Glycotoxins in the Diet Promote Diabetes and Diabetic Complications

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Oxidant stress underlies diabetes and diabetic complications, including cardiovascular, renal, and retinal disease. Advanced glycation end products (AGEs), or glycotoxins, are a significant contributor to oxidant stress in diabetes. The diet is a major, unrecognized source of AGEs. Importantly, reduction of dietary AGEs decreases circulating inflammatory markers in both diabetic patients and prediabetic patients and complications in animal models. This beneficial outcome requires only a 50% decrease in dietary AGEs, making this necessary intervention practical and inexpensive.

Introduction

Elevated advanced glycation end products (AGEs), or glycotoxins, have long been associated with the progression and severity of diabetic complications. Findings from major studies such as the DCCT (Diabetes Control and Complications Trial) have shown that intensive glycemic control, in addition to reducing the rate of development and progression of diabetic microvascular and neuropathic complications in type 1 diabetes, also leads to lower AGEs in tissues [1,2], emphasizing the importance of AGEs in diabetes and diabetic complications. These data also show that AGEs can be decreased by the appropriate therapeutic strategy. The clinical efficacy of anti-AGEs or other antidiabetic agents has been less successful than anticipated.

Recent reports have introduced a new and potentially important view, namely that high levels of AGEs in the diet could play a significant role in the causation of diabetes and diabetic complications. The reduction of the amount of AGEs in the diet of animals can ameliorate diabetes and complications, regardless of glycemic levels. Furthermore, a low AGE diet can lower inflammatory markers and vascular dysfunction in diabetic patients. Similar evidence has begun to gather from nondiabetic adults, especially prediabetic patients, in whom serum AGEs correlate with indicators of oxidant stress (OS), inflammation, and insulin resistance—changes that are directly influenced by the intake of dietary AGEs, and are independent of chronologic age or energy intake. Thus, the intake of excessive amounts of AGEs via the diet could instigate changes in healthy persons and contribute to the development of frank diabetes.

In this article emphasis is placed on recent data with a focus on whether and how diabetes and its complications may be affected by the content of glycotoxins in the diet. We also consider the regulation of AGEs in the body via the AGE receptor system, and their excretion by the kidneys.

Reconsidering the Sources of Glycotoxins

There are at least three major sources of AGEs in diabetic as well as nondiabetic subjects: 1) those formed intracellularly; 2) those formed in the extracellular space; and 3) those consumed with the standard diet [3–5]. AGE formation is especially accelerated during food processing under elevated temperatures. Various forms of glycation intermediates derived from the food enter the circulation where they may react with cellular and extracellular components, forming long-term AGE storage sites.

As will be discussed next, the dietary content of AGEs depends on the concentrations of protein, lipids, and carbohydrates, as well as on the temperature used during preparation (Table 1) [4,5]. Foods cooked at high temperature and under dry conditions have the highest AGE content, as well as the highest proinflammatory activity (Table 2) [6].

Endogenous AGE Levels Are Only Partially Dependent on Blood Glucose Levels

AGEs are formed by a nonenzymatic reaction between reducing sugars, such as glucose, and free amino groups on certain amino acids (ie, lysine or arginine residing on proteins, lipids, and nucleic acids) [7–9]. They form a series of intermediates of a Schiff base and an Amadori product that are initially reversible (ie, the Amadori product identified on glycated hemoglobin, hemoglobin A_{1c}), but which ultimately generate a series of more stable products, known

Table 1. Thermal exposure determines AGE content of common foods

Dietary items	AGE, *U/g of food*
Fish (boiled)	8967
Fish (broiled)	31,588
Chicken (boiled)	11,700
Chicken (broiled)	73,881
Egg yolk (boiled 10 min)	17,200
Egg white (boiled 10 min)	443
American cheese	96,000
Cottage cheese (1% fat)	16,222
Margarine, soft	16,342
Butter	36,742
White bread	296
White bread (toasted)	1026
Potato (boiled 8 min)	174
Potato (roasted)	2183
Potato (french-fried)	4600
Rice (boiled)	91
Carrots (canned)	103
Green beans (steamed)	176
Banana	87
Apple, fresh	127
Apple (baked)	445

AGE—advanced glycation end product.

as AGEs [7]. This reaction is largely driven endogenously by hyperglycemia, although the oxidation of other sugars and/or lipids can create compounds that use highly reactive mono- or dicarbonyl groups that bind amino acids and form AGEs [8]. Certain AGE precursors form stable crosslinks with other peptides, including intracellular proteins and extracellular structural proteins, membrane phospholipids, DNA, and lipoproteins [9]. These changes permanently alter their structure and function.

