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Role of Advanced Glycation Endproducts and Potential Therapeutic Interventions in Dialysis Patients

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Abstract

It has been nearly 100 years since the first published report of advanced glycation end products (AGEs) by the French chemist Maillard. Since then, our understanding of AGEs in diseased states has dramatically changed. Especially in the last 25 years, AGEs have been implicated in complications related to aging, neurodegenerative diseases, diabetes, and chronic kidney disease. Although AGE formation has been well characterized by both in vitro and in vivo studies, few prospective human studies exist demonstrating the role of AGEs in patients on chronic renal replacement therapy. As the prevalence of end-stage renal disease (ESRD) in the United States rises, it is essential to identify therapeutic strategies that either delay progression to ESRD or improve morbidity and mortality in this population. This article reviews the role of AGEs, especially those of dietary origin, in ESRD patients as well as potential therapeutic anti-AGE strategies in this population.

It has been approximately 100 years since the first published report of advanced glycation end products (AGEs) by the French chemist Maillard (1). AGEs were initially explored by food chemists, but for several decades now they have been described to play a crucial role in the development of complications related to aging (2), diabetes (3), neurodegenerative diseases (4), rheumatoid arthritis (5), and chronic pulmonary diseases (6). In addition, elevated AGEs have also been implicated in uremic states (7).

Advanced glycation end products are a large group of heterogeneous substances produced by the nonenzymatic reactions of sugars with free amino groups on proteins, peptides, or amino acids (the so-called Maillard reaction). AGEs may also form through several other pathways, including oxidation of sugars, lipids, and amino acids to create reactive aldehydes that covalently binds to proteins. The metabolism of glucose generates glycolytic intermediates, which also contribute to this pool of reactive aldehydes. Moreover, neutrophils and monocytes, upon inflammatory stimulation, produce myeloperoxidase and

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activate NADPH oxidase, which form AGEs by oxidizing amino acids. Although not all AGEs have been well characterized, *N*-carboxymethyl-lysine (CML), pentosidine, and methylglyoxal (MG) derivatives are among some that have been well described (8–10).

Although traditionally described in relation to diabetes and thought to be generated only endogenously in response to hyperglycemia, it is now clear that AGEs can also form in the body in conditions with high oxidative stress (OS), independent of hyperglycemia (5). More recently, it has become recognized that consumption of a contemporary diet, cooked under dry and high heat conditions, contributes significantly to the total body AGE pool (11,12). Although direct demonstration of gastrointestinal AGE absorption has not been clearly documented, there is significant indirect evidence of this process (11,12). Another important, but frequently ignored source of exogenous AGEs is cigarette smoking (13).

AGEs, either formed endogenously or of dietary origin, can produce tissue damage by protein cross-linking that causes direct alteration in the protein structure and function. Tissue damage can also occur by other mechanisms, which may include activation of receptors that trigger proinflammatory and pro-oxidative cellular signaling pathways (14). Besides the cell surface AGE receptors that bind AGEs and initiate cell activation, there are some receptors that bind, internalize, and degrade AGEs (14). The best-studied receptor that binds and initiates OS is the receptor for AGE (RAGE). Binding of AGEs to RAGE initiates a cascade of intracellular signaling leading to activation of several inflammatory responses and pathological gene expression that eventually increases OS (15). In contrast, AGER1, also a well-studied AGE receptor, has marked antioxidant properties by modulating AGE/RAGE mediated activation of nuclear factor kappa-B (16), epidermal growth factor receptor, extracellular receptor kinase, and p66shc (17,18). Of note, AGER1 is down-regulated in the presence of chronically elevated AGE levels, as observed in diabetes or chronic kidney disease (19).

In this review, we discuss the importance of AGEs, specifically those of dietary origin, in patients with end-stage renal disease (ESRD), with or without diabetes and we propose potential therapeutic interventions.

