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Dietary Advanced Glycation End Products and Cardiometabolic Risk

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Abstract
Purpose of Review This report analyzes emerging evidence about the role of dietary advanced glycation end products (AGEs) as a cardiometabolic risk factor. Two important aspects are discussed: First, the modulation of AGE load by dietary AGEs; second, if the evidence of clinical and observational studies is enough to make dietary recommendations towards lowering AGE intake.
Recent Findings Clinical studies in subjects with diabetes mellitus have shown that high intake of dietary AGEs increases inflammation markers, oxidative stress, and could impair endothelial function. In subjects at risk for cardiometabolic diseases (with overweight, obesity, or prediabetes), dietary AGE restriction decreases some inflammatory molecules and improves insulin sensitivity. However, studies in healthy subjects are limited, and not all of the studies have shown a decrease in circulating AGEs. Therefore, it is still unclear if dietary AGEs represent a health concern for people potentially at risk for cardiometabolic diseases.
Summary The evidence shows that dietary AGEs are bioavailable and absorbed, and the rate of excretion depends on dietary intake. The metabolic fate of most dietary AGEs remains unknown. Regardless, most studies have shown that by diminishing AGE intake, circulating levels will also decrease. Thus, dietary AGEs can modulate the AGE load at least in patients with DM, overweight, or obesity. Studies with specific clinical outcomes and large-scale observational studies are needed for a better risk assessment of dietary AGEs and to establish dietary recommendations accordingly.

Keywords Cardiometabolic risk · Advanced glycation end product · Maillard reaction · *N*-ε-(carboxymethyl)-lysine · Dietary AGEs

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Introduction

Cardiovascular diseases (CVD), such as coronary heart disease (CHD), cerebrovascular disease, and chronic heart failure (CHF), along with related complications from diabetes mellitus (DM) are the primary cause of death globally [1]. A close relationship between DM and CVD has been shown to exist: Patients with DM have a high risk of atherosclerotic CVD [2•, 3], and the Framingham Heart Study showed that the risk of CHF and CVD death was doubled in men and tripled in women with DM [4]. The prolonged exposure to hyperglycemia plays a decisive role in the atherosclerotic damage which could progress to CVD in DM [2•]. It is important to know the factors associated with these diseases to prevent deaths attributable to them. The cardiometabolic risk is defined as the cluster of traditional factors for CVD (hypercholesterolemia, hypertension, smoking, age, and male gender) in addition to the metabolic syndrome presence [5, 6], or in other words, the overall risk of presenting CVD and DM [5, 7]. Obesity (a body mass index (BMI) higher than 30 kg/m^2), physical inactivity, and the modern diet are also significant cardiometabolic risk factors [1, 6, 8]. Indeed, the modern diet (standard western diet), which is high in fat, rich in red meat, processed foods, and primary sources of some compounds called advanced glycation end products (AGEs) [9], has some deleterious effects on cardiovascular physiology, particularly in the context of diabetes [10]. This review will present information about

the relationship of AGEs with diabetes, CVD, and the underlying mechanisms, insulin resistance, oxidative stress, and low-grade inflammation. Additionally, the implication of dietary AGEs as a risk factor for cardiometabolic diseases and interventions designed to reduce AGE load will be discussed.

Advanced Glycation End Products in Diabetes and Cardiovascular Diseases

Advanced glycation end products (AGEs) are a large and heterogeneous group of compounds that can have an endogenous or exogenous origin. AGEs have been associated with DM and its complications and more recently with different diseases such as CVD, arthritis, cancer, osteoporosis, and Alzheimer disease [11, 12].

Endogenous Formation of AGEs

Endogenous AGEs are mainly formed by the Maillard reaction as part of physiological metabolism and normal aging. However, several factors could increase AGE production, such as hyperglycemia [11], oxidative stress [13], and an increase in free radicals by transition metals [14]. AGE formation is a complex process involving several substrates (such as amino acids, reducing sugars, and dicarbonyls, among other) and different endogenous pathways. For instance, the Namiki pathway, the Wolf pathway, the autoxidation of glucose, the lipid peroxidation, and the polyol pathway also participate in AGE formation by producing short-chain reactive carbonyl species known as α-oxaldehydes or α-dicarbonyl (such as glyoxal and methylglyoxal (MG)) [15–17]. These α-dicarbonyls can form AGEs by reacting with an amino acid or by acting as a substrate for the Maillard reaction [17].