The glycation of nucleotides, lipids, and proteins is partly regulated, under normal conditions, by enzymatic detoxification. Thus, reactive AGE precursor molecules such as glyoxal and methylglyoxal are detoxified by glyoxalase I and II, at a rate proportional to the cytosolic levels of glutathione [10]. Alternatively, they can be reduced by aldehyde reductase, aldose reductase, or carbonyl reductase [11]. AGE proteins are also removed by proteolytic digestion to soluble peptides, which are partially excreted by the kidneys. However, AGE-derived crosslinks are particularly resistant to degradation, especially those that have been oxidatively modified. These modifications diminish the normal turnover of macromolecules, which impairs normal organ function.

Other glucose-independent AGE pathways involve activated leukocytes (ie, neutrophils, monocytes, and macrophages). Activated leukocytes produce enzymes, including myeloperoxidase and NADPH oxidase, causing AGE formation by oxidation of amino acids [12].

Cell activation by AGEs (ie, via binding to receptor for AGEs [RAGE]) can also promote OS and AGE formation via the NADPH oxidase pathway, the myeloperoxidase pathway, or possibly through the nuclear protein amphoterin (also termed high mobility group box 1) [13], which can activate RAGE and thus amplify AGE formation [14].

Another mechanism of AGE formation is the aldose reductase–mediated polyol pathway [15]. Glucose entering the polyol pathway may directly form AGEs via reactive intermediates (ie, glyoxal, methylglyoxal, or 3-deoxyglucosone), as well as via depletion of NADPH or glutathione-raising intracellular reactive oxygen species (ROS), all of which indirectly result in further formation of AGEs [16].

Therefore, AGEs and ROS are two mutually enhancing processes that are tightly linked. Accordingly, interventions targeting one will inevitably have an impact on the other.

The Role of the Diet in AGE Levels of Patients with Diabetes

The reduction of the amount of AGEs in the diet of animals can ameliorate diabetes and its complications, regardless of the continuing presence of hyperglycemia [6,17–20]. The diet is a significant source of AGEs in diabetic subjects, as shown by the fact that a short period of exposure (6 weeks) to a low AGE diet resulted in a significant decrease in levels of AGEs, and of inflammatory mediators [6]. A low AGE diet for a period of 4 weeks in nondiabetic peritoneal dialysis patients, a group that has very high AGE levels, led to a similar reduction in the levels of AGEs and C-reactive protein [21]. These studies point out the fact that a relatively short period of restriction of AGEs in the diet can lower AGEs and AGE-induced inflammatory changes in patients with especially high levels of AGEs, some of which were of endogenous origin. If this diet were to be combined with other therapies known to lower AGE levels, it may be possible to derive a greater therapeutic effect.

Dietary restriction has not been tested in the prevention of diabetes or the amelioration of diabetic complications. However, we recently studied 178 nondiabetic adults and found that those who had self-selected a diet with a low AGE content had lower levels of markers of inflammation and OS, compared with those consuming a diet with a higher AGE content [22••]. Independent of age, the levels of serum glycotoxins correlated with the levels of established markers of OS and inflammation. A significant association was also noted between serum AGE and homeostasis model of assessment, an indicator of insulin resistance. Importantly, dietary AGE intake—not calories, nutrients, glucose, or lipids—was found to be an independent predictor of serum AGEs, as well as of high-sensitivity C-reactive protein [22••]. Because many subjects thought of as being

Table 2. Levels of immunoreactive AGEs correlate with levels of inflammatory and cross-linking properties of dietary AGEs

Food items	CML, *U/mg**	MG, *nmol/mg**	GSH depletion†	TNF-α, *ng/mg*	Cross-link formation‡
Muscle, white (chicken, broiled)	73.8 ± 12	2.4 ± 0.8	80	8	110
Muscle (fish, broiled)	31.8 ± 4.2	2.5 ± 0.8	60	6	90
Egg yolk (boiled, 12 min)	18.0 ± 3.2	0.9 ± 0.6	50	5.5	20
Bread (white toasted)	1.0 ± 0.4	0.7 ± 0.1	15	4	3
Pasta (boiled 12 min)	2.4 ± 0.3	0.6 ± 0.2	10	1.5	2

