Effect of diet-derived advanced glycation end products on inflammation

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Advanced glycation end products (AGEs) formed via the Maillard reaction during the thermal processing of food contribute to the flavor, color, and aroma of food. A proportion of food-derived AGEs and their precursors is intestinally absorbed and accumulates within cells and tissues. AGEs have been implicated in the pathogenesis of diabetes-related complications and several chronic diseases via interaction with the receptor for AGEs, which promotes the transcription of genes that control inflammation. The dicarbonyls, highly reactive intermediates of AGE formation, are also generated during food processing and may incite inflammatory responses through 1) the suppression of protective pathways, 2) the incretin axis, 3) the modulation of immune-mediated signaling, and 4) changes in gut microbiota profile and metabolite sensors. In animal models, restriction of dietary AGEs attenuates chronic low-grade inflammation, but current evidence from human studies is less clear. Here, the emerging relationship between excess dietary AGE consumption and inflammation is explored, the utility of dietary AGE restriction as a therapeutic strategy for the attenuation of chronic diseases is discussed, and possible avenues for future investigation are suggested.

INTRODUCTION

Advanced glycation end products (AGEs) are a heterogeneous class of compounds reported to play a pathogenic role in the development and progression of aging-related chronic diseases. AGEs and their precursors are slowly produced throughout the body during the normal process of aging but are also widely distributed in heat-treated food and in cigarette smoke, providing an additional avenue for AGE accumulation. While excessive endogenous AGE production within the body has been associated with proinflammatory processes underlying conditions such as insulin resistance, atherosclerosis, and the vascular complications of diabetes, less is known about the activity and metabolic fate of diet-derived AGEs. Here, the current state of knowledge about the formation of AGEs and their precursors within food; the digestion, absorption, and excretion of dietary AGEs; and the potential role of dietary AGEs in the etiology of chronic inflammation is presented. In addition, dietary intervention studies involving restriction of AGEs in animals and humans, along with possible strategies for reducing the formation of AGEs in the food supply, are outlined. An enhanced knowledge of how diet-derived AGEs negatively regulate cell metabolism is critical for understanding the links between excess consumption of highly processed diets and development of chronic disease.

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THE MAILLARD REACTION

AGEs are formed via the nonenzymatic reaction of amino acids with sugars, termed the Maillard reaction, which consists of a complex network of degradative reactions.\(^7\) In general, within the early stage of the Maillard reaction, the first stable products to be formed are the Amadori products, generated as a result of condensation reactions and subsequent chemical rearrangement of carbonyl groups of reducing sugars (such as, but not limited to, glucose, fructose, maltose, and lactose) and amino groups of amino acids, peptides, or proteins (see Henle\(^7\) for a more comprehensive review). During the intermediate stages of the Maillard reaction, Amadori products undergo degradation and are subsequently converted to α-dicarbonyl compounds such as 1-deoxyglucosone, 3-deoxyglucosone, glyoxal, and methylglyoxal. Several chemical reactions can produce these highly reactive intermediates, including Schiff base oxidation, degradation of triosephosphates (during glycolysis), and lipid peroxidation (recently reviewed by Rabbani and Thornalley\(^8\)). Subsequently, in the advanced stages of the Maillard reaction, dicarboxyls, which are potent glycating agents, react with lysine or arginine side chains of proteins to form stable peptidyl- and carboxymethyllysine (CML), carboxyethyllysine, pyrraline, pentosidine, crossline, vespersline, glucosepane, and hydroimidazolone adducts.\(^9\)

FACTORS AFFECTING FORMATION OF ADVANCED GLYCATION END PRODUCTS IN FOOD

Food-derived AGEs and their carbonyl precursors are present within highly heated foods and beverages.\(^7,10–14\) The yellow-brown pigment produced by the Maillard reaction contributes to the organoleptic properties of food, such as appearance, flavor, aroma, and texture. In fact, the Maillard reaction is utilized by the food industry to obtain favorable sensory attributes of foods, thereby increasing palatability. Improvements in aroma, taste, and color are the key characteristics provided by AGEs. The majority of the effects of the Maillard reaction within foods are considered desirable to the food industry, such as the golden brown colors or the caramel aromas that develop upon heating.\(^15\) Studies have shown that the Maillard reaction can also give rise to compounds that may exert an antioxidative activity, such as protecting against lipid peroxidation,\(^16–18\) thus potentially promoting stability and longer shelf life.

