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# The Low AGE Diet: A Neglected Aspect of Clinical Nephrology Practice?

Jaime Uribarri John Cijiang He

Division of Nephrology, Department of Medicine, The Icahn School of Medicine at Mount Sinai, New York, N.Y., USA



**Key Words**
Advanced glycation end products · Carboxymethyllysine · CKD · Diabetes · Endothelial dysfunction · Inflammation · Insulin resistance · Oxidative stress · Nutrition

**Abstract**
Increasing evidence in the literature suggests an important role for advanced glycation end products (AGEs) in the generation of a state of increased oxidative stress and chronic subclinical inflammation, which underlies most modern chronic diseases, including diabetes, cardiovascular disease and chronic kidney disease (CKD). Although AGEs were originally thought to form only endogenously, primarily as the result of the hyperglycemia of diabetes, it is now clear that exogenous AGEs, specially incorporated in foods, are an important contributor to the body pool of AGEs. Over the past decade, several clinical trials have been performed in a variety of conditions demonstrating that the application of an AGE-restricted diet reduces not only the systemic levels of AGEs but also the levels of markers of oxidative stress and inflammation. This has been shown in CKD patients before and after the initiation of dialysis and either in the presence or absence of coexistent diabetes. Reduction of the AGE content in food is obtained by simple changes in culinary techniques and appears to be a feasible, easily applicable and safe intervention, even in advanced CKD patients.



A large body of evidence suggests that advanced glycation end products (AGEs) play a major role in diabetic vascular complications such as kidney disease through the activation of pro-oxidant and pro-inflammatory responses [1, 2]. Recent studies demonstrate that exogenous AGEs from diet have an important contribution to these processes [3, 4]. Moreover, reduction of dietary AGE intake significantly prevents or attenuates pro-oxidant and pro-inflammatory responses in several human studies [5–10]. Since dietary AGE restriction is simple, feasible and safe, we believe the time has come for its wide application in clinical practice. In this mini review, we will develop these concepts in some detail.

## Increased OS/Inflammation

Increased oxidative stress and inflammation (OS/Inf) underlies many chronic diseases including diabetes, cardiovascular disease and kidney disease. AGEs are known pro-OS/Inf factors and are markedly increased in chronic kidney disease (CKD) of any etiology, both before and after the initiation of dialysis [1, 11].

AGEs are a large and very heterogeneous group of compounds originating from the spontaneous reaction of reducing sugars with free amino groups in amino acids. That was Maillard's original reaction, although we know now that AGEs can be generated by a variety of other re-

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Dr. Jaime Uribarri
The Icahn School of Medicine at Mount Sinai
One Gustave Levy Place
New York, NY 10029 (USA)
E-Mail Jaime.uribarri@mssm.edu

actions including oxidation of sugars, lipids, and amino acids to create reactive aldehydes that covalently bind to proteins. A few commonly measured and well-described AGEs are carboxymethyllysine (CML), methylglyoxal-derivatives (MG) and pentosidine.

AGEs form continuously in the body through a variety of reactions, which are markedly increased in conditions of hyperglycemia or elevated OS. It is not widely recognized that AGEs can also form in any system as long as the required reagents are available. For example, AGEs form spontaneously in food and cooking with heat significantly accelerating their formation [12, 13]. A small fraction of the ingested food AGEs gets absorbed and incorporates into the body AGE pool becoming indistinguishable from their endogenous counterpart, both in terms of structure and function.

AGEs, endogenous or exogenous, contribute to tissue injury by protein-crosslinking producing direct modifications of protein structure and function and by activating pro-inflammatory and pro-oxidative cellular signaling pathways through receptor- and non-receptor-mediated mechanisms. For example, binding of AGEs to the receptor for AGEs (RAGE) or Toll-like receptor (TLR) 2 and 4 initiates intracellular signaling and activates several inflammatory responses, contributing to OS [14]. Activation of the AGE receptor 1 (AGER1), on the other hand, contributes to catabolism of AGEs and leads to an antioxidant state by regulating AGE/RAGE-mediated activation of nuclear factor kappa B (NF-κB) [15].

The kidneys are major players in maintaining AGE homeostasis both by excretion and catabolism of these compounds. AGE-peptides undergo filtration followed by partial tubular reabsorption, and possibly also secretion after tubular uptake from the peritubular blood flow. Once in the renal tubules, AGEs undergo variable degree of catabolism. As expected, any reduction in the renal function is accompanied by an elevation of AGEs in the body [16], which may initiate a vicious cycle that facilitates progression of the initial underlying renal condition.