*AGE-rich extracts from food items were affinity purified and AGE levels were measured based on enzyme-linked immunosorbent assay by anti-CML and anti-MG-derivative monoclonal antibodies.
†Macrophages were exposed to equal amounts of AGE (10 U/mL); then GSH depletion and tumor necrosis factor (TNF)-α production were determined. GSH is shown as percent depletion compared with control (bovine serum albumin).
‡Crosslinking is shown as the amount of large molecular weight complexes formed by AGE-rich samples and normal peptides (fibronectin fragments, shown as times above control).
AGE—advanced glycation end product; CML—carboxymethyllysine; GSH—glutathione; MG—methylglyoxal.
(*Adapted from* Vlassara et al. [6].)

in the normal serum AGE range may become diabetic if they continue an excessive glycoxidant intake, the diet as a specific source of AGE toxins is becoming of particular concern. Thus, the diet can be a major source of AGEs in both diabetic and diabetic persons. Importantly, lowering the intake of AGEs via the diet decreases body AGE levels and the attendant toxic effects.

The Link Between AGEs and OS

High levels of AGEs are thought to underlie many of the complications of diabetes. One of the ways by which AGEs induce these changes is by generating ROS, which promote the formation of more AGEs. This sets up a vicious action/reaction cycle, which progressively increases OS and the risk for both micro- and macrovascular disease. Understanding how this process occurs and how it may be prevented or treated is an important challenge in the management of diabetes and its complications, across all medical disciplines.

Fortunately, this chain of events can be interrupted by reducing glycation. The fact that reduction of glycation prevents diabetic complications in many animal models of diabetes corroborates the importance of AGEs in their pathogenesis and urges the search for optimal interventions in the clinical setting. The accumulation of AGEs is already demonstrable in early adulthood and progressively increases with normal aging humans and animals [22••,23]. As the process develops, it significantly contributes to inflammatory processes, which promote the metabolic syndrome and the subsequent development of diabetes, as well as macrovascular (atherosclerosis) and microvascular (kidney, retinal) diseases [17–19]. One of the concomitants of elevated AGE levels and the resultant inflammatory response is the further induction of ROS [24]. Although ROS or nitrogen species play an important role in normal metabolism, when present in excess they augment oxidative damage of nucleic acids, lipids, and proteins. These changes result in their degradation and removal, or induce OS-responsive genes, which may cause cell damage or death. As noted earlier, excessive ROS also accelerate the formation of additional glycation products, further compounding toxicity. Interventions that reduce AGEs also reduce ROS [25]. As a consequence, there is an accompanying decrease in the expression of OS-response genes, as well as cardiac and vascular diseases, which has been shown to lead to an increased life span [26].

Metabolism of AGEs

The innate immune system is one of the major body defenses that respond to OS [27]. AGEs and other oxidants are among the noninfectious stimuli that can trigger OS and inflammatory cytokines, such as tumor necrosis factor-α or interleukin-6 [28]. Because AGEs are ubiquitous in vivo and inflammation represents a universal aspect of the body's innate response to injury, the innate immune system serves as a check on AGE toxicity and may be activated at various levels in "normal" persons as a function of age and AGE burden. The latter depends on the net balance between the formation of endogenous AGEs, dietary AGE intake, and the efficacy of the systems, which regulate AGE degradation and excretion. These include enzymatic mechanisms, such as the glyoxalase I and II [29] system, antioxidant defenses [30], and receptor-dependent intracellular uptake and destruction [31], followed by excretion in the urine [25].

The AGE receptor system is as complex as the AGEs themselves. It includes both classical cell surface receptors and molecules that bind AGEs and remove them from contact with cells and extracellular molecules to which they might bind and cause damage. Among the cell surface receptors, one group serves to recognize AGEs as ligands, but does not lead to their uptake, a major example being RAGE [32]. The second group of AGE receptors, which bind and lead to uptake and degradation of AGEs, includes AGER1, AGER3, and CD36 [23,31].

