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Managing Chronic Inflammation in the Aging Diabetic Patient With CKD by Diet or Sevelamer Carbonate: A Modern Paradigm Shift

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The maintenance of normal metabolism and body defenses depends on the balance between cellular antioxidant and anti-inflammatory factors. This balance can be disrupted by agents/mechanisms in the extracellular milieu that induce excess reactive oxygen species (ROS) and inflammation. Cytopathic advanced glycation endproducts, present in ever increasing amounts in the modern diet, are one of the major environmental factors that cause excess ROS and/or inflammation at all ages and induce complications in aging, such as chronic kidney disease (CKD) and type 2 diabetes. Increased ROS and/or inflammation are present in both aging and CKD, and are associated with reduced cellular defenses against ROS and/or inflammation. Affected individuals have reduced defenses against further stress and are predisposed to organ failure, a well-known phenomenon in aging. Thus, new methods are urgently needed to safely reduce ROS and/or inflammation in the aging type 2 diabetes patient with CKD. Studies of both normal aging and diabetic patients with kidney disease underline the fact that increased ROS and/or inflammation can be managed in these conditions by economical, safe, and effective interventions that reduce the uptake of advanced glycation endproducts by either modifying preparation of food or an oral drug. This communication reviews these data and adds new information on the efficacy of a drug, sevelamer carbonate, required to reduce ROS and/or inflammation in the aging type 2 diabetes patient complicated by CKD. If larger and longer studies confirm the hypothesis that one or both of these interventions reduce progression of CKD, it could represent a new paradigm in the management of complications in the type 2 diabetes patient with CKD.

Key Words: Diabetes—Hemodialysis—AGEs—Diet—Inflammation—Aging.

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Coupled with data showing that AGEs can directly cause damage to pancreatic beta cells (9), these data suggest that cytopathic AGEs could be a factor in the development of T2D in aging, as well as its complications.

Several studies demonstrate that the source of AGEs is largely of dietary origin in both normal individuals and those with diabetes mellitus (DM) (10,11). It is equally well documented that reducing dietary AGEs improves glucose homeostasis in both normal adults and those with T2D (10,12–14). Namely, although endogenous glucose or lipids contribute to the formation of AGEs (12), exogenously derived AGEs (from preformed AGEs generated during food processing by heat) are an important source of AGEs in normal human participants, those with T1D or T2D (10,15), or CKD (14). Based on a significant reduction in serum AGEs and plasma lipid peroxides (8-isoprostanes) and inflammation after AGE restriction, it was concluded that elevated AGEs in T2D result from increased dietary AGE intake, and that this could be independent of glycemic control (3). In addition, dietary AGEs increase the intracellular oxidants and decrease the ability of cells to handle cell-generated OS. Recently it was found that dietary AGEs bind to a nonabsorbable drug, sevelamer carbonate (16). Coupled with the fact that exposure to AGEs in the diet can be reduced by modifying the preparation of food, it seems reasonable that the coadministration of this drug, and restriction of the intake of AGEs from food could represent a complementary and nontoxic means to reduce ROS and/or inflammation and reduce the risk of organ damage in the aging diabetic patients with CKD.