The accumulation of AGEs in CKD in turn will play a major role in the high prevalence of endothelial dysfunction and subsequent cardiovascular disease in this population [17]. Several studies have shown an association between elevated serum AGEs and cardiovascular morbidity/mortality [18, 19], although these findings have not been universal [20].

By the time CKD patients end up performing dialysis, their circulating AGE levels are markedly increased. Conventional hemodialysis (HD) does not effectively remove circulating AGEs [11]. Short daily dialysis, hemodiafiltration and hemofiltration have been shown to be more effective in lowering serum AGE levels than conventional (four hours and three times a week) HD [21, 22]. Moreover, at least in one study, hemodiafiltration significantly lowered serum AGE levels as compared to high-flux HD by the end of the treatment period [23]. As with HD, circulating AGE levels are also increased in peritoneal dialysis (PD) patients. Despite the evidence of increased intraperitoneal AGE formation, patients on PD have been shown to have lower circulating AGE levels as compared to HD patients [11, 24]. Circulating AGE levels fall significantly following successful kidney transplantation [25].

## Experimental Evidence Linking AGEs and Renal Tissue Damage

*In vitro Studies*

AGEs have been shown to directly cross-link proteins in the kidney extracellular matrix resulting in multiple abnormalities: altered matrix protein structure and function, aberrant cell-matrix interactions leading to changes in cellular adhesion, altered cell growth and loss of the epithelial phenotype [26, 27].

AGEs bind mesangial cells leading to increased production of matrix proteins with simultaneous diminished expression of major metalloproteinases that normally would degrade matrix proteins. AGEs also act on glomerular endothelial cells increasing production of collagen IV and fibronectin. AGEs also affect podocytes inducing podocyte apoptosis and reducing expression of nephrin [28].

*Animal Studies*

Several lines of evidence support a role for AGEs causing kidney damage in vivo. Intraperitoneal administration of AGEs for 4 weeks into mice induced a marked increase in glomerular extracellular matrix alpha 1 (IV) collagen, laminin B1 and transforming growth factor (TGFβ); these changes were reduced with the coadministration of an AGE inhibitor, aminoguanidine. Long-term administration of intravenous AGE-albumin to normal rats induced albuminuria and morphologic changes of diabetic nephropathy, including glomerular hypertrophy, mesangial matrix expansion, and basement membrane thickening. Overexpression of RAGE in diabetic mice intensified the signs of kidney disease, while blockade of RAGE by a soluble truncated form of RAGE prevented structural and functional characteristics of nephropathy in db/db mice [29, 30].

Moreover, strategies aimed at preventing AGE accumulation in the kidney of diabetic rats with AGE inhibitors such as aminoguanidine, benfotiamine, pyridoxamine, OPB-9195, and AGE breakers have all been shown to ameliorate diabetic nephropathy without influencing glycemic control [31, 32].

A more direct link between dietary AGEs and development of kidney disease was demonstrated in a study in which diabetic nephropathy, highly prevalent in non-obese diabetic mice with type 1 diabetes and db/db mice with type 2 diabetes fed with regular chow (rich in AGEs), was almost completely abrogated in the same groups of mice randomized to a low AGE diet [33].

## Human Data

### *Clinical Trials with Dietary AGE Restriction in CKD Patients without Diabetes*

There have been two clinical trials testing the effects of an AGE-restricted diet in patients with kidney disease in the absence of diabetes. In one of them, a group of Stage 3 CKD patients was randomly assigned to a regular diet or an isocaloric diet containing 50% lower AGEs for a period of only 4 weeks. At the end of this period, patients on the low AGE diet exhibited a significant decrease in extracellular and intracellular markers of inflammation and oxidative stress, including AGEs, tumor necrosis factor (TNF-α), vascular cell adhesion molecule (VCAM-1) and RAGE [7]. In the second trial, a group of non-diabetic end-stage renal disease (ESRD) patients on maintenance PD was randomized to follow either a regular or low AGE diet for 4 weeks. The low AGE diet group showed a significant decrease of circulating AGEs and high sensitivity C-reactive protein (hsCRP) [6].