The Maillard reaction refers to many subsequent and parallel reactions that can be described in three phases. The first phase starts with a nucleophilic addition between a free amino group of a biomolecule (mainly primary amines, R-NH2, commonly from lysine and arginine) and a carbonyl group of a reducing sugar. This first reaction forms a Schiff base. Then, through a more stable rearrangement, ketoamines known as Amadori products are formed. Finally, through several reactions including dehydration, cyclization, fragmentation, and oxidation, the irreversible compounds known as AGEs are formed [18].

The wide range of precursors and the several pathways leading to AGE formation contributes to heterogeneity of AGEs with the difference in their structures and properties. For instance, fluorescent AGEs, cross-linking AGEs, and low- and high-molecular-weight AGEs (depending if they bind to amino acids, peptides or proteins). *N*-ε-(carboxymethyl)-lysine (CML) is perhaps the most studied AGEs, and it is used as glycation markers for several chronic diseases [19, 20]. A list of some representative AGEs is shown in Fig. 1.

AGES in Diabetes and Cardiovascular Disease, Mechanism of Action

Accumulation of AGEs in tissues and urine has been found in healthy aging and in vascular and metabolic disorders like diabetes mellitus, atherosclerosis, and renal disease [11, 21]. AGEs may cause cardiac and vascular dysfunction in two ways: by increasing vascular and myocardial stiffening, through the cross-linking of elastin and collagen which results in the development of stiffness of blood vessels and cardiac fibrosis, and by stimulating inflammation and oxidative stress (OS) through the receptor for advanced glycation end products (RAGE) [22–24]. Therefore, AGEs can induce tissue damage by the following mechanisms, through a receptor-independent mechanism and a receptor-dependent mechanism.

Receptor-Independent Mechanism

The proper function of proteins is disrupted after glycation by changing their molecular conformation, thus altering their biologic function and interfering with receptor recognition [25].

The increased endogenous production of AGEs in DM has been associated to cross-linking of body proteins. Long-lived proteins as extracellular matrix proteins, such as collagen type I, type IV, and elastine, are more often glycated. Therefore, AGEs cross-linking with proteins depends on glucose concentration and the turnover rate of proteins [22, 26]. AGEs cross-linking with vascular and myocardial collagen may contribute to increased vascular and myocardial stiffness, and cause the diastolic dysfunction observed in DM and aging [22].

Other proteins are also prone to cross-linking, for example, the low-density lipoprotein (LDL). Two components of this lipoprotein are glycated, the apolipoprotein B and the phospholipid. After glycation, there is a reduction in LDL uptake and clearance by its receptor. Consequently, glycated LDL accumulates in circulation and its uptake by monocyte-derived macrophages stimulates the formation of foam cell which promotes atherosclerosis [25].

Receptor-Dependent Mechanism

Receptor-dependent damage has an essential role in related complications from DM, CVD, and other chronic diseases. It is triggered by the binding of AGEs to the cell surface receptor for AGEs, RAGE. Since RAGE discovery, significant progress has been made in understanding its function [27]. RAGE is a multi-ligand cell surface receptor of the immunoglobulin superfamily with three extracellular immunoglobulin domains, C1, C2 and V [28, 29]. Different cell types express RAGE, for example, endothelial cells, adipocytes, podocytes, cardiomyocytes, neutrophils, monocytes/macrophages, and T and B lymphocytes [28].

