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Role of Dietary Advanced Glycation End Products in Diabetes Mellitus

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Abstract

Dietary advanced glycation end products (AGEs) can be formed via the Maillard reaction and several alternative pathways. AGEs exert their deleterious effects by damaging protein structure and function, as well as through activation of cellular mechanisms. At the cellular level, the damaging effects of AGEs have been attributed to several AGE-binding proteins. Increased levels of AGEs have been implicated in several chronic diseases, including diabetes-related complications such as renal diseases, retinopathy, neuropathy, and cardiovascular diseases, as well as delayed wound healing. To investigate the role of AGEs thoroughly, a reliable assessment of dietary AGEs is needed. Varying methodology, diverse food preparation, and quantification of a variety of dietary AGEs makes this a complex goal. In addition, some antiglycation food products may balance or offset the negative impact of dietary AGEs.

Keywords

advanced glycation end products, dietary AGEs, carboxymethyl-lysine, diabetes mellitus, Maillard reaction, Amadori product, hemoglobin A1c

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According to the latest report from the International Diabetes Federation, 366 million people have diabetes mellitus worldwide with almost 80% of them living in low- to middle-income countries. The International Diabetes Federation also reports that 11% of the health care expenditures are due to diabetes mellitus.[1] In the United States, the prevalence of diabetes is 8.3%, and it is the seventh leading cause of death according to the 2011 report by the Centers for Disease Control and Prevention.[2] According to the 2011 National Diabetes Fact Sheet by the Centers for Disease Control and Prevention, diabetes complications represent a health care burden with diabetes being the leading cause of new blindness and the leading cause of renal failure and heart diseases.[2]

A causal relationship between chronic exposure to hyperglycemia and microvascular and macrovascular diseases found in diabetes mellitus has been well established.[3] There are at least 3 theories about how high levels of blood glucose could lead to the development of complications in diabetes mellitus: oxidative stress, protein kinase C activation, and the accumulation of a heterogeneous, complex group of compounds called advanced glycation end products (AGEs) that are formed mainly via the Maillard reaction.[4]

The activation of the protein kinase C system in insulin independent cells has been identified as one of the mechanisms responsible for the metabolic consequences of hyperglycemia. Dihydroxyacetone phosphate and glyceraldehyde-3-phosphate, glycolytic intermediates, promote the formation of diacylglycerol, which is a cofactor for protein kinase C activation. The activation of protein kinase C triggers the transcription of several growth factors, including the transforming growth factor-β, which has been involved in the thickening of capillary basement membrane (an abnormality seen in tissues in diabetes).[5]

Hyperglycemia also could increase intracellular production of reactive oxygen species by 3 mechanisms: the mitochondrial electron transport chain, the autoxidation of glucose, and the production of AGEs. Oxidant stress appears to be involved in the activation of the protein kinase C system as well as in AGEs formation.[4,6]

The Maillard reaction occurs when a reducing sugar reacts in a nonenzymatic way with amino acids in proteins, some lipids, or DNA to produce AGEs. This reaction has been studied for years in the food industry because its products add a

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desirable color and taste to foods. However, the study of the products of this reaction in vivo has received increasing attention in recent years because of the association of AGEs with certain chronic diseases, such as diabetes mellitus, cardiovascular diseases, and Alzheimer's disease, as well as during the aging process.[7]

In addition to those AGEs formed in vivo, the role of dietary AGEs (dietary AGEs) on health and on diabetes-related complications has been studied. Clinical studies have measured the effects of high dietary AGEs in terms of levels of blood AGEs and levels of inflammation and oxidation markers. In these studies, dietary AGEs intake has been assessed with 3-day food records. However, there is not a standardized assessment method for AGEs quantification in the diet, and the association between dietary AGEs consumption and diabetic complications has not been studied because of the longitudinal data needed for both AGEs intake and complications development. To appreciate the complexity of AGEs and complications related to diabetes, this article will review AGEs formation, metabolism, and excretion, as well as the current literature related dietary AGEs to diabetes complication. In addition, some challenges to researchers will be reviewed, including diverse analytical measurement of dietary AGEs and how to measure AGEs in the diet to generate data on usual intake and establish a safe intake. Finally, dietary strategies to lower AGEs damage will be discussed.

Formation of Advanced Glycation End Products

Formation In Vivo

Several AGEs have been described and complex pathways for their formation have been elucidated. Their detailed description is outside the scope of this review, but a brief description on the Maillard reaction and alternative pathways is described.

Maillard reaction. The Maillard reaction consists of 3 well-described phases. First, the carbonyl group of a reducing sugar interacts in a nonenzymatic way with an amino acid to form an unstable compound called Schiff base. Lysine and arginine are the amino acids most often described as taking part in this reaction, but hydroxylysine and glycine have also been described. During the second phase, the Schiff base has 2 fates; it could undergo hydrolyzation and generate the original sugar and amino acid, or it could undergo cyclization and further Amadori rearrangements to form more stable compounds called Amadori products. Despite their stability and similarity to the first phase, under physiological and nonoxidative conditions 90% of Amadori products could sustain a reversible reaction to the initial sugar and amino acid.[8] In the last phase, Amadori products can generate AGEs by 2 different ways, either oxidative or nonoxidative cleavage. The oxidative cleavage of Amadori compounds will yield 2 intermediates that after autoxidation and further rearrangements will produce AGEs. The principal AGEs produced in this form is carboxymethyl-lysine, one of the first AGEs characterized in vivo and the major AGEs' biomarker in human tissues.[9] In contrast, the nonoxidative cleavage of Amadori products will produce the α-dicarbonyl derivative 3-deoxyglucosane. This derivative can react with an amino acid and also form carboxymethyl-lysine or other AGEs crosslinks such as pyrraline, pentosidine, or imidazolone (Figure 1).[8-11]

A study of the kinetics of AGEs formation measured the fluorescence of final AGEs and it showed that ribose is the most reactive sugar, followed by fructose and lastly glucose. However, ribose and fructose concentration in tissues is significantly lower that the concentration of glucose. In addition, when glucose remains for a long time it will produce the same amount of fluorescence,[12] which makes glucose the principal contributor for the Maillard reaction.[11]

Alternative pathways, formation of α-dicarbonyl: methylglyoxal, glyoxal, and 3-deoxyglucosane. Other pathways generate AGEs by producing short chain carbonyl compounds known as α-dicarbonyl or α-oxaldehydes as glyoxal, methylglyoxal and 3-deoxyglucosane. The α-dicarbonyl compounds are very reactive, participating in the formation of intra- or inter-protein crosslinks. In addition, α-dicarbonyls also have the ability to form AGEs either by directly reacting with an amino acid or by starting the Maillard reaction instead of a reducing sugar. For this reason, α-dicarbonyls have been suggested as the main precursors for AGEs formation, particularly methylglyoxal.[13] Among the pathways that produce α-dicarbonyls, the Namiki and the Wolff pathways are the more important. The Namiki pathway occurs when a Schiff base degrades and forms glyoxal, whereas the Wolff pathway involves the autoxidation of monosacharides. For instance, the autoxidation of glucose at physiological conditions produces α-dicarbonyls. In addition, other metabolic intermediates have been implicated in α-dicarbonyl production with subsequent generation of AGEs. For example, glycolytic intermediates (glucose-6-phosphate, glyceraldehyde-3-phosphate, and dihydroxyacetone phosphate), a polyol pathway intermediate (fructose-6-phosphate), an intermediate from ketone body and threonine metabolism (acetol), and lipid peroxidation also generate methylglyoxal (Figure 1).[13-15]