In all of the above studies the diets were lowered only in AGE content, while maintaining same baseline caloric and nutrient content. Participants received detailed instructions on how to prepare their food at home by a study dietitian who was in frequent telephone contact with them.

### *Clinical Trials with Dietary AGE Restriction in Diabetic Patients without CKD*

There have been a few of these trials in diabetic patients without overt kidney disease. The first clinical study on the effect of a low AGE diet on ambulatory diabetic patients was published in 2002 [5]. This was a cross-over study between low and regular AGE diets for a period of 6 weeks. Meals were prepared in the clinical research unit metabolic kitchen and patients picked them up twice a week during the duration of the study. Patients in the low AGE diet experienced decreased levels of circulating AGEs (both CML and MG) as well as markers of endothelial function and inflammation such as VCAM-1, hsCRP and TNFα. Indeed, circulating AGE levels decreased by as much as 40% despite similar degree of diabetic control during the study. Prior to this study, high serum AGE levels in diabetic patients were thought to result exclusively from hyperglycemia-induced endogenous overproduction. The significant fall of serum AGE levels while maintaining overall same glycemic control was unexpected and novel finding. Although none of these patients had CKD, this study is pertinent to our discussion since diabetes is a major risk factor for CKD in the United States.

A more recent study in type 2 diabetic patients showed that the application of an AGE-restricted diet for four months also decreased homeostatic model assessment index (HOMA), a marker of insulin resistance [8]. The reduction of HOMA, which implies improvement of insulin sensitivity, raises a very important consideration. Although it is widely recognized that hyperglycemia in diabetes can increase endogenous production of AGEs, this study suggests that AGEs in turn have an important role in modifying insulin resistance itself and therefore diabetes. If this effect of the low AGE diet is further confirmed, it opens a major avenue for a safe, inexpensive and effective dietary modulation to prevent or improve diabetes and therefore future development of CKD.

More recently, it has also been shown that a low AGE diet increases AGER1 and sirtuin (SIRT1), two protective markers that tend to be suppressed in conditions of high OS such as diabetes and CKD [34]. The restoration of their levels by the low AGE diet suggests the previous suppression is due to an environmental factor, most likely the high AGE-induced high OS.

A third trial performed in Mexico also demonstrated that a low AGE diet decreased markers of inflammation and oxidative stress in a group of type 2 diabetic patients [10].

### *Clinical Trials in Diabetic Patients with CKD While Maintaining Same Dietary AGE Intake, But Receiving an Oral AGE-Binder*

A recent crossover study of 20 diabetic CKD patients comparing sevelamer carbonate versus calcium carbonate for 8 weeks revealed that sevelamer therapy, in contrast to calcium carbonate, reproduced all the findings observed on the low dietary AGE intervention, despite unchanged dietary intake during the study period [35]. In

other words, use of sevelamer was associated with reduced circulating levels of AGEs, 8-isoprostane, TNFα, all of which were high and increased AGER1 and SIRT1, both of which were low. In vitro tests have documented that sevelamer binds AGEs quite effectively and presumably this is what happens in patients.

A larger randomized study comparing sevelamer carbonate with calcium carbonate as parallel groups in 117 patients with type 2 diabetes and stages 2–4 CKD has essentially reproduced all the findings described in the previous crossover study [36]. Of interest, although the urinary albumin/creatinine ratio did not change in the overall group on sevelamer, subgroup analyses showed that the ratio was significantly decreased in subjects less than 65 years of age and in non-Caucasians [36].

The low AGE diet has also been shown to be effective in reducing markers of inflammation and oxidative stress in healthy subjects and in obese subjects without diabetes [7, 9].

### Effects of Acute Oral AGE Loads

An acute anti-endothelial effect of dietary AGEs has been demonstrated in both healthy subjects and diabetic patients. First, a single oral dose of a high-AGE beverage was administered to both healthy subjects and diabetic patients. Within two hours, subjects manifested elevation of serum AGE levels in association with transient impairment of flow-mediated vasodilatation, a noninvasive index of endothelial function. Pretreatment with benfotiamine, an inhibitor of glycation, prevented the anti-endothelial effect [37]. Second, a single high-AGE solid meal given to diabetic patients was also followed by marked impairment of flow-mediated vasodilatation, as compared with an isocaloric low-AGE meal [38]. These results suggest a mechanistic link between dietary AGEs and cardiovascular disease since endothelial dysfunction is the earliest abnormality in atherosclerosis.