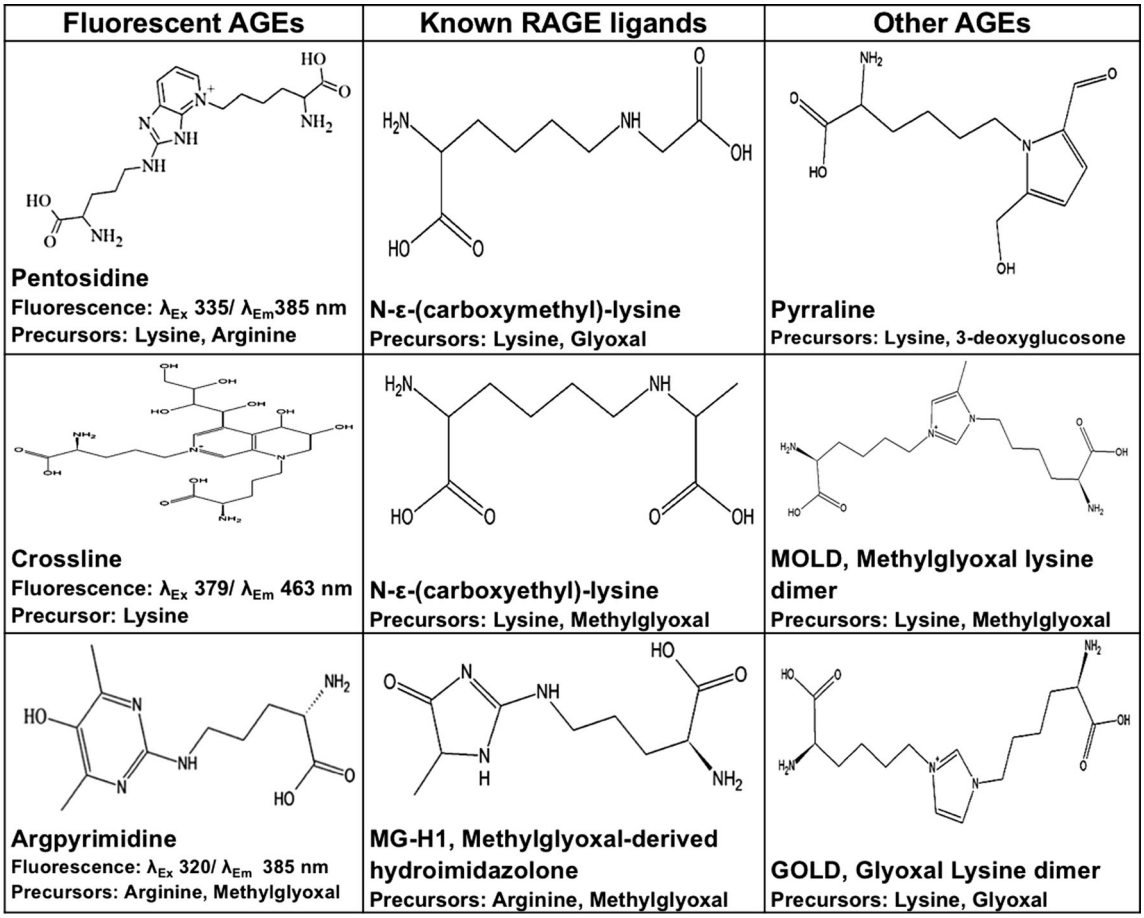

Fig. 1 Some representative AGEs are shown, AGEs intrinsically fluorescent, known RAGE ligands, and other AGEs

AGEs bind to RAGE activating several intracellular pathways that increase oxidative stress and proinflammatory molecules [28, 30]. RAGE activation triggers several signaling cascades: mitogen-activated protein kinases (MAPKs), p21 RAS, p38, extracellular signal-regulated kinase (erk) 1/2, and the nicotinamide adenine dinucleotide phosphate oxidase (NADPH), a complex of enzymes which enhances production of reactive oxygen species (ROS) [31]. These signaling cascades trigger the activation and translocation of the nuclear factor κB (NF-κB) from the cytoplasm to the nucleus. Thereafter, NF-κB will trigger the transcription of genes for several proinflammatory cytokines [such as interleukin 1α (IL-1α), interleukin 6 (IL-6), and tumor necrosis factor-α (TNF-α)], growth factors, and adhesive molecules [like intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), endothelin-1, tissue factor, vascular endothelial growth factor (VEGF), E-selectin, and thrombomodulin] [30–33]. These cytokines and adhesion molecules have roles in both inflammation and atherosclerosis [22, 28, 34]. RAGE transcription is also regulated by NF-κB. Therefore, AGE-RAGE interaction promotes the maintenance and amplification of the signal with a sustained induction of the inflammatory response, the prothrombotic activity, and the expression of adhesion molecules [28, 30] (Fig. 2).

Other AGE cell receptors include oligosaccharyltransferase complex protein-48 (AGE-R1), 80 K-H protein (AGER2), and galectin-3 (AGE-R3), which have a different function, clearance of AGE [35, 36]. Only a few AGEs have been shown to bind RAGE, imidazolone-type AGEs [37], and two well-characterized AGEs, CML, and CEL are physiological ligands for RAGE [29, 38]. As previously mention, CML (major AGE in vivo) is of significant importance, and most studies have focused on this AGE.