Since the Maillard reaction represents many thousands of individual reactions, each is influenced by different factors that include temperature, time, water activity, pH, and composition of the system.\(^15\) Factors that enhance food-derived AGE formation include low water content during cooking, increased pH, and the application of high temperatures over a short time period. An increase in temperature increases the rate of Maillard browning. More AGEs are generated in foods exposed to dry heat (grilling, frying, roasting, baking, and barbecuing) than foods cooked at lower temperatures for longer time periods in the presence of higher water content (boiling, steaming, poaching, stewing, or slow cooking).\(^11\) Microwaving does not generate the AGE levels observed during conventional cooking methods because it cooks foodstuffs over a relatively short time period and does not achieve a sufficiently dry environment to result in excessive browning.\(^19\) The addition of sodium bicarbonate (baking soda) during the production of bakery foodstuffs increases the pH of the mixture, enhancing AGE formation and associated browning, whereas the addition of vinegar or lemon juice reduces the pH (increases the acidity) of the cooking environment, lowering the potential for AGE generation.\(^20\)

The chemical structure of individual sugars present within food also determines the level of reactivity to the Maillard reaction, with pentose sugars, such as ribose, reacting more readily than hexoses, such as glucose. In contrast, disaccharides such as lactose are less reactive.\(^15\) Amino acids or peptides with free amino groups must also be present within the food to enable the Maillard reaction to take place. As a result of structural and processing factors, foods thought to contribute large quantities of AGEs and AGE-precursors to the Western diet include powdered milk and cheese; meats, fish, and chicken cooked by dry heat\(^11,12;\) heat-processed or alkaline-treated cereal-based products (bread, biscuits, bakery products, extruded breakfast cereals)\(^7;\) sweet sauces\(^21;\) and carbonated soft drinks containing high-fructose corn syrup.\(^22\) As microorganisms readily produce and release AGEs and their carbonyl precursors, alcoholic drinks and fermented foods also contain significant levels of AGEs.\(^9\)

MEASUREMENT OF ADVANCED GLYCATION END PRODUCTS

A variety of different analytical techniques have been used to measure the AGE content of foods. Most studies have estimated the CML concentration in foods using methods based on an enzyme-linked immunosorbent assay (ELISA). Although ELISA is rapid and inexpensive, most of the available CML ELISAs previously utilized have not been fully validated, and therefore the accuracy and reliability of reported AGE levels based on this technique have been questioned.\(^23\) Incomplete characterization of antibody epitope recognition is the main problem in utilizing immunological techniques to quantify AGE content.\(^24\) The most extensive food AGE
There is a paucity of knowledge regarding the metabolic fate of diet-derived AGEs. It has been estimated that humans consume up to 1200 mg of Amadori products and up to 75 mg of AGEs in food and fluids daily. In food, glycated amino acids are bound in protein and cannot be absorbed intestinally until the proteins are digested by gastric and intestinal peptidases into peptides and free amino acids. AGE-modified peptides are able to penetrate the gastrointestinal mucin layer, where they undergo further proteolytic cleavage into di- and tripeptides at the intestinal brush-border in order to facilitate their absorption. Low-molecular-weight AGEs (AGEs on free amino acids and those bound to di- and tripeptides) are likely to be well absorbed by either simple diffusion or by peptide transporter proteins such as peptide transporter 1. However, crosslinking low-molecular-weight AGEs are less available for absorption because of their resistance to digestive enzymes. Moreover, most high-molecular-weight AGEs also escape digestion in the upper gastrointestinal tract, primarily as a result of crosslinking and protein aggregation, and pass through to the large intestine, eventually being excreted in feces and/or acting as a fermentation substrate for colonic microorganisms. Following bacterial fermentation, amino acids may become available as substrates for the formation of further toxic metabolites.

Kinetic studies have estimated that 10%–30% of diet-derived AGEs consumed are absorbed intestinally and enter the circulation. Studies involving the administration of radioactively labeled AGEs indicate that, in addition to a generalized whole-body distribution, absorbed AGEs accumulate preferentially in renal and hepatic tissue. Whether different postabsorptive AGEs and carbonyl compounds demonstrate unique binding affinities for distinct body proteins is currently unknown.

Currently, limited data are available concerning bioavailability and intestinal absorption of dicarbonyl compounds. Daily dietary intake of 3-deoxyglucosone and methylglyoxal has been estimated to range between 20 and 160 mg and between 5 and 20 mg, respectively. Recent in vitro studies suggest that dicarbonyls can react with digestive enzymes, leading to a reduction in bioavailability. However, this reduction in dicarbonyl concentration may indicate degradation during the process of de novo AGE formation, after which absorption could occur.

A number of human studies have investigated the relationship between dietary AGE intake and circulating AGE levels, with conflicting results. Some studies have found moderate to strong correlations between dietary intake and circulating AGE levels, whereas others have found no association. The conflicting results of these studies are likely due to differences in methods of measuring dietary intake and serum or plasma AGEs, inconsistencies in study duration, variation in the types and preparation of foods administered, and the physiological diversity of research subjects involved. In particular, it is well known that changes in renal function lead to enhanced urinary excretion of AGEs. Urinary excretion of AGEs may also be a more informative marker of whole-body AGE accumulation, although it is difficult.
to differentiate the AGEs generated endogenously from comorbid conditions from those consumed via the diet.