The exact mechanisms how dietary AGEs contribute to vascular complications remain unclear and may not just result from direct gastrointestinal absorption raising serum AGE levels that in turn induce elevated systemic OS/Inf. Other potential mechanisms linking dietary AGEs to tissue injury may include AGEs binding to RAGE or Toll-like receptors in gut cells inducing a local inflammatory response with subsequent release of inflammatory mediators into the circulation or AGEs altering the microbiome profile in the gut leading to release of toxins into circulation. These hypotheses, however, remain to be tested.

### The Low AGE Diet

Dietary AGE intake can be easily decreased by simply changing the method of cooking from a high dry heat application to a low heat and high humidity, independent of its nutrient composition. A large database with the AGE content of common foods has been published and can be used to estimate dietary AGE intake as well to give advice on how to reduce this intake [12, 13]. Dry heat-cooking methods, such as broiling, searing, and frying significantly increase the AGE content of foods, compared to methods that use lower temperatures and higher moisture (i.e., stewing, steaming, and boiling). The basic concept of the low AGE diet is that the same amount of a nutrient can provide very different amounts of oxidant substances depending on the cooking method. Since the emphasis of the low AGE diet is on the cooking method, and not on the food being cooked, the same can be applied for any group of people. In other words, the same principles will apply whether the patient has diabetes or not or whether the patient has CKD or not.

Unfortunately, there is no specific threshold temperature above which AGEs start to generate. Therefore, one can only make the general recommendation that the lower the temperature the lesser the amount of AGEs generated.

The immediate critique to a dietary intervention that relies on changing culinary technique is that patients will not follow it. The argument is often made that stewed chicken would be less tasty than fried chicken and therefore people will abandon this diet very easily. Based on our studies, however, consumers can be educated as to how to use low-AGE-generating cooking methods such as poaching, steaming, stewing, and boiling. The sparing use of herbs, condiments and spices, some of which may have intrinsic antiglycation activity, would definitely make the low AGE food very tasty. For example, although the highest AGE values are found in meats and meat-substitute food groups, pre-treatment of meats with lemon, vinegar or with any acidic marinade prior to cooking has a significant effect preventing too much increase of the AGE content. These culinary techniques have long been featured in Mediterranean, Asian, and other cuisines throughout the world to create palatable, easily prepared meals.

Currently, no official recommendations exist which point out the acceptable range or identify the upper limit on dietary AGE intake. We have previously proposed that half of the current mean AGE intake, or about 7,500 kU per day, is a very realistic goal [11, 12]. Studies have shown

that dietary AGE reduction of this magnitude is feasible and can significantly alter levels of circulating AGEs, while at the same time reducing levels of markers of OS/Inf and enhancing insulin sensitivity in diabetic patients [5–9].

We proposed a multipronged strategy: (1) decrease intake of foods rich in AGEs (based on existing databases) [12, 23], (2) increase use of foods that have been shown to be associated with decreasing body AGEs, for example, brown rice and mushrooms, (3) high intake of foods rich in anti-oxidants, (4) use of pharmacological agents such as benfotiamine and pyridoxamine that can decrease endogenous AGE formation, and (5) sparing use of herbs, spices and condiments that improve taste of food and also have antiglycation effect (curcumin, cinnamon, parsley, thyme, clove and extracts from a variety of other culinary herbs and spices) [39]. We must state clearly, however, that we have tested only the AGE-restricted diet and we are assuming the simultaneous application of points 2–5 will have beneficial and synergistic effects. Avoidance of cigarette smoking, which are rich in AGEs, should also be a prominent part of the same strategy [40].

## Conclusions

Dietary AGEs, abundantly present in the food commonly consumed in a typical American diet, contribute significantly to body pool of AGEs, which in turn is at least partly responsible for the elevated OS/Inf observed in diabetics and CKD patients. A final proof of a therapeutic role for the low AGE diet will require large, prospective and randomized clinical trials, which indeed may never take place. In the meantime, however, we believe a careful analysis of the current data makes it reasonable and prudent to advice limitation of dietary AGEs in CKD patients. This is particularly important since consumption of lower-AGE foods and preparation methods can easily be integrated into meal patterns that are consistent with current recommendations designed to promote public health and prevent cardiovascular disease, cancer, diabetes and obesity.

## Disclosure Statement

The authors declare no conflicts of interest.

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