**Studies on the Control of ROS and/or Inflammation in Aging Animals**

The importance of food-derived AGEs noted in humans was established by studies in diabetic patients, ApoE−/− hyperlipidemic (17) as well as aging mice (18,19). Aging mice were kept under normal energy balance via diets that contained either the regular or a lower amount of AGEs (AGE-restricted diet). Somewhat surprisingly, it was found that excess metabolites, such as glucose or lipids, whether as single or combined entities, were not sufficient to promote significant diabetic tissue injury without the excess amounts of AGEs found in standard heat-processed experimental diets (17–22). Significant diabetic vascular and kidney disease did not appear in the absence of additional (external) oxidants provided by excessive amounts of AGEs. Importantly, restriction of external (food-derived) AGEs was found to reduce both the vascular and kidney disease. To determine if AGEs were the actual “cytopathic element” causing the metabolic changes, mice were pair-fed a low-AGE diet or the same diet supplemented with a well-defined AGE (methylglyoxal [MG]-BSA; MG diet) (19,23,24). The amount of MG-AGE in the MG diet was similar to that found in the commercial mouse diet. This MG diet resulted in the development of OS, insulin resistance (IR; and ultimately, T2D), and renal/vascular disease as the mice aged. However, if AGEs were restricted, without altering caloric or nutrient intake, the result was reduced OS and inflammation, IR was ameliorated and life span was extended (19). The significant increase in systemic AGEs and OS in mice fed the MG-supplemented diet provided firm evidence that diet-derived AGEs increases the normal levels of OS and alters the cellular and metabolic phenotype of these animals as well as that of their progeny. This results in a cycle of continually increasing levels of ROS and AGE formation. Despite numerous studies showing an association between RAGE and pro-OS conditions, RAGE does not appear to have a primary etiologic role in the development of diabetes, other than that of an ROS transducer (25–27). Current evidence suggests that extracellular and/or intracellular OS appears to be the most important biomodulator of RAGE. Thus, a decrease in basal OS, by simply restricting availability of external AGEs was sufficient to suppress the RAGE gene and protein levels in diabetic or older mice (18,19,24).

**Studies in Aging Healthy Study Participants and Those With DM**

The initial evidence that food-derived, preformed cytopathic AGEs were an important source of systemic AGEs and led to ROS and/or inflammation in diabetic and normal participants was obtained in a study of T2D with or without evidence of kidney disease and five healthy participants who were given a single meal of egg white, cooked with fructose (high-AGE meal) or without fructose (control meal) (5). Serum and urine samples were collected for 48 hours, and were monitored for the presence of pathogenic AGEs, which was assessed by the formation of AGE-specific cross-links in vitro. Serum obtained from participants ingesting the high-AGE meal exhibited increased AGE cross-linking activity independently of the presence or absence of T2D. Importantly, the increased cross-linking was inhibited by aminoguanidine, a compound that chelates AGEs (5). Consumption of the high-AGE meal, but not the control meal, resulted in elevations in serum AGE levels that directly correlated with the amount of ingested AGEs (r = .8, p < .05) and the severity of the CKD.

Approximately 10% of the ingested AGE was absorbed, and approximately 30% of that was excreted in the urine. The amount excreted correlated inversely with the degree of albuminuria, and directly with creatinine clearance (r = .8, p < .05). An important finding was that renal excretion of AGEs was reduced to less than 5% in diabetic participants with advanced CKD. There were several important conclusions from this study: (a) the daily influx of dietary AGEs includes cytopathic glycoxins that may constitute an added risk for renal vascular injury in DM, (b) the renal excretion of orally absorbed AGEs is markedly suppressed in diabetic patients with nephropathy, and (c) dietary restriction of the intake of food with a high-AGE content may greatly reduce the burden of AGEs in diabetic patients. These conclusions
have now been substantiated in further studies of healthy persons and in patients with DM (11,13,14). Importantly, participants with no obvious disease, but who have elevated AGEs and increased inflammation and/or ROS, also show a significant decrease in these abnormalities when placed on a low-AGE diet (13).

**Studies on the Effects of Dietary AGEs on Circulating AGEs and Vascular Function in Aging Diabetic and Healthy Participants**

In a recent study, it was found that diabetic patients had higher baseline levels of serum AGEs and vascular cell adhesion molecule-1 (VCAM-1) (a measure of endothelial injury) than healthy participants (28,29). They all had normal blood flow at baseline, but 90 minutes after a single oral AGE challenge, serum AGEs and PAI-1 levels increased and the percentage of increasing blood flow in response to hyperemia (flow-mediated dilation [FMD]) decreased significantly in both healthy participants and diabetic participants, whereas serum glucose and VCAM-1 levels did not change. It was concluded that acute increases in serum AGEs coincide with decreased FMD and a marker of acute vascular injury. This led to the postulate that repeated or chronic exposure could either induce new vascular disease or accelerate existing vascular disease.