Formation of Dietary Advanced Glycation End Products

Since its first description in 1912 by Louis Camille Maillard, the Maillard reaction has been extensively studied in food science to explain the nonenzymatic darkening of fruits, the modification of skim milk during storage, and the production of off-flavor and pleasant aromas of some foods. It has also been used for caramel production, coffee roasting, and bread baking.[16,17] In the food industry, proteins are used for emulsifying, foaming, gelling, and solubilizing foods, and protein glycation increases emulsifying activity, improves foaming properties, increases protein solubility, promotes the formation of compounds with antioxidant activity (extending shelf life on food via delaying lipid oxidation), and improves food texture.[18]

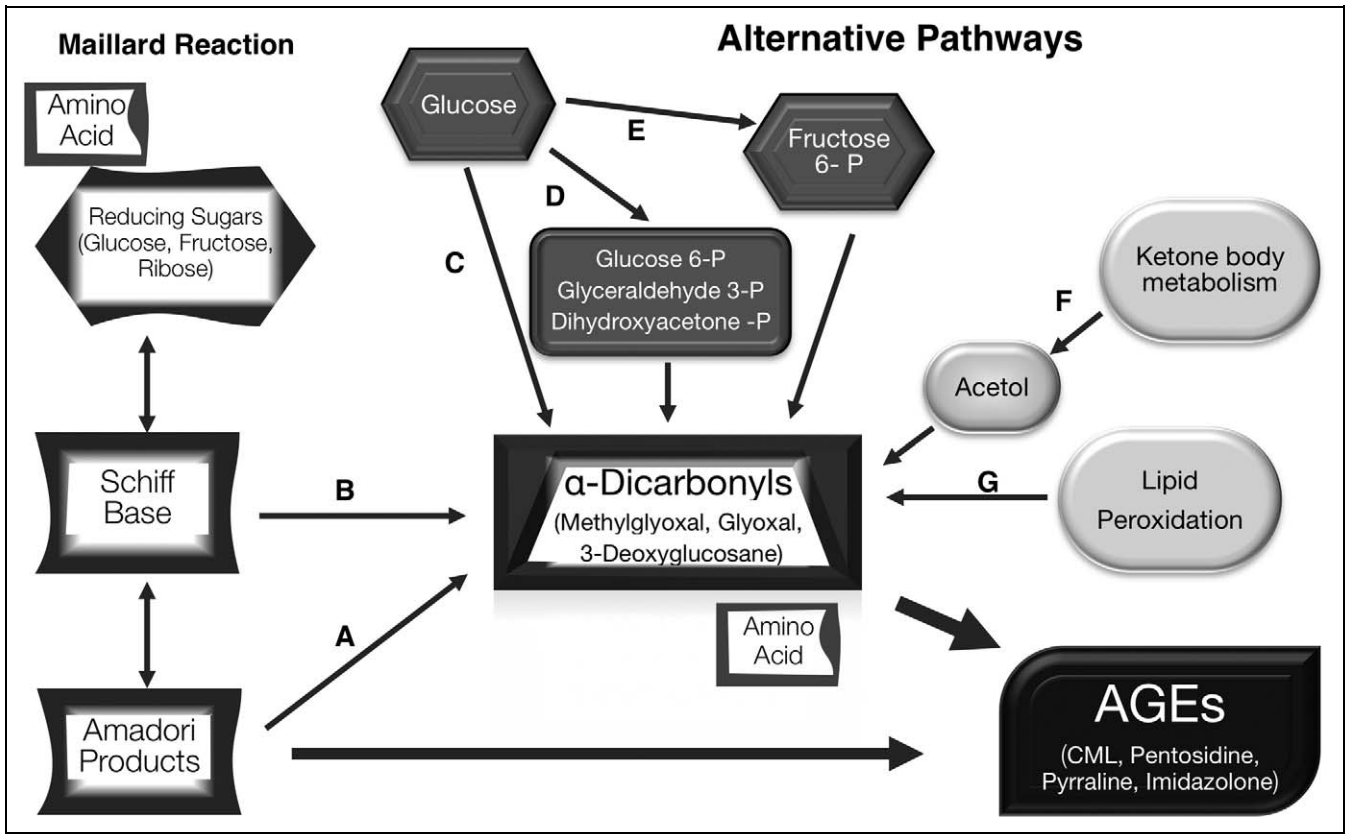

Figure 1. Different pathways for advanced glycation end products formation in vivo: (A) nonoxidative Amadori product cleavage, (B) Namiki pathway, (C) Wolff pathway, glucose autoxidation, (D) glycolytic pathway, (E) polyol pathway, (F) ketone body and threonine metabolism, (G) lipid peroxidation

In addition to in vivo formation, AGEs production in foods (dietary AGEs) involves the Maillard reaction. An amino acid from a protein, amine, or phospholipid reacts in a nonenzymatic fashion with carbonyl groups from reducing sugars and with degradation products of carbohydrates, lipids, and ascorbic acid, and the resulting products often are referred to in the food science literature as Maillard reaction products. The reaction occurs in three well-identified stages previously described. There are low molecular Maillard products such as aldehydes, ketones, acryl amides, and AGEs, as well as high molecular products such as melanoidins.[17,19] Other products formed during this intricate reaction are furfurals, pyrralines and α-dicarbonyl compounds such as methylglyoxal. The last products formed in the Maillard reaction, very well studied in food science, are the melanoidins, which are brown pigments.[10] Some other dietary AGEs studied in foods are furosine, which is a degradation product of Amadori compounds, as well as carboxymethyl-lysine and pentosidine formed in the last stage of the Maillard reaction.[20]

Another source of dietary AGEs could be autoxidation of fatty acids and amino acids.[21] Chao et al[20] proposed that heat could cause oxidation of unsaturated fatty acids from soybean oils and some fishes such as salmon and cod. The oxidative products could participated in the rearrangement of Amadori adducts to form irreversible crosslinks like pentosidine or carboxymethyl-lysine.[20]

Regardless of the diversity of AGEs, carboxymethyl-lysine has been reported as one of the most abundant in vivo and it was one of the first to be characterized in foods (milk and milk products). For this reason, in most studies carboxymethyl-lysine is chosen as a marker of AGEs in foods and in vivo.[22]

Metabolism of Advanced Glycation End Products

Increased levels of AGEs have been implicated in several chronic diseases, including diabetes-related cardiovascular complications and renal disease, as well as aging.[23,24] AGEs exert their deleterious effects by damaging protein structure and function, and they are also implicated in activation of cellular mechanisms. Besides endogenous AGEs, dietary AGEs also have been shown to be a major source of the body's pool of AGEs, and it is believed that they are also involved in tissue damage. An important point to review is how dietary AGEs are absorbed and if they can exert damage similar to that of endogenous AGEs.