Determining the relative contributions of diet-derived and endogenously produced AGEs to the total AGE content in body fluids and tissues is of particular interest. Urinary CML measurement is often used as a marker of food AGE absorption because it responds rapidly to short-term changes in dietary AGE intake in individuals with efficient renal function. In serum, the concentration of free CML has been suggested to be a better correlate of dietary AGE intake than protein-bound CML. The background AGE content of the diet also appears to influence the efficiency of AGE absorption from food. Urinary CML output appears to correlate with AGE intake but reaches a saturation point at high levels of dietary AGE consumption, and fecal CML excretion also increases in proportion to dietary CML intake. One obvious problem associated with the measurement of CML in body fluids is that it does not provide any indication of the metabolic fate of the many other dietary AGEs entering the body. Future studies investigating the intestinal transit and absorption of dietary AGEs and their dicarbonyl precursors need to be carried out using synthetic AGEs of known molecular weights in order to exclude the confounding effects of food processing and interactions with other dietary components.

The fate of the remaining 70%–90% of dietary AGEs that escape digestion and absorption in the human small intestine warrants further investigation. Since amino acids molecularly modified by heat are more likely to escape digestion in the upper gut, a significant proportion of dietary Maillard reaction products (MRPs) reach the colon, where they may modulate gut microbial growth.35,52

**GUT HOMEOSTASIS**

In vitro studies have shown that glycated proteins encouraged the preferential growth of greater numbers of detrimental colonic bacteria (clostridia, bacteroides, and sulfate-reducing bacteria) when exposed to colonic microbiota derived from patients with ulcerative colitis. Recent studies indicate that consumption of a high-AGE diet for 2 weeks is sufficient to alter the colonic bacteria profile in humans. A 2-week randomized crossover trial in which healthy male adolescents were fed a diet high in MRPs resulted in a decrease in lactobacilli, enterobacteria, and copy numbers of the Escherichia/Shigella group, while the intake of Amadori products (AGE precursors) was negatively correlated with bifidobacterial growth. Parallel studies in male rats fed a diet high in MRPs for 3 months revealed inhibition of the growth of cecal lactobacilli.54

In contrast, Anton et al. found that a highly heat-treated diet improved inflammatory bowel disease in the dextran-sulfate-sodium–induced colitis mouse model. The authors speculated that these MRPs might have encouraged the growth of microorganisms beneficial to the host. Indeed, Borrelli and Fogliano found that MRPs derived from bread crust promoted the growth of species of beneficial bacteria in in vitro studies designed to mimic hindgut conditions. Limitations associated with this area of research include the use of in vitro models unable to replicate the intestinal environment, the large number of different MRPs and their intermediates that can act as potential substrates for bacterial fermentation, and, in human in vivo studies, the use of stool samples, which can indicate colonic bacterial growth but may not adequately reflect microbial activity in the proximal large intestine.

Low-molecular-weight AGEs and their reactive dicarbonyl precursors are most likely absorbed from the diet. However, it is conceivable that, in circumstances of increased intestinal epithelial cell permeability, greater quantities of dietary AGEs may be able to gain entry into the systemic circulation. Indeed, elevated levels of circulating AGEs are frequently observed in individuals with diabetes. Moreover, diabetes is associated with an increased prevalence of upper and lower gastrointestinal symptoms and an increase in intestinal permeability, lending weight to the concept that dietary MRPs may gain access to the circulation through disrupted gastrointestinal physiology. Interestingly, inflamed gut biopsy tissue collected from patients with inflammatory bowel disease demonstrated upregulation of the receptor for advanced glycation end products (RAGE) in tandem with activation of nuclear factor–κB (NF-κB), a major driver of inflammation, suggesting that AGE accumulation within the gut can lead to inflammation. A recent study found that the reactive dicarbonyl methylglyoxyl mediated glycation of tight junction proteins, which impaired protein function, albeit within the blood–brain endothelial barrier. These studies indicate that MRPs/AGEs are likely to have disparate effects within the gastrointestinal tract, which may affect the gut barrier homeostasis.

A recent study found that small intestine segments from streptozotocin-induced diabetic rats had greater AGE protein content, measured by immunohistochemistry, compared with nondiabetic controls, whereas RAGE was increased in the small intestine and the ganglia of the colon. Intestinal AGE–RAGE interactions are likely to stimulate localized production of proinflammatory cytokines and reactive oxygen species (ROS), both of which have been shown to compromise tight junctions between epithelial cells, thereby disrupting the integrity of the intestinal barrier. Increased
gastrointestinal permeability may enable not only AGEs but also other toxic compounds to translocate from the gut into the circulation, activating host immune responses and amplifying inflammatory signals throughout the body. Some studies have demonstrated that a high-AGE diet results in increased intestinal inflammation and reduced antioxidant activity, while others have shown a significant anti-inflammatory effect of AGEs. Exploration of the effect of dietary AGEs on colonic inflammatory processes is also complicated by the production and secretion of AGEs by intestinal bacteria, which are thought to be capable of inducing an inflammatory response in vitro.