Formation of AGEs in Chronic Dialysis Patients

The markedly increased levels of circulating AGEs in dialysis patients reflect not only decreased clearance, but also increased addition of AGEs to the body pool, either from increased endogenous formation or continuous exogenous supply from the diet. Increased endogenous AGE formation has been attributed to multiple etiologies. First, hyperglycemia is an obvious cause in diabetic patients. Moreover, ESRD patients receiving long-term hemodialysis (HD) are known to have increased OS due to elevated free radical production as well as reduced antioxidant levels (20). This increased OS contributes to the formation of AGEs (21). In addition, Miyata et al. has described the role of reactive carbonyl compounds as a contributing factor to the formation of AGEs in uremic patients, independent of hyperglycemia (5). Specifically, it was observed that small size reactive carbonyl compounds (<5000 Da) contributed to the generation of pentosidine, a reaction inhibited by aminoguanidine or OBP-9195 (known inhibitors of Maillard reaction) (5).

The interaction of blood with the dialysis membrane also contributes to formation of AGEs (22–24). In a cohort of 126 long-term HD patients using various dialysis membranes, protein-linked and free plasma pentosidine levels were measured by HPLC. Patients using high-flux polysulfone membranes had significantly lower levels of pentosidine in comparison with patients using low-flux membranes (23). The use of high-flux dialysis membranes to remove certain AGEs, as well as carbonyl precursors, has also been confirmed in other studies (22,24).

Although the use of high-flux membranes reduces the free pentosidine and CML levels, the removal of total pentosidine and CML is marginal since more than 95% of pentosidine is protein bound (24). Interestingly, the notion that removal of AGEs is dependent on the porosity of the membrane has been questioned since pentosidine levels with nonpolysulfone high-flux membranes are similar to those with nonpolysulfone low-flux membranes (23). This suggests that the material coating the dialysis membrane may play a more significant role in the generation or removal of AGEs than the porosity of the membrane. Other investigators have also reported that the use of high-flux HD does not effectively remove AGEs as there is a return to pretreatment serum AGE levels within 3 hours post treatment (25).

As conventional HD does not effectively remove circulating AGEs (26), other dialysis modalities and prescriptions have come to the forefront. For example, recently, short daily dialysis, hemodiafiltration, and hemofiltration were more effective in lowering serum AGE levels than conventional (4 hours and three times a week) HD (27,28). In addition, in a 6-month longitudinal study in 2001, hemodiafiltration significantly lowered serum AGE levels when compared with high-flux HD by the end of the treatment period (29).

As with HD, the levels of circulating AGEs are also increased in peritoneal dialysis (PD) patients, regardless of their diabetic status. It has long been established that the use of glucose containing dialysate in PD can contribute to increased AGE formation in the peritoneum (30–32). Specifically, it has been shown that AGEs accumulate in the mesothelial layer of the peritoneum with increasing dialysate dwell time (33). Furthermore, it has been suggested that this peritoneal accumulation of AGEs can contribute to failure of the peritoneal membrane by increasing peritoneal membrane permeability to glucose, creatinine, β_2 m, and albumin (34) (35–37). Peritoneal biopsy specimens from a cohort of 14 PD patients revealed that AGE accumulation (defined by anti-AGE antibodies) correlated with ultrafiltration failure, peritoneal fibrosis, and microvascular steatosis (38). In fact, AGEs were also observed to accumulate more intensely in fibrosed venular media (38). Other Japanese studies have also confirmed that AGE accumulates in the mesothelial layer of the peritoneum within 3 months of PD initiation (34). Finally, heat sterilization of dialysate in PD also increases AGEs and dicarbonyl compound formation, such as 3-deoxyglucosone (3-DG), MG, and glyoxal (GO) (39–43).

Despite this evidence of increased intraperitoneal AGE formation, studies have shown lower circulating AGE levels in patients on PD compared with HD (44,45). In addition, it has been reported that peritoneal dialysis allows for higher clearance of AGEs, such as pentosidine than hemodialysis (37). As AGEs such as pentosidine are predominantly protein bound, the

postulated mechanism by which there is an increased clearance of AGEs has been attributed to the higher albumin clearance in PD compared with HD (46). This evidence warrants prospective studies or clinical trials to determine whether a single dialysis modality truly has a significant effect on AGE removal.