From the quantitative point of view, the contribution of dietary AGEs to the total pool of AGEs in the body is considered more important than the contribution from endogenous AGEs by abnormal glucose metabolism or lipid peroxidation. Henle[25] estimated that 10 to 50 times more dietary AGEs are supplied

by a conventional diet that those found in plasma or tissues of subjects with uremia. Evidence from human studies shows the contribution of dietary AGEs as carboxymethyl-lysine and methylglyoxal to the levels of circulating AGEs. Cross-sectional and randomized studies have demonstrated a correlation between dietary AGEs and circulating AGEs.[26-30] A cross-sectional study with 90 healthy subjects showed significant correlation between carboxymethyl-lysine estimated from 3-day food records and plasma levels of AGEs. When a subgroup decreased their intake of carboxymethyl-lysine, their plasma levels also decreased.[26] A similar study of healthy volunteers compared older (60-80 years, n = 56) versus younger (18-45 years, n = 116) healthy adults. The plasma levels of carboxymethyl-lysine and methylglyoxal were higher in the older group and correlated with levels of inflammation markers and oxidative stress. Additionally, the level of dietary glycotoxins (measured by 3 days of dietary records) correlated independently with serum carboxymethyl-lysine ($r = 0.46$, $P < .001$) and methylglyoxal ($r = 0.37$, $P = .001$), as well as with C reactive protein ($r = 0.200$, $P =. 042$).[27] Vlassara et al[28] found similar results in a study with 325 healthy participants and 66 participants with kidney disease. Serum carboxymethyl-lysine and methylglyoxal were higher in the group of older participants, and serum carboxymethyl-lysine correlated positively with age and with dietary AGEs.[28] These findings support the view that the intake of dietary AGEs is an important contributor to the body's AGEs pool.[26,27,29,30]

In contrast, a recent study by Semba et al[31] found that urinary carboxymethyl-lysine was positively correlated with intake of starchy vegetables, whole grains, sweets, nuts/seeds, and chicken, and negatively correlated with intake of fast foods. Intake of AGE-rich foods such as fried chicken, French fries, bacon, sausage, and crispy snacks were not significantly correlated with serum or urinary carboxymethyl-lysine. In contrast to other researchers, these researchers concluded that the high consumption of foods considered high in carboxymethyl-lysine was not a major determinant of either serum or urinary carboxymethyl-lysine.[31]

Several authors have studied the metabolism and absorption of some dietary AGEs and their precursors. For instance, a study by Erbersdobler and Faist[32] on Amadori products (dietary AGEs precursors) found that their intestinal absorption is by diffusion. They used ^{14}C-labeled fructose amino acids in rats and humans and found that urinary excretion of Amadori products after the ingestion of test meals showed a rapid elimination of the absorbed part, while the fecal output, although low, persisted for 3 days. Only 1% to 3 % of the ingested amounts of protein-bound Amadori products were recovered in the urine, leaving around 90% of Amadori products unaccounted.[32] A review regarding metabolism of premelanoidins and melanoidins showed data suggesting that on average 16% to 30% of absorbed premelanoidins were excreted in the urine and 1 to 5% for melanoidins. A possible explanation suggested for this low recovery of premelanoidins and melanoidins was that digestive microbial enzymes degraded pre- and melanoidins during intestinal transit.[33] For instance, Wiame et al[34] showed that bacteria that reside normally in the large intestine degrades around 80% of dietary Amadori products. It also has been proposed that the rest of premelanoidins are metabolized and retained by different tissues.[33]

Koschinsky et al[35] conducted a study with 43 subjects with diabetes mellitus and 5 healthy subjects. The AGEs were measured using an AGE-specific enzyme-linked immunosorbent assay in urine and serum 24 hours before and 48 hours after a rich AGEs meal. It was demonstrated that ingested AGEs are absorbed, and it was estimated that 10% of ingested immunoreactive AGEs were transported into circulation, two thirds of which remained in the body, and were incorporated covalently in tissues. Only one third was excreted via the kidneys.[35] Foerster and Henle[36] have studied the bioavailability and kinetics of elimination of pyrraline and pentosidine. In a first study, 7 healthy subjects were asked to ingest a normal diet on days 1 and 5, and a diet virtually free of Maillard compounds on days 2, 3, and 4. Urinary excretion of free pyrraline was directly affected by composition of the diet, decreasing from 4.8 mg/d on day 1 to 0.3 mg/d on days 2, 3, and 4. The analysis of the 24-hour urine sample established that most of dietary pyrraline was absorbed and then rapidly excreted via the kidney within 48 hours.[36] Another study with 18 healthy volunteers who received specific amounts of custard, pretzels, and brewed coffee on a single day found the rate of recovery in urine to be close to 50% for pyrraline and 60% for pentosidine. However, the metabolic fate of the pyrraline and pentosidine is unknown.[37] This study raises the question of how pyrraline or other dietary AGEs can cross the intestinal epithelial barrier. An in vitro study trying to answer this question concluded that, in general, free or protein-bound dietary AGEs could cross the intestinal epithelium by simple diffusion, by endocytotic processes or mediated by transport proteins. It was found that pyrraline is absorbed by the peptide transporter hPEPT1 in HeLa cells.[38]

Advanced Glycation End Products Clearance

It has been proposed that levels of serum AGEs depend on the endogenous production, the intake of dietary AGEs, and the clearance system. This clearance system consists of several enzymes (glyoxalase I, glyoxalase II, and carbonyl reductase) and a receptor (AGER1), and they have been proposed to have a role in AGEs detoxification.[28,39] In addition, renal clearance is the predominant means of excretion of AGEs, mainly the low-molecular-weight fraction (glycation-free adducts).[40] The predominant plasma AGEs (imidazolones, carboxymethyl-lysine, and carboxyethyl-lysine) have a high renal clearance,[41] and their levels are inversely correlated with renal function.[42] The AGEs adducts and peptides are filtered through the glomeruli and a small proportion may be reabsorbed and degraded by proximal tubular cells.[43] It has been reported that the presence of near normal renal function is critical to maintain the body load of AGEs and possibly other oxidants at nontoxic levels.[44] However, the AGEs clearance system is altered in

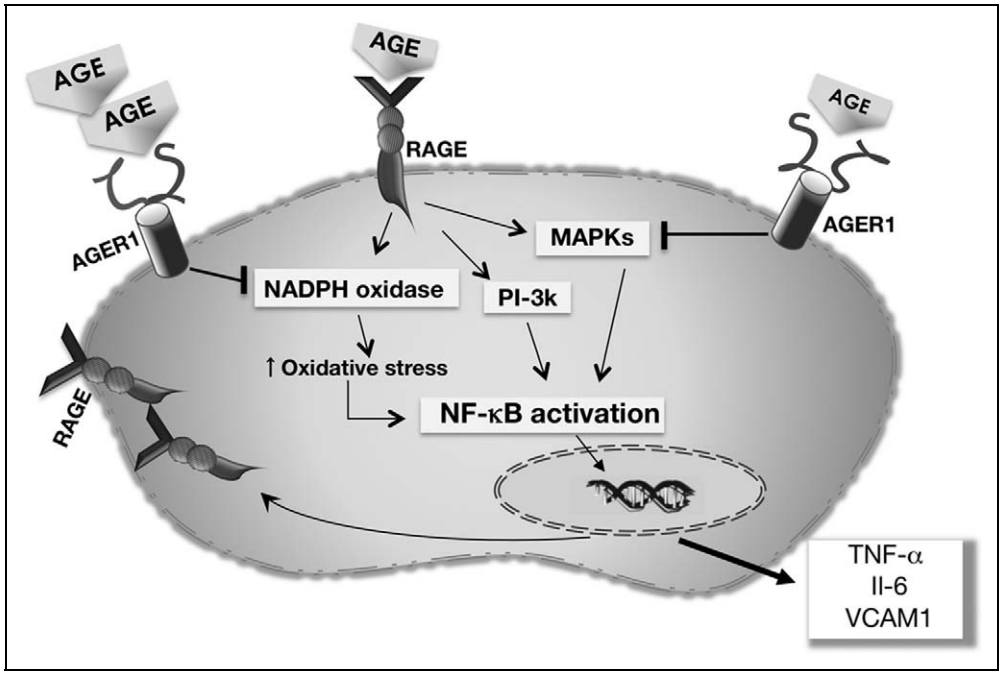

Figure 2. Interaction of AGEs with their receptors

Abbreviations: AGE, advanced glycation end product; RAGE, receptor for AGE; MAPK, mitogen-activated protein kinases; AGER1, AGEs receptor 1; PI-3k, phosphatidylinositol-3 kinase; NAD(P)H oxidase, enzymes complex that produces superoxide; NK-κB, nuclear factor-κB; TNF-α, tumor necrosis factor α; IL-6, interleukin 6; VCAM-1, vascular adhesion molecule 1.

diabetes mellitus and aging, and although the kidney is key in the oxidative stress defense system, it is also a target for AGE-induced injury.[45] Serum AGEs correlate directly with the levels of inflammatory markers and oxidative stress, and inversely with creatinine clearance and urinary AGE clearance also correlates directly with creatinine clearance.[42] Hence, persons with diabetes mellitus and renal disease display elevated serum AGEs levels and reduced urinary AGEs excretion.[46] Limited information concerning absorption, biodistribution, and elimination of AGEs is available. Therefore, studies in this area would help us understand the extent of the role of dietary AGEs on disease.