Dietary Ages and Their Cardiometabolic Effects

Dietary AGEs, Formation, and Sources

Glycation was first described by Louis Camille Maillard at the beginning of the nineteenth century when he heated a mixture of amino acid and sugar, and it became brown [39•]. With this work, he set the basis for the study of the browning reaction that occur in foods while cooking, roasting or baking. During the 1940s, the need for nonperishable dried foods increased the interest in the Maillard reaction [39•]. Since then, food scientists have used it to explain the darkening of fruits, the

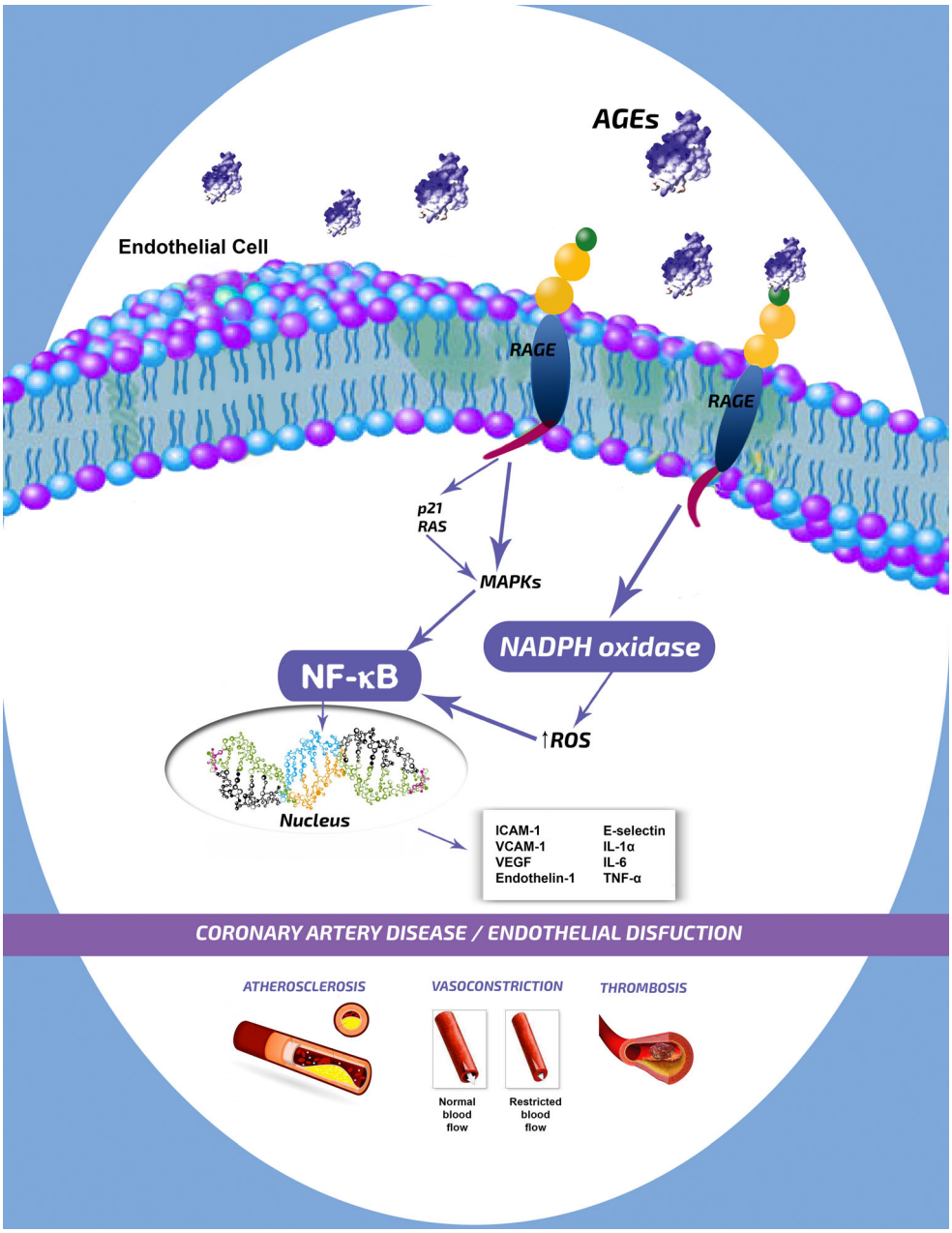

Fig. 2 Interaction of AGEs with RAGE. *AGE* = advanced glycation end product; *RAGE* = receptor for AGE; *MAPK* = mitogen-activated protein kinases; *NAD(P)H oxidase* = enzymes complex which produces superoxide; *TNF-α* = tumor necrosis factor α; *IL-6* = interleukin 6; *VCAM-1* = vascular adhesion molecule 1; *ICAM-1* = intracellular adhesion molecule 1; *Erk* = extracellular signal-regulated kinase (erk) 1/2; *ROS* = reactive oxygen species; *NF-κB* = nuclear factor κB; *IL-1α* = interleukin 1α; *VEGF* = vascular endothelial growth factor; E-selectin

modification of milk during storage, and the production of pleasant aromas in some foods [40]. Even when this reaction was widely used for a long time, it was until the late 1980s that scientists started to hypothesize that exogenous AGEs could have a detrimental effect on health [41].