A significant contribution of dietary AGEs to their high circulating levels in several groups of patients has been demonstrated previously. In a short-term study of nondiabetic ESRD patients on PD, there was about 30% reduction in serum AGE levels at the end of 1-month exposure to a diet low in AGEs suggesting that dietary intake of AGEs is a major contributor to the body AGE pool (47). The fact that a low AGE diet has such a major effect on PD patients as well as in chronic kidney disease (CKD) patients not yet on dialysis (11) suggests that a similar effect is likely in patients on long-term HD. However, studies on AGE intervention in patients on long-term HD have yet to be published.

Although some studies have described that serum AGE levels are similar in long-term dialysis patients with or without diabetes (2,47), several studies have disputed this finding (25,26,48,49). Specifically, Makita et al. has shown that diabetic patients with ESRD had a two-fold increase in AGE accumulation compared with nondiabetics with ESRD (48). In contrast, in a cross-sectional study of 145 patients, no significant differences were observed in ESRD patients with or without diabetes (2). Similarly, no significant differences were observed in patients on chronic PD with or without diabetes (47).

Effects of AGEs on End-Organ Damage in Chronic Dialysis Patients

Several reviews in the literature have discussed in detail the evidence behind the role of AGEs in end-organ damage (50–54). Acceleration of atherosclerosis in chronic dialysis patients has been previously described (55,56). In fact, the accumulation of AGEs has been reported to accelerate atherosclerosis via cross-linking and modification of matrix proteins, platelet aggregation, defective vascular relaxation, and abnormal lipoprotein metabolism (57–59). AGEs in vitro also quench nitric oxide leading to endothelial vasoconstriction (60,61).

In addition, it has been observed that AGEs are associated with coronary artery calcification in chronic dialysis patients. In a cohort of more than 200 HD patients, an increase in serum pentosidine levels was an independent risk factor for coronary artery calcification (62). Hyperlipidemia is a known risk factor for cardiovascular disease (63), but it is the oxidative modification of low-density lipoprotein (LDL) that plays a central role in atherosclerosis (64). Uremic patients have higher serum concentration of glycated LDL (3), which is more prone to oxidation than nonglycated LDL (65). In addition, glycated LDL is cleared from the circulation at a slower rate than non-glycated LDLs (65). The increased rate of oxidation and the reduced clearance of AGE-modified LDL may contribute to the increased rate of atherosclerosis observed in patients on chronic dialysis.

Several studies have shown an association between elevated serum AGEs and cardiovascular morbidity/mortality. For example, in a longitudinal study of 154 patients on long-term HD, serum CML level was associated with increased cardiovascular mortality at the end of the

51-month followup period (66). The association between arterial wall stiffness as a marker of cardiovascular disease and serum pentosidine levels was studied in a cohort of 103 patients on long-term HD. After multivariate regression analysis, serum pentosidine levels significantly correlated with carotid arterial wall stiffness (67). Furthermore, in a cross-sectional Japanese study of 128 chronic HD patients, an increase in skin AGE autofluorescence, a measure of increased AGE accumulation, was associated with an increase in carotid intimal-medial wall thickness (68). Also, in a 3-year single center longitudinal study of 109 HD patients, skin AGE autofluorescence was an independent predictor of overall mortality as well as cardiovascular mortality (69).

Like arterial wall stiffness and left ventricular hypertrophy, C-reactive protein (CRP) is a known marker of cardiovascular disease. In a separate Japanese cohort of 54 chronic HD patients, skin AGE autofluorescence was an independent determinant of serum CRP levels after multivariate regression analysis (70).

It has been previously shown that an incomplete digestion of AGE-modified proteins can result in the formation of low molecular weight (LMW) degradation products. These free LMW degradation products can further react with serum or tissue proteins resulting in tissue toxicity. In addition, studies have demonstrated that fluorescence of the serum at the LMW phase correlates with tissue AGE levels (71). Based on this, a 4-year prospective longitudinal study of 85 patients on chronic HD revealed that an elevated LMW fluorescence level correlated with an increase in overall mortality (72). Moreover, genetic polymorphisms in the receptor for AGE, RAGE, and detoxification system, glyoxalase, were associated with increased mortality in prospective longitudinal study of 214 chronic HD patients (73). All the evidence discussed here supports a strong association between elevated circulating AGE levels and cardiovascular morbidity and mortality.