**Studies of the Effects of Aging on the Accumulation of Food-Derived AGEs**

The question of the age at which AGEs become elevated and whether the uptake of food-derived AGEs in individuals between 20 and 45 years of age differed from those older than 60 years of age was examined in a study of 172 healthy urban participants (11).

Serum AGEs were, in general, higher in older individuals. However, the levels of serum AGEs correlated directly with the consumption of preformed dietary AGEs, independently of age and of calories consumed. In fact, the serum levels of AGEs were equally high in some persons between 20 and 45 years of age as those older than 60 years of age. This led to the conclusion that reduced consumption of AGEs could be an important target for adults of all ages to prevent age-related diseases, but particularly in the aging population.

A study in neonates (30) revealed that serum AGEs in newborns closely correlated with their mothers but that the increase by approximately twofold within the first year of life as they began to consume heat-processed formulas and solid food (31,32). Of note, high serum AGEs correlated with higher insulin levels and lower antioxidant and adiponectin levels, possibly predicting early metabolic dysfunction.

**The Association Between Food-Related AGEs and the Metabolic Syndrome**

In a cross-sectional study of 325 normal participants living in an urban environment a close association was found between serum AGEs (carboxymethyllysine [CML] and MG) derivatives and certain components of the metabolic syndrome, especially BMI and homeostasis model assessment (HOMA), an index of IR (13). There were significant associations between both CML and sMG and the BMI, HOMA, and HDL-C levels. Several findings suggested that these changes were a function of aging. Namely, HOMA levels were significantly higher in older than younger participants (p = .020) and in men compared with women (p = .010). BMI was significantly higher in older than younger participants (p = .001) and in men compared with women (p = .001). These findings are consistent with previous studies showing that ROS and/or inflammation increases with aging (2,33,34). Interestingly, the correlations between both sCML and sMG with HOMA, BMI, and HDL-C remained significant after adjusting for gender and age (13).

Given these positive correlations, it would be important to know if reduction of AGEs in otherwise equivalent diets lowers oxidant stress/inflammation in healthy and aging participants. Furthermore, if these data apply to the general population, the intake of AGEs could affect the transition from the metabolic syndrome to T2D (3). Another new and important conclusion from this study was that the intake of a high-AGE diet could be a significant determinant of systemic OS. Thus, it could represent a risk factor for several diseases associated with chronic inflammatory diseases in adults who are otherwise considered to be healthy. A somewhat surprising and clearly new finding from this study was that increased OS was found both in the aging population and in the younger “normal” study participants. This was the first data showing that elevated OS in association with elevated AGEs can be present at a young age. This implies that inflammation is not an exclusive feature of aging, and secondly, some aspects of aging can commence at a relatively young age. If these data are confirmed they may provide a partial explanation for the current epidemic of obesity and the steadily increasing incidence of T2D in younger age groups (2,34,35). Finally, the unavoidable conclusion from these data is that abnormally high levels of OS may not be “normal” in human aging.

**Reducing the AGE Load in the Normal and Prediabetic Population**

A subset (n = 40) of the normal participants in the above study (11) received either a low-AGE (with 30%–50% lower AGEs) or regular, but isocaloric, diet and was followed for 4 months. OS and inflammation were reduced by the low-AGE diet, regardless of age, providing strong evidence that elevated OS in normal participants may be remediable at any age. Thus, the prevention of chronic diseases related to chronic inflammation could be accomplished by modifying the intake of AGEs, and this measure should be started early in life.

**The Role of the Kidneys in the Removal of AGEs From the Body, Implications for Aging**

If removal of oxidant AGEs via AGE receptor-1 (AGER1) depends on excretion by the kidney via AGE metabolism...
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The Dose of Sevelamer Carbonate Required to Control ROS and/or Inflammation in Hemodialysis Patients, and the Role Played by Phosphate Uptake