Receptors of Advanced Glycation End Products

At the cellular level, the damaging effects of AGEs have been attributed to several AGE-binding proteins, such as RAGE (receptor for AGEs), AGEs receptor (AGER) 1, R2, R3, and scavenger receptors such as CD-36[47] and SCR-II.[48] These receptors are present on vascular, renal, hemopoietic, and neuronal/glial cells, and they serve in the regulation of AGEs uptake and removal. The AGEs receptors also modulate cell activation, growth-related mediators, and cell proliferation, consequently influencing organ structure and function. Furthermore, these receptors have been shown to play distinct functional roles in AGEs toxicity or detoxification.[49]

The most notable receptor is RAGE, and it triggers oxidative stress and inflammation in both acute and chronic diseases, including diabetes mellitus.[50] This receptor is a member of the immunoglobulin superfamily of cell surface molecules,[51] and increased serum and tissue levels of AGEs activate RAGE. The interaction of AGEs and RAGE promotes the activation of the mitogen-activated protein kinases (MAPKs), the phosphatidylinositol-3 kinase (PI3-K), and the nicotinamide adenine dinucleotide phosphate-oxidase (NADPH, a complex of enzymes that produces superoxide) and when this complex is upregulated, it increases intracellular oxidative stress (Figure 2). The activation of these pathways will lead to the activation of the transcription factor NF-κB (nuclear factor kappa B) which activates the transcription of genes for proinflammatory cytokines, growth factors and adhesive molecules, such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), well-known inflammation promoters, and vascular cell adhesion molecule 1 (VCAM-1).[52-55] Induction of these proinflammatory molecules could contribute to cellular dysfunction and damage target to organs, and ultimately lead to complications as atherosclerosis, cardiovascular disease, and nephropathy.[56-58]

Besides the endogenously formed AGEs, dietary AGEs have also been shown to act as RAGE ligands and activate major signal transduction pathways in vitro.[59,60] Dietary AGEs, together with those made endogenously, could promote a systemic glycoxidant burden, oxidant stress and cell activation, which increases vulnerability of target tissues to injury.[61,62]

In contrast, AGER1 suppresses AGEs and their related oxidative stress and inflammation (Figure 2). This receptor is encoded by the gene DDOST, and it is a type 1 transmembrane protein of ~50kDa.[63] Overexpression of AGER1 inhibits the

epithelial growth factor receptor, suppresses RAGE pro-inflammatory signaling pathways, and contributes to maintain AGEs homeostasis.[63-65] Likewise, AGE-R3 (a 32-kDa protein and member of the β-galactoside-binding lectin family) exhibits high binding affinity for AGEs, thus protecting against AGEs-induced pro-inflammatory response.[66] Hence, AGER1 and AGER3 are largely responsible for AGEs-recognition and high-affinity binding.[67,68] Last, AGER2 is implicated in several biological functions, including cell growth, proliferation, differentiation, and apoptosis.[69] It can undergo AGEs-induced phosphorylation and could play a role in signal transduction and cell activation associated with-receptor binding.[70] The AGE-receptor systems may be regulated by factors related to diabetes such as glucose, insulin, AGEs, and reactive oxygen species.[71]

Some data suggest that AGER1 may be suppressed or saturated in the presence of high AGEs induced oxidant stress. For instance, low expression of AGER1 in the kidney of nonobese diabetic mice was associated with high tissue AGEs levels and kidney disease.[72] Furthermore, human circulating mononuclear cells from diabetic subjects with severe diabetes complications showed low expression of AGER1 and high serum AGEs.[73] Although the cause of AGER1 downregulation in diabetes mellitus is not yet known, this effect is reversible by consumption of AGE-restricted diet in both humans and mice.[28,74-76] Indeed, a study with young and old mice fed high or low AGEs found that old mice maintained on high AGEs diets developed insulin resistance, decreased AGER1, increased RAGE, fibrosis in the heart and kidney, a depleted glutathione/oxidized glutathione ratio, and increased serum 8-isoprostane. In contrast, mice kept with low dietary AGEs had an enhanced antioxidant reserve, had no insulin resistance, had higher tissue AGER1 levels and had a reduction on systemic AGEs accumulation.[75] In addition, increased AGER1 expression also has been associated with extended lifespan in mice.[75,76] Similarly, a study in patients with type 2 diabetes showed that the suppressed expression and function of AGER1 in diabetic peripheral blood mononuclear cells were nearly normalized by dietary AGEs restriction.[74] Another study showed that a moderate (30-50%) reduction of dietary AGEs by healthy participants substantially reduced the normal baseline levels of serum AGEs, oxidative stress and inflammation as well as AGER1.[28] The defense mechanism exerted by AGER1 was lost in patients with diabetes mellitus and its efficiency decreased with aging.[63] It has been shown in animal studies that a way to restore this balance is by reducing dietary AGEs.[75] Therefore, efforts should be made to corroborate these results with human studies in those with and without diabetes.

Diabetes and Related Complications

Formation of AGEs in vivo depends of specific intra- and extracellular conditions. Some of the studied factors involved in AGEs production are the rate of turnover of the proteins, oxidant stress in the intra- or extracellular environment, and the degree of hyperglycemia.[77] It has been reported that intracellular AGEs formation significantly increases in endothelial cells after 1 week of hyperglycemia. Additionally, the type of reducing sugar also affects the rate of AGEs formation with intracellular proteins, with the slowest reaction in the presence of glucose when compared with fructose, glyceraldehyde-3-phosphate, and glucose-6-phosphate.[77] Accumulation of AGEs in blood and in tissues has been found in healthy aging persons, and this accumulation is higher during high blood glucose concentrations. In addition, AGEs have been reported to be elevated in human tissues, plasma and urine in cases of metabolic and vascular disorders like diabetes mellitus, atherosclerosis, and renal disease.[46,78-80] Therefore, increased levels of AGEs in physiological matrices often serve as biomarkers for those diseases.