AGER1 has a distinct protective function against cellular OS; namely, it can inhibit AGE-mediated cellular activation [31]. Unexpectedly, the clearance of AGEs by AGER1 may be impaired in the presence of chronically elevated AGE levels [33], a time at which increased function of this receptor would be anticipated. The mechanism(s) underlying this paradoxical response remains to be defined. Finally, a group of circulating proteins such as lysozyme, transferrin, and defensin bind AGEs, effectively keeping them from causing cellular toxicity or binding to other molecules [25,30].

Although considerable information has been obtained from in vitro molecular studies, clarification of the in vivo role of certain AGE receptors has been difficult. For instance, reactive AGEs affect extracellular substances, cells, and cellular AGE receptors alike. RAGE, a receptor closely associated with ROS and nuclear factor-κB activation, is inducible by both AGEs and ROS [32,34]. Although AGER1 may be suppressed or downregulated in the presence of long-term AGE-induced OS, as is typical of severe diabetic complications, it is unclear whether this downregulation is a primary process or results from phenotypic changes.

However, a recent comparative study revealed some interesting relationships between AGER1 expression/function and tissue injury after lifelong exposure of normal mice to different levels of exogenous AGEs. When normal C57BL6 mice were fed isocaloric diets consisting of either a regular (high AGE) diet or a diet 50% lower in AGE for 3 years, those mice fed the regular (high AGE) diet had a depleted glutathione:oxidized glutathione ratio [23], increased serum 8-isoprostanes, insulin resistance, and low or unchanged levels of AGER1. In contrast, mice kept on a low AGE diet had an enhanced antioxidant reserve, had no insulin resistance, and had markedly increased levels of AGER1. The mice fed a low AGE diet also had a 15% increase in life span and a marked reduction of the kidney disease of aging, compared with those on the regular (high AGE) diet. Thus, the ability to upregulate AGER1 levels appeared to be contingent on exposure to a level of dietary AGEs at which the total AGE exposure did not exceed the overall capacity of native defenses to handle oxidants. This suggests that a threshold of "glycoxidant tolerance" may exist. Below this level, AGER1 and similar systems can preserve native antioxidant/anti-AGE defenses over a lifetime. However, if the levels exceed this threshold, OS and oxidants accumulate and may cause injury.

The kidneys play an equally important role in the metabolism and excretion of AGEs. We and others have found that the presence of near normal renal function is critical to maintaining the body load of AGEs and possibly other oxidants at nontoxic levels [19,20]. Serum AGEs correlate directly with the levels of inflammatory markers and OS, and inversely with creatinine clearance [20,25,35•]. This suggests that the kidney may play a primary role in the excretion of oxidants, and that modest changes in renal reserve could lead to significant changes in systemic OS and inflammation. Importantly, a modest decrease (20%) in the glomerular filtration rate is associated with an increased risk of cerebrovascular disease, increased OS, and decreased antioxidant reserves [36]. There is an increased risk of renal failure and cerebrovascular disease in diabetes, a state of high OS. Thus, although the kidney is key in the OS defense system, it is also a target for AGE-induced injury [16,25]. Because AGE restriction in the diet ameliorates both diabetic and nondiabetic kidney diseases, exogenously derived AGEs are likely to contribute to sustained kidney injury [19,21].

It has long been known that the compensatory mechanisms described above do not control AGE accumulation in diabetic persons. It has now become increasingly clear that AGEs can overwhelm normal body defenses, even in persons who appear "normal" by the accepted standards. For instance, we now find that young nondiabetic adults who consume a diet with a high AGE content often have high systemic levels of AGEs. This is associated with decreased antioxidant defenses, elevated oxidants, and inflammatory markers [22••]. These changes are accentuated in diabetic patients consuming a high AGE diet because dietary AGEs can act synergistically with native AGEs. In addition, AGE deposits increase with chronologic age in both humans and animals. The data from animal models lead us to suspect that this is related to a lifelong exposure to the high AGE content of the standard diet, which may also be the case in humans consuming the average Western diet [23]. The prolonged exposure to high levels of exogenous glycoxidants could explain the significant increase in OS and decrease in innate immunity, which is recently suspected to begin in early adulthood and progress throughout life. These changes could also play a key role in the development of the metabolic syndrome, and ultimately of diabetes, in experimental models and humans.