Besides the Maillard reaction, dietary AGEs can be formed by autoxidation of fatty acids [42]. There are a wide variety of AGE precursors, such as reducing sugars, amino acids and peptides with a free amino group, and fatty acids. Therefore, different aroma and color molecules, as well as different molecular weight compounds, can be included in the dietary AGEs group [18]. Several factors affect the amount and rate of AGE formation in foods besides cooking time; four factors will be briefly described next. Temperature notably affects the Maillard reaction in foods. The high cooking temperature for extended periods of time favors AGEs formation, e.g., grilling, roasting, and frying [9, 43]. pH is also fundamental for favoring or interfering with the reaction. Indeed, an alkaline pH favors Schiff base formation, and the optimum pH for AGEs formation is around 10. In contrast, low pH decreases the reaction, and the use of acidic ingredients like vinegar or lemon juice reduces AGE formation in meat [9, 18, 41]. Substrate concentration is critical for any reaction, and in this case, the amino group's concentration from foods is highly relevant [18, 44]. Thus, reduction of foods rich in protein reduces AGE intake. Moisture is also an essential factor for favoring or interfering with the reaction. Meals prepared with water or other

liquid are less likely to form AGEs. During the condensation reaction between the carbonyl and the amino group, a molecule of water is released; thus, in aqueous media, the reaction equilibrium is displaced decreasing AGEs formation. Hence, boiled or steam foods are less prone to form AGEs [9].

Therefore, foods rich in protein and fat had the highest amount of AGEs. Cereals had a lower AGEs amount, but this could increase depending on the processing. Foods that are fried, broiled, grilled, or roasted would produce higher AGEs than foods that are boiled, poached, stewed, or steamed [9, 42, 45, 46••].

As mentioned before, the formation of dietary AGEs is a complex process involving several reactions and many end products. Because of this heterogeneity, one of the challenges in their study is their characterization and measurement in foods. Only a few AGEs, among them CML and pentosidine, have been widely determined in food matrixes [47–49]. Several analytical techniques are used, but chromatographic methods coupled to mass spectrometers are the more accurate and sensitive methods for AGEs quantification [50].

Dietary AGEs and Mechanisms of Action

In addition to endogenous AGEs, mainly formed by cellular metabolism, dietary AGEs may also have a role in cardiometabolic health. Dietary AGEs could act synergistically with endogenous AGEs, and increase systematic AGE load. They can have an impact on health at least through two mechanisms: by accumulating in tissues, thus modifying proteins, and by interacting with RAGE, thus increasing pro-inflammatory and pro-oxidant status. But first, important questions to be addressed are if dietary AGEs are bioavailable and absorbed, and if they could increase AGE load.

Dietary AGE Contribution to Systemic AGE Load: Role of Absorption and Bioavailability

Several cross-sectional and intervention studies have shown positive correlations between circulating AGEs and their intake, as measured by food records. These results have been found in subjects with kidney disease, with DM, and in young and older healthy subjects [51–55]. However, the correlation between dietary AGEs and circulating levels of AGEs does not represent AGEs absorption. Hence, it is important to review bioavailability and absorption mechanisms for dietary AGEs. Pioneering work by Koschinsky and He et al. studied the percentage of absorption after an AGE rich meal in 38 subjects with DM and five healthy subjects. They measured AGEs by ELISA in serum and urine 24 h before and 48 h after the meal, and only around 10% of ingested immunoreactive AGEs were found in circulation. One third (from the 10%) was excreted via the kidneys, and two thirds remain in the body with unknown fate [56]. He et al. also found that intestinal absorption was around 10% (within 72 h) after feeding rats with AGEs bound to a 125I-labeled protein [57].

From these results, it seems that the amount of absorbed AGEs is minimal. However, the concentration of AGEs in a typical diet is much higher (10–50 times) than the levels found in serum, plasma or tissues [58]. The bioavailability of each dietary AGE depends on their structure and if they are bound or not to proteins [39•]. Hence, to address if AGEs are bioavailable, Hellwig et al. used a simulated gastrointestinal digestion system to investigate if dietary AGEs are available for absorption. Casein bound to fructolysine (FL), and CML were used and put through two proteolysis analysis. FL and CML were released from casein in peptides with a weight less than 1000 Da similar to native amino acids. Thus, the authors concluded that FL and CML are available for absorption [59••]. Regarding absorption mechanism, an in vitro study demonstrated that free or protein-bound dietary AGEs could be absorbed by simple diffusion or by endocytotic processes. For instance, free CML is absorbed by simple diffusion [18]. Some AGEs that remain bound to small peptides could be absorbed by the peptide transporter hPET1, that is, the case for CML, CEL, pyrraline, and MG-H1 in dipeptides [60, 61].