One of the main biomarkers of diabetes mellitus is hemoglobin A1c, an Amadori product that results from the reaction of glucose with the valine terminal of hemoglobin A,[81] and it is used as an indicator of the average glucose levels in diabetes mellitus. As mentioned before, high levels of glucose increases glycation of the extracellular matrix, but this also occurs with intracellular proteins, especially in insulin-independent cells such as red blood cells, peripheral nerve tissue cells, endothelial cells, eye lens cells, and kidney cells.[9] It is also hypothesized that glycation of proteolytic enzymes in diabetes reduces their efficiency, resulting in accumulation of additional glycated end products.[9] One of the first studies showing that glycemic status correlates with AGEs levels was carried out by Portero-Otin et al,[82] and their results on the quantification of pyrraline (a nonoxidative glucose-derived Maillard reaction product) in urine showed higher levels for individuals with diabetes mellitus when compared with healthy individuals: 3.4 and 1.1 mg/d, respectively. In addition to higher renal excretion of AGEs, Kalousova et al[79] also found a slight elevation of serum AGEs in patients with diabetes mellitus type 2 ($n = 24$) when compared with healthy controls ($n = 34$). Furthermore, subjects with type 2 diabetes mellitus ($n = 50$) had levels of AGEs in serum, skin, and saliva that increased with the progression of complications in diabetes mellitus.[46]

How these diabetes mellitus complications relate to elevated AGEs levels is not completely known. However, microvascular damage characteristic of diabetes in the kidney, retina, and microvasculature of peripheral nerves could occur when endothelial cells from microvascular beds are damaged with subsequent capillary occlusion, ischemia, and organ damage.[83]

Retinopathy

Changes seen in retinopathy such as capillary occlusion and retinal ischemia could be because of high levels of glucose that could provoke dysfunction of intraretinal blood vessels, increased permeability of capillaries and progressive loss of retinal pericytes and endothelial cells.[83] The level of AGEs from retinal blood vessels has been found to correlate to the degree of retinopathy in subjects with type 2 diabetes mellitus,[72] and it is hypothesized that they could be involved in the damage seen in retinopathy. In a review study, Ahmed[23] described studies in cell cultures that have shown the toxicity

of AGEs for the pericytes, and also that AGEs increase the levels of RAGE mRNA in pericytes and endothelial cells. The interaction of AGE-RAGE in retinal cells could promote upregulation of vascular growth factors as the vascular endothelial growth factor. The vascular endothelial growth factor is capable of increasing angiogenesis and neovascularization (characteristic of proliferative retinopathy). In addition, subjects with retinopathy were found to have increased levels of AGEs and IL-6 in the eye vitreous. IL-6 could also promote angiogenesis by increasing expression of the vascular endothelial growth factor.[23]

Renal Disease

The relationship between renal disease and AGEs has been studied in animal models. Recently, Coughlan and Forbes[84] described a study in which urinary carboxymethyl-lysine excretion was increased 4 weeks after diabetes induction, which preceded the excretion of urinary albumin and continued to rise progressively after 32 weeks. They concluded that the most informative marker of progressive renal damage linked to the AGEs pathway in experimental diabetic nephropathy was urinary excretion of carboxymethyl-lysine.

Researchers have also investigated these outcomes in patients with type 2 diabetes mellitus, and to a lesser extent in older populations. Semba et al[85] demonstrated that in an older population ($n = 1008$), elevated circulating AGEs were an independent predictor of renal function. The study was carried out with men and women, 64 years and older, participating in the InCHIANTI study in Tuscany, Italy. The results of the study included an elevated plasma concentration of carboxymethyl-lysine independently associated with chronic kidney disease and the estimated glomerular filtration rate (an index of kidney function) at baseline, after 3 and 6 years of follow-up. These findings suggest that the potential adverse effects of AGEs on the kidney are applicable to the general population of older community-dwelling adults.[85] In another study of 548 women from the Women's Health and Aging Study I in Baltimore, 51.6% of women had decreased glomerular filtration rates, which were associated with increased serum levels of carboxymethyl-lysine and sRAGE (the soluble form of RAGE).[86] In normal renal function, circulating AGEs are cleared by the kidneys, but high levels of AGEs have been found in patients with uremia as well as in patients with diabetic nephropathy, probably because of inadequate renal clearance.[87] Levels of AGE were measured in a study with patients with diabetes mellitus and no renal damage ($n = 22$), with end-stage renal disease but no diabetes mellitus ($n = 8$), with end stage renal damage and diabetes mellitus ($n = 12$) and healthy controls ($n = 17$). It was found that all groups had higher levels when compared with the healthy controls.[88] AGEs are associated with damage seen in renal disease such as glomerular basement membrane thickening, mesangial expansion, glomerulosclerosis, and tubulointerstitial fibrosis.[89] Some of these changes could be mediated by an increase in the transforming growth factor β that increases synthesis of collagen matrix components responsible for the basement membrane thickening.[23]

Neuropathy

High levels of AGEs have also been found in the peripheral nerves of subjects with diabetes mellitus.[89] In a recent review, Ahmed[23] found that in vitro studies have shown that there is increased glycation of myelin in diabetes. Nerve demyelination seen in diabetic neuropathy could be explained by phagocytosis of the glycated myelin by macrophages. In animal studies, when AGEs are injected into peripheral nerves there is a reduction of sensory motor conduction velocities, nerve action potentials, and blood flow.[23] However, the mechanism by which AGEs could be involved in diabetic neuropathy is not clear.

Cardiovascular Diseases

As previously described,[90] the in vivo accumulation of AGEs over time contributes to changes in the structure and function of the cardiovascular system and presents as arterial stiffening, myocardial relaxation abnormalities, atherosclerotic plaque formation, and endothelial dysfunction. Several authors have described some of the potential mechanisms for these changes. One of the proposed mechanisms involves additional crosslinking on collagen (whose normal structure already contains crosslinking) by glycation of its free amino acids. The collagen-AGEs crosslinking will produce stiffness of blood vessels. Sims et al[91] completed a histological study on 27 samples of postmortem aortas from people with diabetes and controls and found a correlation between AGEs accumulation and aortic stiffness. Another mechanism by which AGEs exert damage to the cardiovascular system is reduction of low-density lipoprotein (LDL) uptake by cell receptors. This occurs through glycation of the LDL particle on the apolipoprotein B and in the phospholipid components of LDL. The glycated LDL is more susceptible to crosslinking with collagen on the arterial wall than nonglycated LDL. Because of this, it is not taken up into the cell and accumulates in circulation. Macrophage uptake of these modified LDL lead to foam cell formation, and the development of atheroma.[88,92,93] Furthermore, decreasing nitric oxide activity is another mechanism by which AGEs can damage the cardiovascular system. Nitric oxide (a vasodilator) biosynthesis in the endothelium counteracts some of the mechanisms for atherosclerosis. Some authors proposed that AGEs reduce nitric oxide synthase half-life in the endothelium. For instance, Xu et al[94] found a decreased in nitric oxide synthase activity after exposure to carboxymethyl-lysine-albumin both in vivo (rabbit femoral artery) and in vitro (rabbit aortic ring). They also found that after 30 minutes of exposure to carboxymethyl-lysine-albumin, there was a reversible inhibition of endothelium and vascular response dependent on nitric oxide in vivo and in vitro.[4,94]

Therefore, the accumulation of AGEs could explain some of the cardiovascular changes associated with the cardiovascular diseases seen in diabetes, such as vascular stiffening, diastolic dysfunction, and endothelial dysfunction.[95]

Wound Healing

Not surprisingly, AGEs have also been implicated in the delayed wound healing associated with diabetes, presumably through vascular, neurological, or intermediary metabolic modifications.[96] Interaction of AGE-RAGE increases the production of inflammatory molecules such as TNF-α that could create a state of chronic inflammation in patients with diabetes as well as production of destructive matrix metalloproteinases. These 2 events could prevent deposition of matrix components that are necessary for wound healing.[23]

Although some of the mechanisms responsible for the complications of diabetes are not well described, an association between the accumulation of endogenous AGEs and those complications is clear. In addition, several research groups[74,97,98] have addressed the role that exogenous AGEs could have on diabetes and its complications.

Managing Dietary Advanced Glycation End Products for Health

Analytical Measurement of Advanced Glycation End Products in Foods

One of the challenges in studying dietary AGEs is knowing the amount of AGEs in foods. Formation of dietary AGEs is a complex process involving several reactions and many end products, and only a few of them have been characterized and measured. Some of the analytical techniques used for this purpose are capillary electrophoresis, autoimmune assays, mass spectrometry, high-performance liquid chromatography, or gas chromatography. Some AGEs have fluorescence properties. By taking advantage of this property, some studies have measured AGEs using fluorescence spectrophotometry. However, according to Zhang et al,[10] high-performance liquid chromatography and gas chromatography coupled with fluorescence, flame ionization, or with mass spectrometry are more specific and sensitive methods for AGEs quantification. However, other authors have measured AGEs by immunohistochemical techniques.[99] There is as yet no agreement among the different groups studying dietary AGEs as to which technique is the best.