The dose of sevelamer carbonate recommended for the control of hyperphosphatemia in hemodialysis patients is well documented (37). It is not known whether phosphate balance is related to AGEs and/or ROS and inflammation. Because AGEs are directly linked to ROS and/or inflammation, which are known risk factors for complications such as cardiovascular disease (38,39) and dementia (40), it is important to determine the appropriate dose for managing AGEs in populations with increased risk for these complications. Furthermore, because the control of phosphate uptake is important for both bone and vascular health, it is important to know if AGEs, ROS, and/or inflammation and phosphate metabolism are directly related. Therefore, researchers analyzed serum specimens from a study of hemodialysis patients. They assessed the levels of serum phosphate and two AGEs, MG and CML. Thus 132 T2D participants, aged 18 and older, were enrolled in this study at 62 centers in the United States. The inclusion criteria included: (a) hemodialysis three times per week for at least 3 months, (b) currently taking a phosphate binder, (c) intact parathyroid hormone less than or equal to 800 pg/mL at screening, and (d) serum phosphorus level greater than 5.5 mg/dL after a 2-week phosphate binder washout. Following the 2-week phosphate binder washout period, after which they were randomized to placebo or to one of three doses of sevelamer carbonate: 2.4, 4.8, or 7.2 g/day. Patients were maintained on this fixed dosage for 3 weeks. The changes in serum phosphorus, lipids, AGEs inflammatory markers, and ROS were examined. The levels of serum AGEs were reduced, both MG and CML, at 4.6 and 7.2 g/day, but remained close to baseline levels at a dosage of 2.4 g/day. On the other hand, there was a dose-dependent decrease (trend) for serum phosphorus ($p < .0001$), suggesting that control of phosphate uptake and serum phosphorus could not be related to the control of ROS and/or inflammation in hemodialysis patients (Table 1). Note, however, that a crossover study of sevelamer carbonate and calcium carbonate failed to show that control of phosphate uptake had a direct effect on ROS and/or inflammation (16). Total cholesterol and LDL cholesterol showed a dose-dependent decrease with increasing levels of sevelamer carbonate ($p < .0001$), but triglycerides showed an increasing trend ($p = .06$). Finally, VCAM-1, a marker of vascular injury, was decreased ($p = .002$) only at 7.2 g/day.

This study showed that high levels of cytopathic AGEs and certain lipids can be markedly decreased by sevelamer carbonate within a period of time as short as 3 weeks in T2D hemodialysis patients. Because AGEs raise risks for cardiovascular disease and other complications, this treatment may prove to be efficacious against these complications. An

Preventing the Uptake of AGEs in Aging CKD Predialysis Patients With a Drug

Recently, sevelamer carbonate was found to bind AGEs in vitro (16). Because this drug has an excellent safety profile and has been utilized for many years in the management of end-stage kidney disease, a randomized crossover study of patients with T2D and stage 2–4 CKD was conducted. Sevelamer carbonate was compared with calcium carbonate. Most patients were being treated with statins and modulators of the renin-angiotensin system, and no medications were changed. Each of the treatment periods was 8 weeks long, followed by a 1-week washout, prior to switching to the other drug for 8 weeks. Sevelamer carbonate significantly reduced HbA1c, FGF-23, several serum lipids, markers of inflammation and OS, and increased antioxidant and anti-OS defenses, independently of phosphorus in these patients. Although calcium carbonate reduced phosphate excretion, it did not affect AGEs or any of the markers of ROS and/or inflammation. Neither intervention affected blood glucose levels. This short study revealed that sevelamer carbonate can reduce several metabolic and inflammatory abnormalities in T2D. However, a longer and larger trial is needed to assess changes in progression of diabetic CKD or other complications of increased ROS and/or inflammation.