Some studies, however, have not supported the association between serum AGE levels and cardiovascular mortality. For example, in a longitudinal cohort of 312 stable HD patients, elevated serum AGE levels did not correlate with an increase in mortality over a 32-month period (74). However, these conflicting findings may have been confounded by a higher number of diabetic patients in the low serum AGE group and a better nutritional status in the high serum AGE group (74). Furthermore, in a small pediatric cohort, plasma AGE levels also did not correlate with a proinflammatory state in patients with chronic renal insufficiency (75). As left ventricular (LV) hypertrophy is a known surrogate marker of mortality in chronic dialysis patients (76), Stein et al. investigated whether serum AGE levels were associated with LV hypertrophy or cardiovascular events (77). In this retrospective analysis, elevated serum AGE levels did not correlate with LV hypertrophy or cardiovascular events (77).

Dysregulation of the immune system has long been shown to contribute to atherosclerosis in chronic dialysis patients (78). Some studies have suggested that this process may be partially mediated by the formation and accumulation of AGEs. In a cross-sectional study of 60 nondiabetic chronic dialysis patients, serum pentosidine levels were associated with monocyte activation (45). Furthermore, Acosta et al. revealed that the glycation of CD59, a complement regulatory membrane protein, can contribute to the insertion of membrane

attack complex pores in endothelial cell membranes leading to the secretion of growth factors and thereby contributing to vascular proliferation (79). Finally, a review by Deppisch et al. suggests that the atherosclerotic complications in uremia are secondary to hyper-responsiveness of the complement system as well as the intermittent complement activation and turnover on artificial surfaces of extracorporeal systems (80).

As studies have shown enhanced AGE deposition in the skin of HD patients (as measured by skin autofluorescence) is associated with both overall and cardiovascular mortality, other dialysis related complications have also been assessed using skin autofluorescence (69). For example, in a case series from 2004, an association was observed between the deposition of immunoreactive AGEs in the papillary dermis of long-term HD patients with chronic prurigo (81). In this study, AGE deposits were only observed in the prurigo nodules, but not in the adjacent nonlesional skin in these patients. In addition, a lack of AGE deposits was also noted in renal-disease free prurigo skin as well as in nonprurigo skin of HD patients (81).

AGEs have also been implicated in the pathogenesis of dialysis-related amyloidosis, a debilitating complication of patients undergoing long-term dialysis. Initial in vitro studies from connective tissues isolated from long-term HD patients revealed that β_2 -microglobulin (β_2 m), an amyloid fibril protein, was brown in color, fluoresced, and acidic in comparison with the normal β_2 m (82). Immunochemical studies showed that this acidic β_2 m reacted with anti-AGE and anti-amyloid product anti-bodies whereas the normal β_2 m did not react with either antibody (82).

Subsequently, it was observed in vitro that this AGE-modified β_2 m enhanced migratory activity of monocytes and increased secretion of TNF- α and IL-1 β from macrophages (83). The release of these inflammatory cytokines leads to an increase in secretion of collagenase and morphological changes in cell shape of human synovial cells in culture (83). Additional immunohistochemical studies also revealed that AGEs were not only localized to β_2 m-positive amyloid deposits but also in infiltrating macrophages with anti-CD68 antibody (83). Specifically, HPLC and ELISA assays demonstrated an increased level of 3-DG, CML, imidazolone, and pentosidine, fluorescent cross-linked glycation endproducts, in the acidic isoform of β_2 m and infiltrating macrophages from the urine and serum of HD patients (84–87).

The role of AGEs in the pathogenesis of dialysis-related amyloidosis was further suggested by the demonstration that the interaction of infiltrating macrophages with AGE-modified β_2 m was mediated by the receptor for AGEs, RAGE (84). Also, macrophages exposed to AGE-modified β_2 m had an enhanced expression of TNF- α , which was inhibited by RAGE blockade (84). In contrast, it has also been suggested that an increase in unmodified β_2 m serum levels in dialysis patients (due to reduced GFR) can lead to preferential binding of AGEs that have deposited in collagen due to normal aging (88). Although primarily based on in vitro studies, this evidence suggests that AGEs likely contribute to the initiation of the inflammatory response in dialysis-related amyloidosis, leading to the destruction of osteoarticular structures.

