B) Patients with diabetes and either microalbuminuria or proteinuria, with relatively preserved renal function, showed higher baseline levels of AGEs, higher and more prolonged peak levels, and a smaller increase in urine AGE levels.

duced eGFR, were given either a standard or AGE-rich meal (Figure 6B). Their responses to a regular meal were quite different.¹⁰ Namely, the baseline levels of AGEs were higher than normal, and the high peak serum levels were maintained for a prolonged period. Note that these changes were present in diabetics that had either a normal or only slightly reduced eGFR and that urinary excretion of AGEs was also diminished. These data suggest that the kidney responds to increased oxidant stress and inflammation by reducing the excretion of AGEs. The data also suggest that AGEs may be actively excreted by the tubules and filtered at the glomerulus.^{28,42}

DRUGS AND THE REDUCTION OF PRO-OXIDANT MOLECULES (AGES)

Vitamins and Other Dietary Supplements

In general, the results of trials of a wide range of oral antioxidants have largely been disappointing.^{43–46} However, none of these studies included an attempt to control baseline levels of OS and inflammation. If our data apply to the general population (Figure 3),¹⁴ the great variation in the baseline levels of oxidants may partly explain these results. This conclusion is supported by the fact that many studies have shown that the Mediterranean Diet, which is low in AGEs, is associated with low levels of OS and inflammation and seems to have beneficial effects on general health.^{47,48}

Anti-AGE/Oxidant Products

Two drugs have been tested for their ability to reduce the levels of AGEs in clinical trials. The focus has been on diabetics in

both cases. Aminoguanidine was the first to be developed and tested in animals and then in patients.⁴⁹ This drug interferes with the generation of AGEs intracellularly. It did not meet the required outcome of decreasing the rise in serum creatinine by 50% in a single trial.⁵⁰ The second drug, a vitamin B₆ analog, pyridoxamine, has long been used in the treatment of hyperoxaluria and has few side effects. It serves to block the early glycation derivatives after the formation of Schiff bases and is also a chelator. In a phase 2 clinical trial, it reduced proteinuria in diabetic patients with progressive renal disease.⁵¹

STUDIES IN HEALTHY AGING MICE

Rodent food contains a relatively large amount of oxidants because of the increased temperature used in its preparation, zzespecially that amount needed to pelletize the granular product. The significance of increased oxidants in the diet becomes clear when comparing kidney and heart lesions in mice given isocaloric diets prepared with standard heating (high-AGE diet) or with less heating during manufacture (low-AGE diet). Namely, both kidney and cardiovascular lesions were markedly reduced, and lifespan was significantly extended in mice given the low-AGE diet.^{7,8} To determine if the inflammation and OS was caused by the AGEs in the diet, we added a specific AGE to a low-AGE diet. Adding methylglyoxal (MG) led to an increase in both OS and inflammation in the serum, paralleling standard mouse chow.⁸ The only other major intervention that reduces OS and inflammation, prevents CKD and CVD in aging, and prolongs life is caloric restriction.⁵² It is not clear whether the beneficial effects of calorie restriction are caused by a 40 to 60% reduced energy intake, since reduction of food intake concomitantly restricts the intake of oxidant by the same amount. Therefore, we designed experiments in which mice were pair-fed the regular diet throughout their lifetime (which has a high AGE content) and compared them with mice fed a calorie-restricted diet (40% decrease in food) and mice fed the same calorie-restricted diet that had a high content of AGEs, prepared with an additional heating step. At sacrifice in late life, the kidney lesions were largely prevented in the calorie-restricted mice, and the heart was essentially normal. However, mice given either of the high AGE diets had sclerotic cardiac and renal lesions. The two high AGE diets (normal mouse chow and calorie restricted, high AGE) were also associated with a decreased life span. These findings suggest that the beneficial effects of calorie restriction may be partly explained by the concomitant reduction in oxidant intake.