or filtration, then decreased renal function in aging may provide one explanation for the increased OS found in the aging population. As the glomerular filtration barrier resists the passage of highly charged molecules (36), like AGEs, the renal handling of AGEs might be expected to be principally by tubular uptake and excretion, rather than by filtration. Because the levels of AGE1R, a receptor involved in the uptake and degradation of AGEs, correlate with levels of circulating AGEs and their amount of AGEs (11), the presence of AGE1R in the kidney tubules could be one way by which the kidneys remove AGEs from the blood, thereby playing a role in the control of systemic ROS and/or inflammation. In mice, the researchers found that the kidney cortex AGE1R levels decreased with aging in mice if they were fed a high-AGE diet, but not if they were fed a low-AGE diet (19,24). This suggested that high levels of AGEs downregulate AGE1R, and that lowering AGE levels can preserve normal AGE1R1 levels. This conclusion was reinforced in a study of T2D patients given a low-AGE diet for 4 months resulted in increased excretion of AGEs in the urine (14). These data suggested that reducing the load of AGEs absorbed resulted in increased tubular levels of AGE1R, and allowed them to more efficiently metabolize and excrete AGEs in patients with diabetes. If this observation is confirmed in larger studies, strategies to reduce the intake of AGEs could be useful in the management of the complications of diabetes, including CKD.
important therapeutic issue pointed out by this study was that sevelamer carbonate at a dosage of 2.4 g/day did not significantly reduce cytopathic AGEs. Because cytopathic AGEs are inducers of ROS and/or inflammation, assuring that patients reach and maintain the 4.8 g/day dosage level may represent an important therapeutic goal.

**CONTROL OF AGEs REDUCES IR IN AGING T2D PATIENTS WITHOUT CKD**

Increased OS and impaired anti-OS defenses play critical roles in the development and persistence of IR (3,34,41). Several anti-inflammatory and cell protective mechanisms, including AGER1 and sirtuin1 (SIRT1) are suppressed in diabetes (42,43). Basal ROS and/or inflammation in T2D patients is also partly regulated by the consumption of AGEs (16). A study was recently conducted to determine if the amount of AGEs in the diet affects IR and if AGER1 and SIRT1 are coordinately regulated (14). Eighteen insulin-resistant T2D patients and 18 normal adults without renal disease who were following the usual Western diet (rich in AGEs) were enrolled and studied for 4 months. At study end, the serum levels of AGEs were decreased in both the normal and diabetic groups. In the DM group, the levels of plasma insulin and HOMA, leptin, TNFα and NF-κB p65 acetylation (acl-p65), serum AGEs, and 8-isoprostanes were decreased in AGE-restricted T2D patients. This group had suppressed levels of antioxidant molecules, including AGER1 and SIRT1 mRNA and protein levels in peripheral monocytes. At study end, these levels were normalized and adiponectin was markedly increased. The levels of 8-isoprostanes were decreased in the AGE-restricted normal participants, but they showed none of the other changes present in the patients with DM. The conclusions from this study were that restriction of oral AGE intake may preserve native defenses and insulin sensitivity in T2D by maintaining lower basal OS.

From the perspective of the management of T2D patients, the data show that chronic exposure to exess exogenous (food) oxidants further lowers native antioxidant defenses and impairs insulin action. Importantly, reducing exposure to oral AGEs partially reverses these defects and improves IR without restricting energy or caloric intake. Because these effects were seen in patients who were receiving the best standard medical therapy, AGE restriction could be a valuable addition to the current management of patients with T2D, with or without CKD. These studies were an extension of earlier clinical studies in healthy participants, as well as diabetic and CKD patients, in which it was shown that AGE restriction substantially reduce OS and inflammation, and improves native defenses, including AGER1 and SIRT1 (11,13).

**DISCUSSION**

Reduced renal function (CKD) occurs in nearly one half of persons over the age of 60 in the western world, based on both the National Health and Nutrition Examination III data and a number of recent studies (44,45). Because decreased renal function is associated with increased ROS and inflammation, which are risk factors for deteriorating function in several other organs, it is important to detect and manage CKD in aging. However, it is clear that reduced renal function in the aged without direct evidence of kidney disease, such as the presence of proteinuria, may not be sufficient evidence for making the diagnosis of CKD. Aging is also accompanied by ROS and/or inflammation, which may be accentuated by the chronic inflammation of CKD. Although the causes of the ROS and/or inflammation in aging are not widely known, multiple animal studies suggest that AGEs are one possible candidate (18,19). One major source of glycoxidants is food-derived AGE peptides and AGE lipids (46,47). The mechanisms of uptake of preformed AGEs from the food are not fully elucidated, but there is a strong link between high oral glycoxidant intake, IR, T2D, and diabetic complications in a wide variety of experimental animals (3).