Kinetic studies in healthy subjects have demonstrated that the rates of excretion and absorption are influenced by dietary intake, at least for pyrraline, pentosidine and CML [62, 63]. Hence, from the previous discussion, it could be concluded that dietary AGEs are bioavailable and are absorbed, and the rate of excretion depends on dietary intake.

Dietary AGE Distribution and Accumulation in Tissues

After absorption, the metabolic fate of AGEs is unknown. Miyata et al. injected marked pentosidine in mice and found that 80% of the radioactivity was recovered in the urine within 72 h, but only 16% was identified as intact pentosidine and 64% was modified [64]. Another study found that after feeding rats with protein-bound labeled CML, the 86% was found in urine and feces, but the fate of the 14% was unknown [57].

Two possibilities have been proposed for the fate of the fraction unaccounted for, transformation to other metabolites, and accumulation in tissues. Indeed, experimental studies have found a higher accumulation of CML in the heart, tail tendons, kidney, and liver of animals fed with high-AGE diets. For instance, He et al. fed rats 5 days with a protein-bound labeled AGEs and found greater deposition in the kidney, lung, and liver [57]. Roncero-Ramos et al. found that high intake of CML for 88 days could result in their accumulation in tissues, specifically in the heart and tail tendons [65•]. Additionally, Li et al. studied the influence of high-CML diet on rats with a high-fat diet, and they found that rats with the higher CML consumption had increased protein-bound CML accumulation in the kidney, heart, lung, pancreas, and muscle [66•]. Recently, Tessier et al. in a groundbreaking study prepared a CML-fortified protein which was

added to mice diets. Moreover, they used a new analytical protocol which discriminated the CML-fortified protein, of dietary origin, from endogenous or native CML. They fed wild-type and RAGE-knockout mice for 30 days with the CML-fortified protein. CML of dietary origin was found in all tissues, except the adipose tissue. The organs with the higher rate of accumulation were the kidneys, ileum, colon, and lungs, and the organs with lower level were the heart, muscle, and liver. The CML accumulation was similar in the wild-type and the RAGE-knockout animals. Thus, it was considered RAGE-independent [67••].

In vitro studies have shown the digestion and absorption mechanism of some AGEs [59••, 60, 61], and in vivo studies observed that CML could be traced into some organs after ingestion [67••]. However, additional studies are needed to strength current evidence and to understand the metabolism of dietary AGEs entirely.

Dietary AGE Interaction with RAGE

One of the controversies in the study of dietary AGEs is if they could interact with RAGE. An in vitro study using serum of patients with DM has shown that RAGE binds mainly to high-molecular-weight ligands. In this study, a greater RAGE binding capacity was observed with serum fractions higher than 30 kDa, as well as modulation of cell-surface RAGE expression, and an increased p65 NF-κB DNA-binding activity [68]. As described before, CML is absorbed as a free CML or bound to small peptides. This raises the question whether dietary AGEs can bind to RAGE. It has been shown that after a high-AGE diet, there is an increase in high-molecular-weight AGEs; therefore, by an unknown mechanism, dietary AGEs could increase the formation of high-molecular-weight AGEs acting as RAGE ligands [54]. In vitro studies have shown an interaction of AGEs of dietary origin with RAGE. Consequently, there may be activation of transduction pathways [69, 70] and an increase in the level of soluble signals such as cytokines and free radicals [29, 71].

In summary, dietary AGEs could modulate and add to the AGE load, accumulate in tissues, and interact with RAGE. Hence, they could indirectly contribute to increasing the pro-oxidant status and the inflammatory response, to affecting endothelial function, and to promoting insulin resistance [53, 55, 72, 73].

In Vivo Effects of Dietary AGEs on Cardiometabolic Diseases

Some of the cardiometabolic effects of dietary AGEs are an increase in pro-inflammatory, oxidation and angiogenic markers, which could lead to endothelial dysfunction and insulin resistance. These effects have been described in several animal and human studies. A brief description of recent research is presented next.