Anti-AGE Strategies in Dialysis

Potential strategies targeting AGEs involve restriction of exogenous sources of AGEs, reduction in formation of endogenous AGEs, antagonizing tissue effects of AGEs, and breakdown of existing AGEs (Table 1).

Decreased Exogenous Sources of AGEs

Decreased Supply of Dietary AGEs—Dietary AGEs, a major source of total body AGE content (11,12), can have adverse effects on health (89–91); restricting their intake may be beneficial. For example, restricting food derived pro-oxidant AGEs improves insulin resistance and enhances innate immunity in patients with type 2 diabetes (92).

Dietary AGE intake can be easily reduced by changing the method of cooking without necessarily changing the nutrient composition of the diet (93). A change in the method of cooking from a high dry heat application to a low heat and high humidity (i.e., roasting/barbecue/grilling to stewing/poaching) significantly reduces serum AGE levels in CKD patients and in ESRD patients undergoing PD (93). The low AGE diet is both feasible and safe in these populations. Table 2 illustrates how simple modification of cooking methods, without changing the nutritional composition of food, can lower AGE formation (94).

Multiple studies have shown that restricting excessive dietary AGE intake can protect against a loss of innate immunity (91) and attenuate diabetic angiopathy and nephropathy (89,90). In contrast to these findings, a recent small cross-sectional study of 38 predialysis CKD patients did not show a positive correlation between CML intake and serum CML (95). The lack of association between dietary and circulating AGEs in this study, however, is not surprising in view of the advanced renal failure in the study population (average creatinine clearance about 15 ± 5 ml/minute) that will predictably decrease appetite and consumption of food in general, including AGEs, whereas the impaired renal function will maintain increased circulating AGE levels. It remains to be determined whether a controlled modification of dietary AGE intake would move circulating AGEs level in the same direction.

GI Binding of AGEs—Reduction of exogenous AGEs in CKD could also be accomplished by blocking the gastrointestinal absorption of dietary AGEs (Table 3). Sevelamer carbonate, a nonabsorbed phosphate-binding polymer, is frequently used in patients with advanced CKD and in patients with ESRD to reduce serum phosphate levels (96,97). Although studies have shown a reduction in LDL levels as well as improvement in insulin resistance (98), it remains unclear whether this reduction is mediated by alteration in AGEs. Recently, however, in a randomized controlled trial of 183 chronic HD patients, Kakuta et al. showed that treatment with sevelamer carbonate, compared with calcium carbonate, significantly attenuated the increase in coronary artery calcification together with decreased AGE accumulation (99).

In addition, Vlassara et al. have recently completed a single-center, randomized, open-label crossover study comparing the role of sevelamer carbonate versus calcium carbonate in patients with Type II Diabetes and CKD stage 2–4 over a 2-month period. Results indicate

that serum AGEs, HbA1c, total cholesterol, and markers of inflammation and OS were significantly reduced in the sevelamer carbonate group compared with the calcium carbonate group (100). Furthermore, antioxidant markers such as AGER1 and SIRT1 mRNA levels significantly improved in the sevelamer group independent of serum phosphate levels. Preliminary in vitro studies also show binding of AGE-modified albumin to sevelamer carbonate, which was reversible and pH dependent with only 5% bound at pH of 1.0 and more than 80% bound at pH of 7.0 (98).

This suggests that sevelamer may act as an adsorbent by binding exogenous dietary AGEs in a high pH environment, such as in the small intestine. Therefore, it would be interesting to test the effect of sevelamer carbonate administration on levels of serum AGEs, markers of inflammation, and oxidative stress as well as progression of kidney disease (i.e., microalbuminuria or albuminuria) in murine models of diabetic and nondiabetic nephropathy. This may identify a potential use for sevelamer in early stages of CKD. It is also interesting to postulate that other binding resins similar in structure to sevelamer, such as colesevelam and cholestyramine, might have similar effects binding AGEs, but this remains to be demonstrated.