AGE-modified proteins and lipids in the extracellular space are sequestered by cellular or soluble AGE receptors, degraded by proteolytic digestion to soluble peptides and are then removed by the kidneys (12,48). One factor contributing to failure of AGE detoxification is that AGE–protein cross-links are resistant to degradation, delaying their turnover and interfering with tissue repair (49,50). Another factor is the downregulation of receptors that clear and lead to the degradation of AGEs, principally AGER1 (42,51).

The kidney plays a major role in the detoxification of AGEs, both by filtration or by active uptake, processes resulting in the net excretion of AGEs in the urine (14,48). Because of their large blood supply, the kidneys are directly exposed to a large amount of circulating AGEs, a fact which makes it a major target for injury by reactive carboxyls, ROS and other toxic substances, which may contribute to reduced renal function and impaired AGE clearance. Any reduction in renal AGE clearance is likely to result in the progressive accumulation of AGEs, which results in an increase in new AGE formation and ROS within the
body, including the kidneys. The fact that AGER1 levels are suppressed by chronically increased levels of AGEs can further exacerbate ROS and/or inflammation. Recent clinical studies show that the levels of serum AGEs rise long before there is clinical evidence of renal disease (11), suggesting that increased levels of AGEs could be an early sign of impaired renal function. One very positive fact emerging from several studies in human participants with diabetic or nondiabetic CKD, is that AGE restriction leads to decreased serum AGEs, restored cellular anti-Ros and/or anti-inflammatory mechanisms, including AGER1 and SIRT1, and significantly decreased systemic OS and inflammation (10,13,15).

The reason(s) that not all aging persons develop decreased renal function (4) and 70%–80% of patients with either T1D or T2D do not develop CKD or other organ complications is unclear (8,44). However, the presence of uncontrolled ROS and/or inflammation, fueled by increased levels of AGEs, could be an important contributor to decreased renal function. A recent study of the role of AGEs in complications of T1D patients followed for 50 years at the Joslin Clinic, the so-called “Medallion” patients, supports this postulate (8). This study revealed that the presence of cardiovascular disease, nephropathy, and neuropathy was tightly correlated with high levels AGEs. The onset of T1D was also shown to be affected by the level of circulating AGEs in a seminal study of islet cell positive, mono- and dizygotic twins, and Finnish children (7). Thus, AGEs may be important in both the onset and complications of T1D. Finally, two recent studies of patients with either T1D or T2D and CKD revealed that those with high levels of TNFR1,2 levels identified those who would progress to more severe renal failure and/or to end-stage kidney disease (52,53). These important studies underline the role of inflammation in the progression of CKD.

The evidence that AGEs are important in the development of T2D and/or its complications in humans is less clearly documented, but most patients with T2D have increased ROS and/or inflammation (3). AGEs are directly cytotoxic to pancreatic beta cells and reduce insulin signaling in fat and muscle cells in mice, both of which could contribute to loss of beta cell function (24). Finally, although AGEs are associated with the metabolic syndrome, long-term controlled studies showing that reduction of AGEs in this population decreases conversion to T2D have not yet been completed.

Acute kidney injury appearing in aged persons results in more severe CKD with a poor prognosis for complete recovery of normal renal function (54–56), suggesting that “renal reserve” may be decreased in the elderly participants. In common with the older patient with reduced renal ability to handle acute ROS and/or inflammation (such as AGEs), younger CKD patients are also more likely to develop more rapid progression after an acute injury (56). Based on a single center longitudinal study presented at a seminar on acute kidney injury, it has been suggested that the course of CKD may be one of successive acute insults (57).

The foregoing data suggest that the kidney could be an “essential organ” in the control of ROS and/or inflammation due to excessive intake or chronic inflammatory diseases, such as DM. Thus, decreased renal function in aging may signal the presence of an excessive load of oxidants that could potent the development of failure in other organ systems when exposed to further increases in ROS and/or inflammation.

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