Animal studies have shown the relation between dietary AGEs and outcomes related to cardiometabolic diseases. These changes have been found not only in long-term studies but also in short-term interventions. For instance, Poulsen et al. showed that RAGE expression could be modified in rats only after 2 weeks of a high-AGE diet [74•]. In a long-term study, Xing and Gao-Xong, et al. fed normal and diabetes-induced mice with a control diet and with a high-AGE diet for 12 weeks. They found increased levels of AGEs, TNF-α, IL-6, LDL, ROS, and RAGE protein/messenger RNA (mRNA) expression, and decreased superoxide dismutase (SOD) levels in diabetes-induced mice with the high-AGE diet. Interestingly, the normal mice with high-AGE diet had also similar changes in comparison with the low-AGE diet [75•]. In another long-term study, Grossin et al. evaluated wild-type and RAGE knockout mice (used as a model of vascular aging). Mice followed either a control diet or CML-enriched diets during 9 months. In the mice fed with CML diets, endothelium-dependent relaxation was reduced, RAGE and VCAM-1 expression were increased in the aortic wall, and the aortic pulse wave velocity was increased. Thus, the authors concluded that CML-enriched diets induced endothelial dysfunction and accelerated the development of arterial aging in a RAGE-dependent manner [76•]. Regarding insulin resistance, Coughlan et al. found that a high-AGE diet could modulate defects in insulin secretion and beta-cell death [77]. Furthermore, Cai et al. found that mice developed insulin resistance, after feeding them a diet supplemented with methylglyoxal (MG), and this persisted for four generations [78].

In humans, in addition to correlations found between dietary AGEs and circulating CML, observational studies have found associations with markers related to endothelial dysfunction, inflammation, and oxidative stress, for instance, correlations between dietary AGEs and high-sensitivity c-reactive protein (hsCRP) [52], TNF-α, VCAM-1, 8-isoprostane, and with mRNA RAGE [53]. Additionally, Chao et al. compared healthy subjects ($n = 74$), and subjects with DM either with a low-AGE diet ($n = 50$) or with a high-AGE diet ($n = 58$). They found that subjects with DM with high-AGE intake also had elevated plasma levels of IL-1a, TNF-α, 8-isoprostane, AGEs, HbA1c, LDL, and glycated LDL, as well as lower SOD [79]. Moreover, Angoorani et al. showed that adults with higher intake of AGEs had increased risk for abdominal obesity and hypertriglyceridemia (risk factors for the metabolic syndrome). However, the associations were not independent of dietary energy and macronutrient intake [80•].

The postprandial response to a high-AGE meal have been measured in several studies, and changes in biomarkers of endothelial function such as ICAM-1 and VCAM-1 and flow-mediated dilation have been found in patients with DM. Indeed, Stirban et al. found increased levels of VCAM-1 and E-selectin, and adiponectin and leptin decreased 2 h after an AGE-rich meal [81]. In a similar study, levels of ICAM-1 and VCAM-1 increased 4 h after the high-AGE meal, and flow-mediated dilatation (FMD) and microvascular

function decreased by 20.9 and 67.2% respectively [82]. FMD also decreased in healthy (n = 10) and DM (n = 44) subjects after an oral single AGE-rich beverage [83]. Finally, Poulsen et al. in a study with overweight subjects found that an AGE-rich meal affects postprandial ghrelin, oxidative stress (as measured by urine isoprostane), and glucose response [84].

From these studies, it can be concluded that dietary AGEs correlated with circulating levels of AGEs, inflammatory markers, OS markers, and mRNA RAGE, and can increase inflammation markers and impair micro and macrovascular function.

Modulation of Systemic Age Load

Reduction of Dietary AGEs

Several clinical trials in subjects with renal disease, DM, or both have shown that low-AGE diets reduce circulating AGEs, oxidative stress, inflammation, and angiogenic markers in comparison to high-AGE or standard-AGE diets [55, 85–89]. These studies have been extensively described elsewhere [18, 21, 90•]. Hence, this section will present results of recent low-AGE interventions in subjects with overweight, obesity, and prediabetes. This population is at higher risk for cardiometabolic diseases. Thus, these studies are of interest. Additionally, a few studies in healthy subjects will also be discussed.