One focus of current research is the potential of diet-derived AGE moieties to induce proinflammatory gastrointestinal changes early in the pathogenesis of a number of chronic diseases. Glycation of epithelial intestinal cell tight junction proteins such as zonulin and occludin, as well as excess generation of ROS, may contribute to increased gastrointestinal permeability and inflammation. Additionally, by acting as a substrate for microbial growth in the colon, dietary AGEs may negatively influence the intestinal balance of gut microbiota, resulting in reduced bacterial production of anti-inflammatory short-chain fatty acids and increased movement of luminal endotoxins into the host circulation.

**ADVANCED GLYCATION END PRODUCTS IN THE PATHOGENESIS OF INFLAMMATION AND CHRONIC DISEASE**

Inflammation is an immune response to the presence of harmful stimuli, such as pathogens, toxins, or damaged cells. Acute inflammation is distinguished by redness, swelling, heat, pain, and loss of function and is mediated by a tightly regulated system of complex cell types, with the ultimate aim of promoting healing and recovery. In contrast, chronic inflammation is a maladaptive response to cellular insult that occurs when inflammatory signals and processes are allowed to remain unregulated within the body, giving rise to further damage, stress, and disease. Chronic low-grade inflammation is characterized by elevated circulating levels of inflammatory markers and activated immune cells and is frequently observed in individuals with conditions such as obesity, the metabolic syndrome, diabetes, and cardiovascular disease.

AGEs and their reactive dicarbonyl precursors are generated endogenously as a normal consequence of metabolism and aging, but their formation is accelerated upon increased availability of substrates for AGE generation, such as in the context of hyperglycemia and dyslipidemia. AGE production is also intensified in the presence of increased oxidative stress, which is frequently observed in obese individuals or those with the metabolic syndrome, diabetes, or cardiovascular disease. Excess ROS generate dicarbonyl compounds by interrupting cellular glycolysis, resulting in the accumulation of glycolytic intermediates that feed into the AGE pathway, increasing the production of methylglyoxal. ROS also promote the oxidation of glucose (auto-oxidation) and polyunsaturated lipids (peroxidation), generating AGE precursors that include glyoxal and methylglyoxal. The products of oxidation of unsaturated fatty acids and glycation of the amino group of phospholipids are called advanced lipoxidation end products, many of which appear to exert pathological effects in vivo similar to those of AGEs. Moreover, in individuals with impaired renal function, urinary AGE excretion may be diminished, resulting in a greater accumulation of AGEs in the body, although this does not appear to be the case for all AGEs. Persistent exposure to elevated levels of endogenous and exogenous AGEs or advanced lipoxidation end products are thought to contribute to the pathogenesis and progression of a variety of chronic conditions associated with immune cell activation and low-grade inflammation, including type 1 diabetes, type 2 diabetes, neurodegenerative conditions, allergy, nonalcoholic steatohepatitis, asthma, inflammatory bowel disease, renal disease, and certain cancers (Figure 1).

The pathophysiological consequences of excessive production and accumulation of AGEs may be broadly categorized into 3 major areas. First, AGE modification of extra- and intracellular proteins results in structural and/or functional changes in these proteins. Glycation of long-lived extracellular matrix proteins results in impaired wound healing, changes in both cellular movement and adhesion properties, and dysregulation of intercellular communication. For example, extracellular collagen modified by AGEs has reduced elasticity and solubility, which results in increased vascular stiffness, disturbed cellular attachment, and reduced turnover, all of which contribute to basement membrane thickening. Common extracellular targets of AGE-induced crosslinking include collagen, elastin, tubulin, myelin, and lens crystallins, all of which contribute to the vascular dysfunction associated with aging and diabetes. Inside the cell, AGE modification of mitochondrial proteins results in aberrant electrolyte transport, increased production of ROS, and mitochondrial dysfunction. Dicarbonyl compounds also glycate guanine bases within DNA, contributing to a reduction in DNA replication and an increased frequency of mutation.

Secondly, AGEs themselves are able to catalyze the formation of ROS and incite oxidative stress and inflammation at sites of AGE accumulation. Protein glycation generates stable active centers for catalyzing...
redox reactions and the subsequent formation of free radicals. The generation of a Schiff base by the cross-linking of dicarbonyls to amino groups of proteins yields ROS as a result of the donation of electrons from the Schiff base to the dicarbonyl compound. Excessive ROS are particularly pathogenic to cells that express low levels of detoxification enzymes or limited antioxidant capacity. Pancreatic β-cells are highly susceptible to ROS, with transient elevations in oxidative stress capable of stimulating sustained β-cell dysfunction and death. Indeed, excess consumption of dietary AGEs in rodent models promotes ROS production, leading to defects in insulin secretion as well as β-cell death.