CONCLUSIONS

CrCl declines, on average, with aging even in individuals without clinical kidney disease. Although this decline occurs in most, a small number of individuals maintain intact renal function up to a very old age, raising the issue that a decline

may not be obligatory. Furthermore, the handling of oxidants by the kidney may be suppressed before a decline in eGFR. One problem in the assessment of renal function in aging is the lack of agreement among nephrologists and geriatricians about which of the currently available formulae to calculate GFR is most appropriate in normal aging. This topic awaits further study. In addition, there is currently no biomarker allowing determination of whether impaired renal function in an older individual is caused by “normal” aging or the effect of some factor(s) as yet unidentified. A study of oxidant stress and inflammation and the role of current high-AGE diets in altering kidney function(s) may also be a fruitful area for future investigation, since there are economical and efficient interventions that reduce oxidant stress and inflammation in both normal adults of all ages and patients with CKD.

TAKE HOME POINTS

- Oxidants in the diet directly lead to increased serum levels of inflammatory mediators and OS
- This process can be interrupted by simply changing the methods of processing and/or cooking the usual foods consumed by adults
- The same outcomes may also be seen in patients with CKD

DISCLOSURES

None.

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REVIEW QUESTIONS: DECLINE OF RENAL FUNCTION IN NORMAL AGING AND ROLE OF OXIDANTS/INFLAMMATION: WHEN DOES IT BEGIN AND IS IT INEVITABLE, PREVENTABLE, OR TREATABLE?

- Which of the following are true?
 - CrCl remains normal with aging in most persons
 - Most of the estimates of CrCl give the same results in aging
 - CrCl, on average, decreases with age
 - CrCl may remain in the normal range in some individuals
- Which of the following statements about oxidants are true?
 - The levels of serum oxidants increases with age, on average
 - The levels of oxidants vary among individuals depending on dietary intake
 - The levels of serum oxidants correlates with CrCl
 - The sources of serum oxidants includes the diet
- Choose the two best answers to describe the effect (s) of decreasing oxidant intake in CKD patients.
 - Decreasing oxidant intake in healthy adults has no influence on inflammation
 - Decreasing oxidant intake in healthy adults reduces inflammation
 - Decreasing oxidant intake reduces the levels of RAGE (pro-oxidant), and increases the levels of AGER1 (anti-oxidant)
 - Decreasing oxidant intake in patients with diabetic nephropathy reduces the levels of RAGE (pro-oxidant), and increases the levels of AGER1 (anti-oxidant).
- Choose the two best answers from the three statements below.
 - Serum AGE levels are paralleled by urinary excretion of AGEs in normal adults
 - Serum AGE levels are unaffected by dietary intake in diabetics with nephropathy
 - AGE excretion in patients with diabetic nephropathy is increased diabetics with normal renal function compared with normal adults
 - AGE excretion in patients with diabetic nephropathy is decreased diabetics with normal renal function, compared to normal adults
 - AGE excretion in patients with diabetic nephropathy in diabetics is impaired only when eGFR is <80 ml/min
- Choose the correct statement from the following statements.
 - Reducing AGEs in the diet has been shown to reduce markers of vascular injury in humans
 - The reduction of oxidants in humans has not proven to be possible, at present
 - Reducing the levels of oxidants in the diet of patients with diabetic nephropathy rapidly results in normalization of the levels of oxidants in the blood
 - Reducing the levels of oxidants in the diet of patients with diabetic nephropathy results in normalization of the excretion of AGEs
- Which of the following statements are false.
 - Anti-oxidant vitamins have been shown to reduce oxidants in controlled clinical trials
 - Drugs that control the formation of AGEs have been conclusively shown to reduce diabetic nephropathy in controlled clinical trials
 - The “Mediterranean Diet” has been shown to be associated with reduced serum levels of oxidants and inflammation
 - The content of oxidants in the diet, rather than the energy intake, has been shown to be critical to reducing organ damage in experimental studies