The Effects of Glycoxidants on Small and Large Blood Vessels

Glycoxidants cause a wide spectrum of vascular abnormalities, including basement membrane thickening and endothelial injury resulting in increased vascular permeability, a prothrombotic state, and decreased blood flow—all of which are traits of microvascular disease affecting the retina, kidneys, and peripheral nerves [25,35•]. The specific role that AGEs play in causing these microvascular abnormalities is clear in retinal blood vessels of human diabetic patients where their levels correlate with the degree of retinopathy [37]. The accumulation of AGEs (carboxymethyllysine and fructosyllysine) correlates with the occurrence of retinopathy and microalbuminuria, independently of age or duration of diabetes [38].

Elevated AGEs are also associated with macrovascular abnormalities, including coronary atherosclerosis, in diabetic subjects [39,40•]. AGEs decrease both endothelial cell nitric oxide levels and activity (by inhibiting endothelial nitric oxide synthase and prostacyclin, or by quenching nitric oxide). These changes, in conjunction with protein kinase C activation and OS, contribute to vasoconstriction [25,35•]. AGEs increase expression of angiotensin II and endothelin in vascular smooth muscle cells, which further contribute to vasoconstriction, and result in both proinflammatory and mitogenic activities. Activation of nuclear factor-κB and activator protein-1 transcription factors by AGEs may lead to increased expression of adhesion molecules (eg, intercellular adhesion molecule-1, vascular cell adhesion molecule-1) and plasminogen activator inhibitor-1, which lead to severe, chronic vascular dysfunction [25,35•,39].

The numerous effects of AGEs on vessel wall function include the formation of chemical crosslinks within and between connective tissue components, or between these elements and plasma constituents, which can impair vasodilation, or low-density lipoprotein (LDL) removal (due to the retention of molecules trapped in the subendothelium and/or by impairing recognition and uptake of AGE-modified LDL by the LDL receptor) [25,35•,40•]. Because AGE-LDL retained in the aortic wall increases the accumulation of foam cells, it is an efficient proatherogenic substance.

AGEs also affect the physical properties of arteries by decreasing their distensibility and elasticity. Both subjects with type 1 and subjects with type 2 diabetes have increased arterial stiffness, which is associated with increased cardiovascular mortality, based on diastolic dysfunction, increased pulse-wave velocity, and decreased arterial compliance [41,42]. This may be due to AGE-induced crosslinks formed in vascular collagen and elastin, which impair arterial distensibility and elasticity [41,42]. This interpretation is reinforced by the observation that AGE inhibition restores these properties in rodents [43].

Pharmacologic Anti-AGE Interventions

Because AGEs make a substantial contribution to the development and progression of microvascular and macrovascular complications of diabetes, they present an important target for therapeutic interventions. Therapeutic directions include decreasing the oral intake of AGEs [6,20], early and later steps in glycation reactions [43–47], decreasing OS [48], and binding or detoxifying dicarbonyl intermediates. These have recently been reviewed in detail [35•]. There are no agents approved by the US Food and Drug Administration that target AGE modification in diabetic patients; however, promising compounds are in preclinical and clinical testing. The effects of a low AGE dietary intervention and its health outcomes should be tested in longitudinal studies and in randomized, controlled trials, in combination with current pharmacologic agents.

Conclusions

AGEs are significant contributors to the increased OS and inflammatory state characterizing diabetes and its complications. Although both hyperglycemia as well as the common diet are equally important driving sources of AGEs, the latter (ie, the diet) has not yet received the full attention it warrants. Because the dietary intake of AGEs has been identified as an independent correlate of serum AGEs and of indicators for inflammation and insulin resistance across all ages, even prior to onset of diabetes, this source is of particular concern for many prediabetic or "normal" subjects. Accordingly, understanding the role of dietary AGEs in diabetes and its complications is an area of great clinical relevance. Interventions that reduce the levels of dietary and endogenous AGEs have been shown to reduce OS, which in turn can prevent the overexpression of OS-response genes. A low AGE diet is safe and equally nutritious as the regular diet and, as shown in mice [49••], it could extend healthy life span. Although many promising pharmacologic anti-AGE therapies exist, their efficacy has been limited.

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