Thirdly, AGEs are able to bind and activate a range of receptors that subsequently trigger a downstream cascade of pathogenic mediators. For example, activation of RAGE promotes sustained activation of NF-κB, with subsequent formation of ROS and upregulation of proinflammatory cytokines such as tumor necrosis factor α (TNF-α), chemokines such as monocyte chemoattractant protein 1 (MCP-1), and profibrogenic mediators such as transforming growth factor-β. Cellular dysfunction and inflammation induced by the AGE-RAGE axis has been implicated in the pathogenesis of multiple chronic conditions, including cardiovascular disease, neurodegenerative disorders, stroke, arthritis, cancer, and complications of diabetes. AGE-RAGE signaling participates in the progression of diabetic nephropathy by enhancing renal mitochondrial production of ROS and glomerular injury, upregulating the expression of transforming growth factor-β and other profibrotic factors. It has been argued that metabolic memory, the observation that the reduced risk of diabetes-related complications associated with a period of good glycemic control can extend for many years after glucose control deteriorates, may be partly mediated by the AGE-RAGE pathway. Indeed, individuals who are relatively free of serious vascular complications after having lived with diabetes for at least 50 years demonstrate lower concentrations of AGE accumulation in tissue.

**THE AGE–RAGE AXIS**

Ligation of AGEs with the cell-surface receptor for AGEs (RAGE, AGER) is currently considered the...
primary mechanism underlying AGE-induced inflammatory processes. RAGE is a multiligand cell-surface pattern recognition receptor. Its ligands include high-mobility group box 1, S-100/calgranulins, amyloid-β-protein, Mac-1, and phosphatidylserine. RAGE is expressed on a range of cell types, including endothelial cells, neurons, smooth muscle cells, lymphocytes, dendritic cells, and macrophages, and RAGE expression is thought to be upregulated in cells and tissue affected by chronic disease. Binding of high-molecular-weight AGEs to RAGE is associated with long-term cellular damage. Engagement of AGEs with RAGE activates NADPH oxidase to increase intracellular ROS production and triggers the sustained activation of NF-κB. Once activated, NF-κB translocates from the cytoplasm to the nucleus, stimulating gene transcription of proinflammatory cytokines (interleukin 6 [IL-6], TNF-α), C-reactive protein, chemokines (MCP-1), procoagulants (thrombin), growth factors (vascular endothelial growth factor), and adhesion molecules (E-selectin, vascular cell adhesion molecule 1 [VCAM-1], and intercellular adhesion molecule 1 [ICAM-1]). NF-κB maintains its own activation by stimulating production of the NF-κB p65 subunit; it also upregulates RAGE expression at the cell surface, thereby amplifying the inflammatory state.

In addition to the NF-κB–dependent pathways, RAGE activates the transcription factors STAT3, AP-1, and forkhead box O1 as well as phosphoinositide 3-kinase/Akt signaling, Jun N-terminal kinase, p38 mitogen-activated protein kinases, extracellular signal-regulated kinases, c-Jun N-terminal kinase, p38 mitogen-activated protein kinases, and ERK.99 The key molecular signature induced by RAGE signaling is inflammation accompanied by cellular migration.69 Indeed, RAGE plays a role in the innate immune system because it can recognize and interact with microbial products (i.e., pathogen-associated molecular patterns) as well as with endogenous molecules released in the context of tissue injury and inflammation (i.e., damage-associated molecular pattern molecules). Recent studies indicate that RAGE is involved in crosstalk with Toll-like receptors to coordinate and regulate immune and inflammatory responses.100

DEFENSE MECHANISMS AGAINST ADVANCED GLYCATION END PRODUCTS

The glyoxalase system

The human body has evolved a number of detoxification systems to reduce the burden associated with AGEs and their dicarbonyl precursors. The glyoxalase system catalyzes the detoxification of a number of dicarbonyls, including methylglyoxal, by conversion to D-lactate. The glyoxalase system consists of the enzymes glyoxalase 1 and glyoxalase 2, and glutathione, a cofactor required for glyoxalase 1 activity.101 Under normal circumstances, more than 99% of intracellular methylglyoxal is detoxified by the glyoxalase system,8 but in circumstances of increased oxidative stress, reactive dicarbonyl compounds accumulate. NF-κB, activated by AGE-RAGE ligation, binds to glyoxalase 1, suppressing its capacity to detoxify dicarbonyls.102 Additionally, an increase in AGE-stimulated production of ROS is believed to deplete cellular levels of glutathione,103 and excessive methylglyoxal intake diminishes circulating glutathione concentrations,104 creating a feed-forward loop of dicarbonyl stress.

It is increasingly appreciated that glucose metabolites can induce inflammation in a variety of settings. In vitro studies have shown that exposure of human vascular endothelial cells to methylglyoxal activates Jun N-terminal kinase and p38 mitogen-activated protein kinase, while glyoxal stimulates cyclooxygenase 2, inflammatory mediators involved in the early pathogenesis of atherosclerosis.105 Administration of methylglyoxal to the microvasculature of healthy mice leads to an increase in leukocyte recruitment, activation of the NF-κB pathway, and upregulation of endothelial cell adhesion molecules.106 Oral consumption of methylglyoxal induced hypertension107 and precipitated inflammatory changes in adipose tissue108 in rats, and acute treatment with methyglyoxal inhibited the contractility of isolated blood vessels.109 Additionally, infusion of methylglyoxal resulted in impaired glucose-stimulated insulin secretion from isolated rat pancreatic islets.78 Chronic dietary intake of methylglyoxal impaired the serine/threonine protein kinase (Akt) pathway in rats, a signaling cascade necessary for myocardial recovery following cardiac ischemia.110