Earlier studies have targeted the role of AST-120, an oral adsorbent, in reducing serum AGE levels in diabetes as well as in CKD patients (101,102) (Table 3). Specifically, in vitro studies showed that AST-120 binds CML and reduces serum AGE levels in nondiabetic patients with chronic renal failure (102). In two prospective randomized control trials with CKD patients AST-120 appeared to retard the progression of chronic renal failure (103,104). In addition, AST-120 administration prior to initiation of dialysis significantly improved 5-year survival rates in a retrospective study of 192 chronic hemodialysis patients (105). Finally, in a retrospective study of 193 Japanese patients with CKD, AST-120 was used as a supplement to current treatment regimens to delay the initiation of dialysis (106). Further prospective studies and randomized controlled trials are required to determine the long-term efficacy as well as safety profile of AST-120.

The use of lysozyme as an adsorbent of AGEs to lower circulating AGE levels cannot be neglected. Lysozyme is an enzyme that has been traditionally used as an antimicrobial and immunomodulator (107). Initially, in vitro and in vivo studies, demonstrated that lysozyme binds noncovalently with high affinity to AGEs (108,109). Although no human studies have examined the role of lysozyme in CKD, lysozyme administration attenuates diabetic nephropathy in a rat model of streptozotocin induced diabetic nephropathy (110). The potential role of lysozyme as an AGE-sequestering agent as well as its safety profile needs to be validated in human studies, but rice containing recombinant human lysozyme has already been used successfully to treat children with acute diarrhea (111).

Smoking Cessation—As tobacco smoke is a known source of AGEs (13), its elimination will decrease the body AGE pool.

Decreased Endogenous Formation of AGEs

Control of Hyperglycemia—As hyperglycemia increases AGE formation, strict blood glucose levels control will help reduce circulating AGE levels.

Medications that Inhibit AGE Formation—Several therapeutic strategies for reducing the formation of endogenous AGEs have been identified. As OS is a major stimulus for AGE formation, antioxidants such as Vitamin E, GSH, and lipoic acid have been tried; they all, in fact, lower serum AGE levels in in vitro and in vivo studies (59,112). Also, liposoluble thiamine derivatives, such as benfotiamine inhibit formation of AGEs in diabetic rats (113). Benfotiamine protects the peritoneal membrane against AGE formation in a rat model of peritoneal dialysis and uremia (114). Furthermore, in this study, rats that were administered benfotiamine had reduced glomerular and tubulointerstitial damage with an attenuation in albuminuria (114). In addition, benfotiamine administration in chronic hemodialysis patients attenuated DNA damage in circulating lymphocytes (115).

Although animal studies of benfotiamine have demonstrated promising results, high dose benfotiamine for a 12-week period did not attenuate albuminuria in a recent randomized controlled trial of 39 patients with diabetic nephropathy (116). Furthermore, no changes in oxidative stress were observed even with the use of high dose thiamine and pyridoxine supplementation in a randomized placebo controlled study over an 8-week period (117). The results of this study may have been hampered by a small sample size of 50 patients, of which only 40 completed the study. In addition, a lack of malnutrition and normal serum albumin in this patient cohort may not best represent patients with chronic HD. Additional randomized controlled trials with large sample sizes are needed to determine if thiamine or thiamine derivatives have a benefit in patients with chronic renal insufficiency.

Although other agents such as aminoguanidine, a nucleophile hydrazine group that binds to carbonyl groups and prevents cross-linking, are effective in lower serum AGEs in in vitro and in vivo studies (118,119), adverse reactions have been documented (52). For example, in rat models of peritoneal dialysis, the administration of aminoguanidine limited AGE accumulation in the peritoneal cavity leads to attenuation in functional and structural damage to the peritoneum (119,120). Although the earlier data showed promise, it has been clouded by a serious side effect profile that includes pernicious anemia (121), development of antinuclear antibodies and myeloperoxidase-antinuclear cytoplasmic antibodies, and rare cases of crescentic glomerulonephritis in clinical studies (122).