Analytical measurement of AGEs in foods was for a long time focused on monitoring the quality of food products and for detecting indications of thermal damage in foods, mainly in milk and milk products. Furosine, pyridosine, pyrraline, and carboxymethyl-lysine have been used for this purpose.[100] Since dietary AGEs have been associated with chronic diseases, some authors have measured dietary AGEs in foods more extensively.

Delgado-Andrade et al[101] studied in a clinical setting how 2 different diets (one rich in AGEs and one low in AGEs) affected protein digestibility in adolescents (n = 18) in Spain. They prepared two 7-day diets and measured the total furosine, hydroxymethyl furfural, and fluorescence by high-performance liquid chromatography in both diets.[101] In another study in Spain, the levels of glyoxal and methylglyoxal were measured in a mixture of 26 commercial cookies. The mean levels of glyoxal and methylglyoxal were 15.0 and 29.9 mg/kg, respectivley.[102] Methylglyoxal was measured in 13 commercial carbonated beverages, 11 of which contained high-fructose corn syrup as the sweetener and 2 of them contained an artificial sweetener. Levels of methylglyoxal were in the range of 23.5 to 139.5 μg/100 mL for the 11 beverages with high-fructose corn syrup and less than 10 μg/100 mL for the beverages with artificial sweetener.[103] In another clinical study measuring risk factors for diabetes mellitus and cardiovascular disease in healthy individuals, the carboxymethyl-lysine content of a standard and a steam diet (foods were cooked with steam techniques) was measured by gas chromatography–mass spectrometry. Total carboxymethyl-lysine intake was 5.4 ± 2.3 and 2.2 ± 0.9 mg/d for subjects in the standard and steam diet, respectively. Individual analysis of foods showed that bread, dough, cookies, meat, and fish were the main contributors of carboxymethyl-lysine to the standard diet.[97]

Chao et al[20] measured pentosidine, carboxymethyl-lysine, and furosine in some sauces used in Asian cuisine: soybean sauce, sour-sweet sauce, and barbecue sauce, as well as in sauce-treated chicken, pork, beef, and salmon. They used 3 cooking methods: boiling, deep frying, and baking. Carboxymethyl-lysine and pentosidine were measured by high-performance liquid chromatography followed by fluorescence detection. The content was reported as micrograms per 100 mg of food. Cooking the food increased the amount of furosine, pentosidine, and carboxymethyl-lysine in all the foods tested in comparison with the raw sample. They found that salmon and cod fried in soybean oil (temperature used 356°F [180°C]) had higher pentosidine and carboxymethyl-lysine than baked samples (temperature used 446°F [230°C]). The authors concluded that the amount of glycation products produced was affected by the interaction of the hot frying oil and food. The authors also noted that cooked salmon had higher levels of pentosidine, carboxymethyl-lysine, and furosine than cooked cod, suggesting a role of polyunsaturated fatty acids, which are higher in salmon than cod, in the formation of dietary AGEs. The authors also concluded that when food was treated with the sauces tested, the sauce and heat could have a synergistic effect on dietary AGEs formation. Their hypothesis was that heat releases amino acids from the tested foods and led to the interaction with reducing sugars found in the sauces, thereby forming dietary AGEs.[20]

The first attempt to measure a considerable number of foods to create an AGEs food content database was made by Goldberg et al.[99] They selected 250 typical foods and measured carboxymethyl-lysine by enzyme-linked immunosorbent assay with an anti-carboxymethyl-lysine monoclonal antibody. The results were expressed as AGEs units per milligram of protein or lipid, and then the AGE value was multiplied by the amount

of protein or lipid per gram of food. The cooking methods used were boiled in water (212°F [100°C]), broiled (437°F [225°C]), deep fried (356°F [180°C]), oven fried (446°F [230°C]), and roasted (350°F, [177°C]). The food group with the higher mean values of carboxymethyl-lysine was the fat group. Butter, cream cheese, cream, and mayonnaise had the highest values followed by oils and nuts with values ranging from 1300 to 450 kU of AGEs. Foods rich in protein and fat also had a high content of carboxymethyl-lysine that increased depending on the cooking method. Foods that were oven fried had higher amounts of carboxymethyl-lysine followed by deep frying, broiling, roasting, and lastly boiling. The authors concluded that the presence of free radicals from lipoxidation reactions could increase formation of AGEs and that glycoxidation and lipoxidation increased by heat could be responsible for the carboxymethyl-lysine content in foods rich in fat with lower protein content. The groups with lower levels of carboxymethyl-lysine were milk, fruits and vegetables; however, infant formula had a 100-fold higher content of carboxymethyl-lysine than cow's milk, which was consistent with similar finding from Sebekova et al.[104] Even when cereals had a lower content of carboxymethyl-lysine, some products in this group had higher amounts depending on the processing. For instance, breakfast cereals with processing temperatures over 446°F (230°C) had higher amounts of carboxymethyl-lysine.[99]

Recently, Uribarri et al[105] published a larger food database with approximately 500 food items, including those published by Goldberg et al,[99] with the carboxymethyl-lysine content using the same enzyme-linked immunosorbent assay. Additionally, they also measured methylglyoxal in some food items to validate their findings. They found the same pattern of carboxymethyl-lysine content in foods depending on their food composition and method of cooking. They attributed the higher amount of carboxymethyl-lysine in meats to the amount of intracellular components in muscle, such as amino lipids and reducing sugars as fructose or glucose-6-phosphate, which in the presence of heat accelerates new AGEs formation. They also highlighted that higher amounts of carboxymethyl-lysine in some cheeses could be because of the curing or aging processes, and that the high content in fats could be because of the extraction and purification procedures involving heat and dry conditions. In addition to exposure to higher temperatures, they also noted that lower moisture increased the amount of carboxymethyl-lysine for the same food. Therefore, frying, broiling, grilling, and roasting would produce higher carboxymethyl-lysine than boiling, poaching, stewing, and steaming. A new observation in this study was that marinating meat in acidic solutions such as lemon juice or vinegar for at least 1 hour could reduce production of new carboxymethyl-lysine by half in comparison with foods not marinated.[105]

This database represents a great tool to assess the carboxymethyl-lysine content of the diets. However, corroboration of the carboxymethyl-lysine values using different technology would help validate this AGEs database.

Restriction of Dietary Advanced Glycation End Products

Findings in several intervention studies, both human subjects and animals, indicate that the high intake of dietary AGEs contributes to tissue damage and increased levels of inflammatory markers that can be prevented by dietary AGEs restriction.