A recent study showed that administration of dietary methylglyoxal increased vascular adhesion and augmented atherogenesis in normoglycemic apoE knockout mice.111 The effects of methylglyoxal were mediated only partly by RAGE, since deletion of RAGE was able to reduce, but not completely prevent, inflammation and atherogenesis associated with methylglyoxal exposure. Overexpression of glyoxalase 1 in diabetic rats reduced intracellular glycation, inflammation, and endothelial dysfunction and attenuated both the loss of podocytes in the glomerulus and the renal excretion of early markers of diabetic nephropathy.112 Recently, it was shown that genetic deletion of glyoxalase 1 in mice recapitulated several features of diabetic kidney disease,113 suggesting that methylglyoxal accumulation is a pivotal mediator of renal disease pathogenesis. Whether diet-derived methylglyoxal can induce end-organ injury is yet to be determined. However, early studies in mice suggest that oral methylglyoxal administration induced
amyloid-β and AGE deposits in the brain by suppressing neural sirtuin 1 (SIRT-1) activity, contributing to cognitive and motor deficits.\textsuperscript{114}

**Nrf2 pathway**

Another endogenous defense system against inflammatory, oxidative, and carbonyl stress involves the nuclear factor erythroid 2–related factor 2 (Nrf2), a transcription factor that increases the production of specific antioxidant enzymes involved in the cellular protection against glycation. Nrf2 activates genes containing an antioxidant response element (ARE) in their promoter and is expressed throughout the body, with particularly high levels found in the intestine, liver, and kidney.\textsuperscript{115} Under basal conditions, Nrf2 is complexed with the adaptot molecule Keap1.\textsuperscript{125} The Nrf2/keap1/ARE system also increases the expression of the Nrf2-negative regulator, Keap1.\textsuperscript{125} The Nrf2/keap1/ARE system also increases the expression of proteins involved in the autophagic degradation of long-lived proteins such as p62/sequestrin.\textsuperscript{122–124} Dietary polyphenols have also been reported to reduce the expression of the Nrf2-negative regulator, Keap1.\textsuperscript{125} The Nrf2/keap1/ARE system also increases the expression of proteins involved in the autophagic degradation of long-lived proteins such as p62/sequestrin-1,\textsuperscript{120} suggesting that it may be involved in the turnover of AGEs. While AGEs have been shown to induce the upregulation of Nrf2-dependent antioxidant genes in endothelial cell culture,\textsuperscript{126} the effects of dietary AGEs on the Nrf2/keap1/ARE system have not been described.

**AGE-binding proteins**

There are other RAGE isoforms that bind AGEs and appear to dampen inflammation. Soluble RAGE (sRAGE) is a soluble isoform of RAGE generated by proteolytic cleavage by matrix metalloproteinases.\textsuperscript{127} As it lacks a membrane-spanning region and a cytosolic intracellular domain, sRAGE is incapable of catalytic activity and may function in the circulation as a decoy AGE receptor, reducing the pool of serum AGEs and other RAGE agonists available to engage with full-length RAGE. Moreover, one of the mechanisms whereby angiotensin-converting enzyme inhibitors are thought to achieve AGE reduction and renoprotection is through increased sRAGE production.\textsuperscript{128}

Because sRAGE sequesters RAGE ligands and acts as a cytoprotective agent in vitro, multiple studies have explored the relationship between sRAGE and inflammation. Subjects with types 1 and 2 diabetes, particularly those with coronary artery disease or renal dysfunction, display elevated sRAGE levels in comparison with non-diabetic controls.\textsuperscript{129,130} Some studies have found sRAGE concentrations to positively correlate with circulating inflammatory markers such as MCP-1 and TNF-α in people with diabetes.\textsuperscript{131} In contrast, reduced serum levels of sRAGE have been found in individuals with inflammatory conditions such as obesity, atherosclerosis, rheumatoid arthritis, and chronic obstructive pulmonary disease.\textsuperscript{132–135} The contradictory findings in serum sRAGE levels between people with diabetes and those with other inflammatory conditions might be explained by increased levels of matrix metalloproteinases. Elevated circulating AGEs (frequently seen in people with diabetes) are associated with enhanced expression and production of matrix metalloproteinases, thereby increasing the proteolytic cleavage of sRAGE from the cell surface.\textsuperscript{136} Subjects with diabetes may also be affected by varying degrees of renal impairment, which is known to positively correlate with sRAGE concentrations.\textsuperscript{137} Individual genetic polymorphisms in \textit{RAGE} or glyoxalase genes may also result in altered sRAGE levels.\textsuperscript{138}

Administration of recombinant sRAGE to rodents with experimentally induced inflammatory and autoimmune conditions has successfully suppressed the development of micro- and macrovascular complications of diabetes, reduced the expression of proinflammatory cytokines, and attenuated vascular dysfunction.\textsuperscript{139} Therapeutic administration of sRAGE also reduced inflammation and disease progression in murine models of inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis.\textsuperscript{140} However, sRAGE levels are...
undetectable in wild-type mice and rats, so it is not yet known whether results in rodent systems have any application in human disease.