A 2 weeks cross-over study in subjects (n = 11) with overweight and obesity found an improvement in the renal function after the low-AGE diet. Also, a decrease in inflammatory molecules [monocyte chemoattractant protein-1 (MCP-1) and macrophage migration inhibitory factor (MIF)] was found [91]. Mark et al. studied 37 overweight women for 4 weeks, and they found that insulin resistance measured by the homeostatic model (HOMA-IR) decreased in the low-AGE diet [92••]. Likewise, de Courten et al. evaluated 20 overweight individuals in a cross-over intervention. Each diet (high or low in AGEs) was given for 2 weeks. They found that insulin sensitivity increased by 1.3 mg/kg/min after the low-AGE diet [93••]. Additionally, a 24-week randomized dietary intervention was conducted in 62 subjects with prediabetes. It was found that subjects in the low-AGE diet had a significant reduction in total cholesterol, apolipoprotein B, LDL, hsCRP levels, and intima-media thickness compared with controls [94]. Finally, in a long-term intervention (1 year) with a low-AGE diet versus a regular diet, Vlassara et al. studied 100 subjects with obesity and a risk factor for metabolic syndrome. They found that the low-AGE diet improved insulin resistance and modestly decreased body weight. Also, AGEs (CML, MG), plasma 8-isoprostane, and inflammatory factors (TNF-α protein, and RAGE mRNA) decreased, and mRNA levels of sirtuin 1, AGER1, and glyoxalase 1 (protective factors) increased [95].

In healthy individuals, a 4-week intervention found a decrease in total cholesterol, HDLc, and triglycerides [54]. A long-term study on the effects of restricted dietary AGEs (4 months) in an elderly healthy group (n = 18) found lower levels of serum CML, MG, 8-isoprostane, and TNF-α when compared with to the regular AGE intake group [55]. However, another intervention in 24 healthy adults after 6 weeks did not find changes in inflammation markers or endothelial function, but the low-AGE diet reduced serum CML and urinary CML [96].

In summary, dietary AGE restriction seems to be a simple, novel, and efficient strategy for decreasing circulating AGEs, pro-inflammatory and oxidation markers, and to improve insulin sensitivity in subjects with overweight, obesity. More studies are needed in healthy subjects.

Exercise Interventions

Physical activity has demonstrated metabolic benefits including a decrease in insulin resistance, glucose, lipids, and BMI in different populations including children, adolescents, and adults [97–99]. The results of a cross-sectional study suggested that endurance exercise could reduce age-related accumulation of AGEs and partially counteract the aging process in connective tissue [100]. For this reason, some studies have evaluated the effect of exercise on AGEs accumulation. These interventions include walking [101], Tai Chi [102], and aerobic training plus exercises with dumbbells [103], and they showed a decreased in serum CML, pentosidine, or total AGEs. Additionally, a study controlling for the effect of the diet found that exercise alone did not diminish CML levels. This 12-week intervention evaluated the influence of 3 different maneuvers: low-AGEs diet, exercise alone, and low-AGEs diet plus exercise (moderate exercise, three times per week). The authors found that the low-AGE diet intervention was more effective for decreasing CML levels, and an additive effect of the low-AGEs diet plus exercise treatment group was reported [104]. Not only that this group decreased CML levels, but also they had a reduction on triglycerides and increased HDLc levels. The authors concluded that perhaps the lack of result on decreasing CML levels with exercise alone was due to the type and intensity of exercise in comparison to other interventions where a decrease in AGEs levels was found [101–104].

Conclusions

Dietary AGEs may act synergistically with endogenous AGEs and have a role in cardiometabolic diseases. Experimental studies in animal models have shown the effect of high-AGE diets, in short-term and long-term interventions, for example, it has been found a greater accumulation of CML in

several organs. Additionally, CML-enriched diets induced endothelial dysfunction and accelerated the development of arterial aging.

In humans, observational studies and randomized clinical trials in patients with DM have shown consistently that dietary AGEs increase inflammation, oxidative stress, and markers of endothelial dysfunction. Also, studies in subjects with a higher risk for cardiometabolic diseases have demonstrated a decreased in some inflammation markers, HOMA, and lipids after a low-AGE intervention. However, a few studies with healthy subjects and a recent large-scale study fail to show an association between individual components of the metabolic syndrome and dietary AGEs after adjusting for energy and macronutrient intake.

Although a role for dietary AGEs in cardiometabolic diseases seems supported by the literature, additional information is needed before dietary recommendations could be made. Some areas demand further research, such as the absorption mechanisms and metabolic fate of dietary AGEs, the analytical measurement of AGEs in foods, and the impact of AGEs on healthy individuals.

The optimal cardiometabolic protection requires making changes in lifestyle to prevent diseases. Therefore, it seems that modification of cooking procedures to diminish dietary AGEs may be a simple, promising approach to decrease AGE load.

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Compliance with Ethical Standards

Conflict of Interest Claudia Luévano-Contreras, Armando Gómez-Ojeda, Maciste Habacuc, Macías-Cervantes, and Ma. Eugenia Garay-Sevilla declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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