Clinical trials on restriction of dietary AGEs in human subjects are presented in Table 1. The effects of reducing dietary AGEs have been studied in nondiabetic peritoneal dialysis patients, a group that has very high AGE levels, and the results showed significant reduction in the levels of AGEs. For instance, Uribarri et al[106] studied 18 non-diabetic patients with peritoneal dialysis, in whom the intake of AGEs was reduced for 4 weeks by exposing meat to different cooking methods by participants. Subjects with the low-AGE diet showed 34% reduction in serum carboxymethyl-lysine and 35% reduction in methylglyoxal when compared with baseline. Subjects with high-AGE diet had elevation of serum carboxymethyl-lysine and methylglyoxal by 29% and 26%, respectively.[106] In a similar study, decreases in vascular adhesion molecule 1 and TNF-α were also found in the low-AGE diet compared with the high-AGE diet.[107] Another study with overweight and obese volunteers randomized to a low- and high-AGE diet during 2 weeks found that renal function and the inflammatory profile improved following the low-AGE diet.[108]

Intervention studies with patients with diabetes mellitus have had similar results. In a study of 13 patients with type 2 diabetes mellitus, decreasing the intake of dietary AGEs (meals were provided to participants) for 6 weeks contributed to decreased levels of circulating AGEs and inflammatory markers (vascular adhesion molecule 1 and TNF-α).[30] In another study, 24 patients with diabetes mellitus were randomized to 1 of 2 groups with different diets for 6 weeks (meals were provided), one with a high level of dietary AGEs and the other with low AGEs. It was found that the LDL in the group with high dietary AGEs intake was more glycated than in the group with low AGEs intake.[62] In addition, the acute effect of a meal rich in dietary AGEs has also been measured in type 1 and type 2 diabetes mellitus. It was found that flow-mediated dilation of the brachial artery (used as a measure of endothelial function) decreased after a single challenge with dietary AGEs and inflammatory markers as vascular adhesion molecule 1 increased.[109,111] Finally, a recent study in patients with type 2 diabetes mellitus ($n = 18$) and healthy controls ($n = 18$) found a lower homeostatic model assessment and lipoxidation markers in subjects with lower dietary AGEs intake. The participants were randomly assigned to a low dietary AGEs (instructions were given for lowering AGEs in foods) or left with their usual dietary AGEs intake (around 20 equivalent of AGEs, measured by 3 days of dietary records) during 4 months. Patients assigned to the low dietary AGEs diet had lower levels of serum carboxymethyl-lysine, methylglyoxal, 8-isoprostane (a lipoxidation marker), and insulin, as well as a lower homeostatic model assessment when compared with the subjects with the regular dietary AGEs intake.[74]

Table 1. Clinical Studies With Dietary AGEs Restriction in Human Subjects

	Study	Design	Diets	Results
Vlassara et al (2002)[30]	11 subjects with DM	2 weeks crossover; meals were provided to participants with different AGEs content	Low AGEs: 3.67 ± 1.2 × 10^6 AGEs units	Serum AGEs ⇓ 30%, VCAM-1 ⇓ 50%
			High AGEs: 16.3 ± 3.7 × 10^6 AGEs units	Serum AGES ⇑ 64%
	13 subjects with DM	6-week study; meals were provided with different AGEs content	Low AGEs: 3.67 ± 1.2 × 10^6 AGEs units	CML ⇓ 40%, CRP ⇓ 20%, VCAM-1 ⇓ 20%
			High AGEs: 16.3 ± 3.7 × 10^6 AGEs units	CML ⇑ 28%, CRP ⇑ 35%, TNF-α ⇑ 86%
Uribarri et al (2003)[106]	26 subjects with peritoneal dialysis (non-DM)	4-week study; participants ate meat cooked with different methods	Low AGEs: basal, 13.8 ± 3; final, 17 ± 3 × 10^6 AGEs units	Serum CML ⇓ 34%, MG ⇓ 35%, and CML-LDL ⇓ 28%
			High AGEs: basal, 12.4 ± 1.5; final, 5.5 ± 0.9 × 10^6 AGEs units	Serum CML ⇑ 29%, CML ⇑ 26%, and CML-LDL ⇑ 50%
Cai et al (2004)[62]	24 subjects with DM	6-week study; meals with different AGEs content	Low AGEs: 3.67 ± 1.2 × 10^6 AGEs units	LDL was 50% less glycated and 80% less oxidized
			High AGEs: 16.3 ± 3.7 × 10^6 AGEs units	⇑ MAPK phosphorylation, NF-κB activity, and VCAM-1 production on endothelial cells
Negrean et al (2007)[109]	20 subjects with DM	6-day study; acute effect of 2 different AGEs diets on days 4 and 6; single meal was provided	Low AGEs meal: 2750 kU	CML and MG ⇓
			High AGEs meal: 15 100 kU	CML and MG ⇑ after 4 hours. Impaired macrovascular function: flow-mediated dilation ⇓ 36.2%. Markers of endothelial dysfunction: E-selectin ⇑ 51%, ⇑ I-CAM and ⇑ VCAM. Marker of oxidative stress, TBARS ⇑ 21%
Stirban et al (2008)[110]	20 subjects with DM	6-day study; acute effect of 2 different AGEs diets on days 4 and 6; single meal was provided	Low AGEs meal: 2750 kU	
			High AGEs meal: 15 100 kU	Leptin and adiponectin ⇓
Vlassara et al (2009)[28]	40 healthy subjects	4-month study; instructions to change cooking methods	>13 AGE 10^6 AGEs units	Low AGEs: Reduction on CML, MG, and AGER1, RAGE, and p66Shc, 8-isoprostane, VCAM-1 and TNF-α
	9 CKD-3 subjects	4-week study; instructions to change cooking methods		
Birlouez-Aragon et al (2010)[97]	62 healthy subjects	4-week study; meals were provided with different cooking preparations	Low AGEs: 2.2 ± 0.9 mg	⇓ Total cholesterol, HDL, and triglycerides
			High AGEs: 5.4 ± 2.3 mg	⇑ CML, fasting insulinemia, HOMA
Uribarri et al (2011)[74]	18 healthy and 18 subjects with DM	4-month study; instructions to change cooking methods	High AGEs: 20 000 kU AGEs	Low AGEs: Lower levels of CML, MG, 8-isoprostane (a lipoxidation marker), and insulin in serum, as well as a lower HOMA

Abbreviations: AGEs, advanced glycation end products; DM, diabetes mellitus; AGER1, AGEs receptor 1; CML, carboxymethyl-lysine; CML-LDL, carboxymethyl-lysine low-density lipoprotein; CRP, C reactive protein; HDL, high-density lipoproteins; HOMA, homeostatic model assessment; ICAM-1, intracellular adhesion molecule 1; MAPKs, mitogen-activated protein kinases; MG, methylglyoxal; p66 Shc, Shc adaptor protein; RAGE, receptor for AGE; TBARS, thiobarbituric acid-reactive substance; TNFα = tumor necrosis factor α; VCAM-1, vascular adhesion molecule 1.

These results suggest that dietary AGEs could exert similar effects as those studied from endogenous AGEs. However, it is important to note that the same research group has performed most of the intervention studies presented here, and more studies from different groups are needed to corroborate these results.

Antiglycative Dietary Factors

There are a number of different pathways by which glycation of end products may be interrupted. These include cleaving AGEs crosslinks; blocking of RAGE; blocking carbonyl groups on reducing sugars, Amadori products, and 3-deoxyglucosones; deglycating Amadori products (Amadoriases); protecting against glycation-derived free radicals (antioxidants); and preventing autoxidation of glucose and Amadori products through chelators that remove transition metals. These last 4 processes are thought to occur through food or food components. The first 2 processes occur through pharmacological means.[112]

The most profuse process for antiglycation is through antioxidants, which scavenge free radicals. Antioxidants are abundant in foods containing large amounts of vitamins C and E, carotenoids, and selenium, as well as phenolic compounds such as anthocyanins, flavonoids, catechins, and lipoic acid. These nutrients and food components are present in fruits and vegetables (vitamin C, anthocyanins, flavonoids), green tea (catechins), nuts seeds and oils (vitamin E), wine and chocolate (flavonoids), and liver, spinach, broccoli, and potatoes (lipoic acid). Additional food components with antioxidative properties include curcumin and aged garlic extract.[112]