Endogenous secretory RAGE is a truncated splice variant of the RAGE gene that is secreted from cells and appears to confer protection against low-grade inflammation, with cross-sectional studies finding inverse correlations between endogenous secretory RAGE concentrations and ROS, the metabolic syndrome, atherosclerosis, and microvascular complications of diabetes. However, because it is present in very low levels in serum, it is questionable whether this soluble form of RAGE is able to effectively reduce ligand concentration. It may instead simply have a use as biomarker of risk.

The advanced glycation end product receptor 1 (AGER1, oligosaccharyltransferase subunit 48 [OST48], or dolichyl-diphosphooligosaccharide-protein glycosyltransferase subunit [DDOST]) is a cell-surface AGE receptor involved in binding AGE ligands and facilitating their degradation. AGER1 may reduce AGE-induced intracellular ROS generation and downregulate RAGE-mediated inflammatory signaling. In healthy individuals, elevated levels of AGES and oxidative stress in the circulation enhance AGER1 expression, which in turn reduces the expression of both RAGE and the oxidative stress-dependent epidermal growth factor receptor. Moreover, AGER1 transgenic mice were protected from diabetes, methylglyoxal exposure may explain, in part, why people with diabetes exhibit lower resistance to infection.

Complement is a key component of the innate immune system. Under normal conditions, complement is tightly regulated by a number of fluid-phase and cell-surface proteins. When complement is hyperactivated, as occurs in autoimmune diseases or in individuals with dysfunctional regulatory proteins, it drives a severe inflammatory response. There is some evidence that the glycation pathway can modulate complement. AGE-modified low-density lipoproteins are able to bind to immunoglobulin G antibodies to form stable immune complexes capable of stimulating the complement system. CD59, a regulatory protein that limits complement activation and the formation of the membrane attack complex, is inactivated by glycation. Glycated CD59 was found in the urine of patients with diabetes and also in the kidneys, nerves, and vasculature of patients with diabetes. Preliminary laboratory data indicates that dietary MRPs can activate the complement pathway, since excess MRP consumption in rodents for 6 months led to an increase in complement C3 in the circulation and to urinary excretion of C5a, a key mediator of inflammation, in the context of renal dysfunction, inflammation and oxidative stress (authors’ unpublished observations). These data provide a direct link between dietary AGES and immune-mediated inflammation. Interestingly, the complement component C3a is a high-affinity RAGE ligand, providing an additional mechanism for the promotion of RAGE-mediated inflammatory signaling.

**Metabolite-sensing G-protein–coupled receptors**

An emerging area of nutrition research is the role of diet and bacterial metabolites in regulating gut homeostasis and inflammation (recently reviewed). Diet-related metabolites engage metabolite-sensing G-protein–coupled receptors, including GPR41 and GPR43, which are expressed on a variety of cell types,
including gastrointestinal, adipose, and immune cells. These metabolites also include short-chain fatty acids produced by the microbial fermentation of dietary fibers in the colon. Functions of GPR41 and GPR43 include the regulation of energy intake and expenditure, modulation of glucose metabolism, and the resolution of inflammatory responses via, for example, activation of the NLRP3 inflammasome. Short-chain fatty acids can also exert anti-inflammatory effects by inhibiting histone deacetylases, thereby regulating gene transcription and the post-translational modification of proteins such as NF-κB.

It is plausible that dietary AGES, by inhibiting the growth of short-chain fatty acid–producing bacterial species in the colon, may contribute to heightened inflammatory signals in the gastrointestinal tract and a variety of other body tissues. AGES have also been found to selectively increase the in vitro expression of histone deacetylases known to be upregulated in the pathogenesis of diabetes complications. It is widely appreciated that this area of research is still in its infancy, and further studies must explore whether dietary AGES have the capacity to negatively regulate metabolite sensors in the gut.

### Incretin axis

The interaction between the incretin and glycation pathways is less studied. Incretins are gut-derived glucoregulatory hormones secreted postprandially from intestinal cells. Glucagon-like peptide 1 signals the glucose-dependent secretion of insulin from pancreatic β cells and thus acts to lower blood glucose. Glucagon-like peptide 1 also slows gastric emptying and enhances satiety signals in the brain. Another incretin hormone secreted in response to food intake, glucose-dependent insulinotropic polypeptide, regulates energy storage through direct actions on adipose tissue and stimulates β-cell proliferation and insulin secretion. Both glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide have been reported to demonstrate anti-inflammatory properties through their effects on the advanced glycation pathway. In addition, they have both been found to downregulate AGE-induced ROS generation and subsequent RAGE expression in vitro by enhancing the generation of cyclic AMP. A 24-week high-AGE dietary intervention in rats reduced plasma levels of glucagon-like peptide 1 and impaired insulin secretion in comparison with a low-AGE dietary intervention in rats, suggesting that dietary AGES play an important role in the early endocrine dysfunction that precipitates the development of diabetes. In an in vitro study, AGES upregulated endothelial cell production of DPP-4 (dipeptidyl peptidase-4, an enzyme that degrades glucagon-like peptide 1 soon after its secretion from intestinal cells), but the precise mechanism by which dietary AGES modulate incretin signaling is still unknown.