Similar to the mechanism of aminoguanidine, OPB-9195, a thiazolidine derivative, binds to carbonyl groups and prevents cross-linking. OPB-9195 is more potent and reduces the formation of pentosidine in vitro; it also reduced thickening of the neointimal layer in a rat model of carotid artery injury (123). In addition, earlier animal studies showed that pyridoxamine and BST-4997, an agent that inhibits the conversion of amadori intermediates to AGEs, reduces the formation of AGEs (124,125). Also, in vitro studies showed that treatment of pyridoxamine in rat peritoneal mesothelial cells inhibited the overproduction of VEGF and TGF- β 1, known fibrotic and angiogenic factors (126). However, human studies are still pending to validate these findings.

The use of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) reduces the production of reactive carbonyl precursors for AGE formation (127). In addition, studies in animal models of in both diabetic and nondiabetic nephropathy have validated these initial in vitro findings (128–130). Although there is a lack of human

studies on the role of ACEI or ARB in lowering serum or total body AGE content, an open-label randomized controlled trial of 60 patients on chronic peritoneal dialysis for a 12-month period showed that ramipril slowed the rate of decline of residual renal function (131). Although this does not prove a direct link between ACEI, inhibition of AGEs, and an improvement in renal function, these studies together with others suggest that a potential mechanism may exist. Also, other in vitro studies have shown that hydralazine, an antihypertensive agent, can reduce AGE formation by trapping reactive carbonyl compounds and modification of oxidative metabolism (132).

Several other medications also inhibit formation of AGEs, including metformin, pioglitazone, and pentoxifylline (133). Both metformin and pioglitazone produce a modest, but significant reduction of serum pentosidine levels in diabetic patients (134), but a role for these compounds in dialysis patients has not been studied.

Dialyses Techniques—Studies have shown that modifications in dialysis modality and prescription can reduce endogenous AGE formation. Similar to the AGE-lowering effect of polysulfone-coated dialysis membranes (23), Vitamin E coated dialyzers have also been associated with lower free and protein bound pentosidine serum levels (135). In addition, within 32 weeks posttreatment with Vitamin E coated dialyzers, patients had a significant improvement in endothelial function as determined by brachial artery flow-mediated dilatation (135).

Methods to minimize AGE formation have also been studied in peritoneal dialysis. For example, Erixon et al. showed that the separation of glucose from electrolyte buffer solution during heat sterilization and mixing them only prior to use can reduce the formation of highly reactive glucose degradation products in vitro (136). Also, switching from glucose containing solutions to icodextrin or amino acid solutions reduces AGE formation in the peritoneum (36,37,137). Although icodextrin solutions lowers AGE levels in the effluent fluid (137), Posthuma et al. showed that patients who receive a day dwell of icodextrin fluid do not have lower levels of AGE formation in the peritoneum (138). Based on these strategies, it can be clearly seen that modifications in dialysis prescriptions or equipment can have a significant impact on AGE formation in the peritoneum. However, further studies are needed to determine if this change in peritoneal AGEs affects systemic AGE levels and morbidity and mortality in the patients on chronic PD.

Increased Breakdown of Existing AGEs

Other potential strategies to lower body AGEs include breakdown of existing AGEs and increasing the urinary excretion of AGEs. As patients on chronic dialysis have minimal urine output, the focus here will be on reviewing novel strategies to break down existing AGEs. Agents such as ALT-711 (alagebrium), a stable 4,5-dimethylthiazolium derivative, have been proposed as potential therapeutics in animal models to lower AGEs by cleaving the covalent cross-links between AGE modified proteins (139,140). Moreover, in a 16-week open-label trial with 23 elderly patients with diastolic heart failure, ALT-711 decreased left ventricular mass, improved diastolic filling, and improved quality of life (141). In addition, in a

multicenter RCT in elderly patients with arterial wall stiffness, ALT-711 for 56 days significantly increased arterial wall compliance (142).

Although these initial studies showed promise, ALT-711 did not improve exercise tolerance nor have any effect on secondary endpoints, such as systolic function and New York Heart Association Class in a recently completed prospective, randomized, double blind, placebo-controlled trial of 102 patients with heart failure (143). However, a lack of change in skin autofluorescence levels with ALT-711 treatment suggests an absence of drug effect. As this is one study in a select patient population, further studies are needed to validate these findings.