Aged garlic extract contains a higher concentration of antioxidants than whole garlic. During the aging and extraction over 10 months, the garlic can become odorless as the organosulfur compounds become water soluble.[113] The aged garlic extract contains many compounds that have been investigated for health benefits, including lectins, fructooligosaccharides, apigenin, which is a flavonoid, fructosyl arginine, which is a Maillard reaction product, and tetrahydrocarbolines.[114] Although aged garlic extract has primarily been investigated for cardiovascular,[115,116] cancer,[117-119] and immune system effects,[120] it has also been used in in vitro experiments to determine its ability to inhibit AGEs products. Aged garlic extract inhibited the crosslinked glycation end products and an ingredient of garlic extract, *S*-allyl cysteine, also inhibited non-crosslinked AGEs.[121] An in vitro study also found that aged garlic extract scavenged superoxide radicals in at dose-dependent manner over 3 dosages.[113]

Curcumin is a major component of turmeric, a popular ingredient in Asian foods. Curcumin has been reported to interact with a number of immunoregulatory enzymes and transcription factors, and therefore has been evaluated for its role in cancer treatment and prevention,[122,123] as well as inflammatory conditions,[124] dementias,[125] and obesity-related disorders.[122] However, intestinal metabolism of curcumin results in metabolites with short half-lives and limited cell permeability.[126] Nevertheless, numerous studies have reported antidiabetic properties of curcumin.[127] In one animal study, diabetic rats fed curcumin with their diet for 16 weeks had lower fasting blood glucose and urinary glucose as compared with control animals. A variable effect of curcumin on lysosomal enzymes was found depending on which lysosomal enzyme and where in the body it was measured.[128] However, one animal study reported increased oxidative stress and AGEs formation with hyperglycemic animals fed curcumin, as evidenced by faster cataract formation. Nondiabetic rats showed beneficial effects at very low levels of curcumin.[129] Recently, an in vitro work concluded that curcumin induced gene expression of AGE-receptor 1(AGER1), which facilitates the clearance of AGEs.[130]

Other antioxidants have also shown promising results in animal and in vitro studies. A number of fruits, vegetables and herbs were evaluated using in vitro techniques to assess their antiglycation ability. Ginger, cinnamon, and cumin have been reported to reduce AGEs formation in vitro by more than 50% at 1.0 mg/mL.[131] In one animal study, the phenolic acids, caffeic acid and ellagic acid, were added to mouse chow at 2.5 or 5 g per 100 g diet and fed to diabetic mice for 12 weeks. Hemoglobin A1c, glycated albumin, and renal carboxymethyl-lysine levels were lower for animals fed the phenolic acids, with more significant effects seen with the higher intakes.[132] A study to investigate the effects of Pu-erh tea, which is a fermented tea, on AGEs accumulation associated with diabetic nephropathy found that Pu-erh tea prevented diabetes-induced accumulation of AGEs and led to decreased level of RAGE expression in glomeruli.[133] In another animal study, green tea extract was administered to rats for 4 weeks (300 mg per kg body weight per day). Fluorescence of AGEs, blood glucose, and hemoglobin A1c was significantly reduced when compared with diabetic rats not receiving the extract ($P < .05$).[134] However, in a study where green tea or vitamins C and E were added to the rats' drinking water, there was no difference in glycemia when compared with control animals but did decrease lens fluorescence. Surprisingly, the group fed the additional vitamins C and E exhibited worsened collagen glycoxidation in certain tissues. Additionally, tendon breaking time in urea, which can be used as a marker for total crosslinking, increased with both vitamin C and E administration and with green tea, leading the authors to speculate that treatment of oxidative stress alone may not ameliorate complications of diabetes, but that other stresses as well as attention to intracellular and extracellular activities, could be important.[135] Indeed, in vitro experiments suggest some caution concerning flavonoids and AGEs. In general, lower concentrations were found to be inhibitory whereas higher concentrations were more often enhancing of carboxymethyl-lysine production, presumably through increased hydrogen peroxide production.[136]

Few studies have evaluated these foods or ingredients in human studies. However, Klein et al[137] evaluated mate tea's impact on blood glucose and lipid values in diabetes and prediabetes. Each group was divided into receiving the mate tea, an educational intervention, or both the tea and education. Those instructed to drink the tea were to make it from 6.6 g of yerba mate leaves and 330 mL of boiling water, drinking the

330 mL three times per day for 60 days. No differences were found in the prediabetes group across treatments. In the diabetes group, those drinking mate tea demonstrated significant decrease in blood glucose and hemoglobin A1c.[137]

Of course, drugs have been developed for their antiglycation properties, particularly alagebrium, which has been shown to have positive effects in animal models.[108,138]

Summary and Implications for Research

The health impact of dietary AGEs has increasingly been studied since recognition of their potential deleterious effects. Some of these effects can be attributed to changes in the nutritional composition of the foods from which the dietary AGEs are derived. The nutritional consequences of the Maillard reaction in foods include the loss of some amino acids, such as lysine, arginine, tryptophan, and histidine. Good indicators of loss of lysine in foods are furosine, pyrraline, and carboxymethyl-lysine.[100] There is also some evidence that AGEs could affect mineral metabolism. Studies in rats have shown increased urinary excretion of calcium, magnesium, sodium, zinc, and copper compared with animals fed a control diet.[17] Similar studies in adolescents have shown impaired iron bioavailability.[139]

Second, dietary AGEs can have an impact on health through a variety of systematic mechanisms. Studies focusing on the effects of dietary AGEs have been shown to increase circulating AGEs, to accumulate in tissues, to affect endothelial function, to increase pro-inflammatory cytokine and oxidation markers, and to act as a ligand for the advanced glycation end products receptor (RAGE). Furthermore, data from our group show that AGEs intake was higher in participants with presence of cardiovascular disease complications when compared with those without complications.[140]

Although a role for AGEs in diabetes-related complications seems well supported by the literature, in other areas the role of AGEs in general and dietary AGEs in particular is less clear. For instance, there is no consensus among the researchers investigating dietary AGEs about their health impact, probably because of the diversity in AGEs, their effects, and dose–response issues. Indeed, some studies have found some beneficial or no effects from dietary melanoidins (late products of Maillard reaction in foods) or other AGEs such as pentosidine. For instance, Ames et al[141] found that melanoidins from bread crust increased the number of anaerobes, clostridia, and bifidobacteria in a culture of human fecal bacteria, indicating a possible potential prebiotic effect of bread crust melanoidins.[142] In addition, other study showed an increase in the activity of chemopreventive enzymes as glutathione-*S*-transferase.[143]

Moreover, AGEs heterogeneity has made measuring them in foods and comparing data from different research groups difficult. Also, only short-term effects have been measured and long-term effects have not been studied yet. The methodological design of long-term studies represents a great challenge. One of the difficulties is achieving diets with different dietary AGEs content, but with similar content in other nutrients, such as heat-sensitive vitamins. Pouillart et al[144] demonstrated that diets with different dietary AGEs content but similar thiamine, vitamin E, and other heat-sensitive vitamins content, are challenging but possible.

Future studies on the role of dietary AGEs on diabetes mellitus and their related complications also should address the methodological problem for their measurement in the diet. Most studies of dietary AGEs have used 3 days food records for their quantification in the diet. However, 7 days food records are better for measuring proteins and fat.[145] Although the database for dietary AGEs has grown, consensus about how dietary AGEs should be measured has not been reached. Finally, human studies including antiglycation food products need to be conducted to elucidate any valid role these foods and food components may have in health.

Author Contributions

CLC provided the first draft of the article with MEGS submitting the section on Metabolism and Receptors of AGEs and KCN submitting the section on Antiglycative Dietary Factors. All authors reviewed the final draft with minor modifications.

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