Antagonizing the Effects of AGEs

Since the mid 1990s animal studies have shown that blockade of the receptor for AGE (RAGE) attenuates oxidative stress and endothelial dysfunction (144). Although, novel agents targeting the RAGE receptor are being developed to treat diabetic vascular complications (145), there is still a dearth of human studies examining the therapeutic benefit of RAGE inhibition in kidney disease. It has been recently demonstrated that elevated serum levels of the RAGE ligand, S100A12, is associated with all-cause as well as cardiovascular mortality (146). Therefore, strategies inhibiting S100A12 may have a role in attenuating inflammation and oxidative stress in chronic dialysis patients.

Conclusions

In this review, we describe the current evidence involving the role of AGEs in patients on chronic renal replacement therapy. By reviewing the current mechanisms involved in AGE formation, clearance, and end-organ damage, we propose potential animal and human studies to validate these findings. Also from this review, it remains clear that several novel therapeutic strategies have come to the forefront in recent years. However, a lack of large prospective studies or randomized control trials has limited the potential use of these agents in clinical practice. As the financial and psychosocial repercussions of managing patients ESRD becomes more complicated, there is an unequivocal need to identify mechanisms and therapeutic strategies that either delay the progression to ESRD or improve morbidity and mortality in this population.

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TABLE 1**Current anti-AGE strategies**

Restriction of exogenous sources of AGEs
Dietary restriction of AGEs
Inhibition of GI absorption of dietary AGEs (Sevelamer Carbonate, AST-120, Lysozyme)
Smoking cessation
Reduction of endogenous AGE formation
Antioxidants (Vitamin E, GSH, Lipoic acid)
Thiamine derivatives (Benfotiamine)
Aminoguanidine
OPB-9195
Pyridoxamine
ACEI/ARBs
Modifications in dialysis modality and prescription
Increase breakdown of existing AGEs
ALT-711
AGE receptor inhibitors

TABLE 2Changes in food AGE content depending on cooking methods^a

Food item	Kilounits AGE/100 g food	Food item	Kilounits AGE/100 g food
Beef, broiled	7479	Beef, stewed	2391
Chicken, breast, broiled	5245	Chicken, breast poached	968
Salmon, broiled	3012	Salmon, boiled	974
Potato, white, French fries	1522	Potato, white, boiled	72
Tofu, broiled	3696	Tofu, boiled	565
Apple, baked	45	Apple, raw	13
Mushrooms, grilled	261	Mushrooms, raw	129

^aData modified from reference (94).

TABLE 3

Clinical studies involving manipulation of dietary AGEs in renal disease^a

Anti-AGE strategy	Reference	Study design	Study population	N	Primary endpoints	Results
Low AGE diet	(47)	RCT	Nondiabetic PD	26	Serum AGE level	Reduction in serum CML, MG, CML-LDL, CML-apoB levels
Low AGE diet	(91)	RCT	Nondiabetic CKD	9	Circulating levels of AGEs and markers of OS/Inflammation	Reduction in circulating levels of AGEs and markers of OS/Inflammation
Sevelamer carbonate	(100)	RCT	Diabetic CKD	20	Circulating levels of AGEs and markers of OS/Inflammation	Reduction in circulating levels of AGEs and markers of OS/Inflammation
Sevelamer Carbonate	(96)	RCT	HD	108	Coronary artery calcification score (CACS), Lipid profile, inflammatory markers	Reduction in CACS, LDL, total cholesterol, apoB, β_2 M, and CRP serum levels
Sevelamer Carbonate	(99)	RCT	HD	183	CACS, serum pentosidine levels	Reduction in CACS and in serum pentosidine levels
AST-120	(103)	RCT	CKD	26	Creatinine clearance	Reduction in rate of decline in creatinine clearance
AST-120	(106)	Cohort	CKD	156	Onset of dialysis	Prolonged dialysis-free period
AST-120	(104)	RCT	CKD	43	Glomerular filtration rate	Reduction in rate of decline in GFR
AST-120	(105)	Cohort	HD	192	5-year survival rate	Improved 5-year survival rate

^aWe have assumed that sevelamer carbonate and AST-120 act by reducing circulating AGE levels through their effect binding dietary AGEs in the gastrointestinal tract, as discussed within the text.