### DIETARY ADVANCED GLYCATION END PRODUCTS AND INFLAMMATION: ANIMAL INTERVENTION STUDIES

Dietary AGES have been shown to potentiate inflammation in vitro. Food-derived AGES (prior to ingestion) increased proinflammatory cytokine production and depleted antioxidant levels in human endothelial cells in culture. Whether the toxic effects of dietary AGES outside of the body are replicated in vivo is still being determined. Experimental AGE-restricted diets have prevented or arrested inflammatory processes in animal models and have reduced markers of inflammation in human trials. However, further studies are required to confirm the long-term benefits of dietary AGE restriction in humans.

Animal models represent a unique opportunity for the investigation of the health effects of dietary AGE consumption. Selected studies involving dietary AGES and their inflammatory effects in animals are shown in Table 1. Animal models are less expensive than human trials, and large numbers of animals can be followed for extended time periods. Moreover, dietary intake can be strictly controlled, and MRPs can be provided in food at concentrations that are several orders of magnitude greater than those provided to controls. Other advantages of the study of dietary AGES in animal models include the ease of profiling proinflammatory genes in target organs and cells and the use of genetically modified mouse models with genetic deletion or overexpression to better elucidate the effects of dietary AGES on inflammatory pathways. Animal studies have successfully demonstrated clear relationships between dietary AGE consumption and many of the low-grade inflammatory processes associated with both the pathogenesis and the long-term complications of noncommunicable chronic diseases.

Despite the advantages of animal models, it is uncertain whether the investigation of excessive AGE consumption in animals is applicable to human health. High-AGE diets consumed by experimental animals have generally contained 3 to 10 times the AGE content of standard or control diets. In comparison, low-AGE diets in human studies contain only 40% to 50% fewer AGES than the standard or high-AGE diet in order to maintain palatability and dietary compliance over relatively short time periods (2–16 wk) (Table 1). Accordingly, a major caveat when examining AGE-overfeeding studies is the administration of supraphysiological doses of AGES or dicarbonyls, which
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<td>Anton et al. (2012)</td>
<td>Wild-type mice With DSS-induced colitis</td>
<td>High-MRP diet vs standard diet (3 wk)</td>
<td>5:1 CML</td>
<td>High-MRP diet resulted in: ↓ Colonic lesions ↓ MPO activity in colonic tissue Low-AGE diet resulted in: ↑ GSH/GSSG ratio, ↑ plasma 8-isoprostanes, ↑ AGER1, ↓ RAGE and ↓ p66shc expression in spleen, ↑ lifespan</td>
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<td>Cai et al. (2007)</td>
<td>Male wild-type mice</td>
<td>Regular (high-AGE) diet vs low-AGE diet (96 wk)</td>
<td>2:1 CML</td>
<td>Low-AGE diet resulted in: ↓ GSH/GSSG ratio, ↓ plasma 8-isoprostanes, ↓ AGER1, ↓ RAGE and ↓ p66shc expression in spleen, ↑ lifespan</td>
</tr>
<tr>
<td>Cai et al. (2012)</td>
<td>Wild-type mice</td>
<td>Standard (high-AGE) diet vs low-AGE diet</td>
<td>2:1.5:1 CML</td>
<td>Low-AGE, MG-supplemented diet resulted in: ↓ SIRT-1 and ↓ PPARγ expression in brain, ↑ amyloid-β and AGE deposits in brain, ↑ cognitive and motor deficits, ↑ metabolic syndrome</td>
</tr>
<tr>
<td>Cai et al. (2014)</td>
<td>Wild-type mice</td>
<td>Standard (high-AGE) diet vs low-AGE diet</td>
<td>2:1.5:1 CML</td>
<td>Low-AGE, MG-supplemented diet resulted in: ↓ SIRT-1 and ↓ PPARγ expression in brain, ↑ amyloid-β and AGE deposits in brain, ↑ cognitive and motor deficits, ↑ metabolic syndrome</td>
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<td>Cassese et al. (2008)</td>
<td>Female wild-type mice</td>
<td>High-AGE diet vs low-AGE diet (20 wk)</td>
<td>3:1 CML</td>
<td>High-AGE diet resulted in: ↑ Formation of RAGE-PKCe-Src in skeletal muscle, ↑ insulin resistance in skeletal muscle</td>
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<tr>
<td>Chatzigeorgiou et al.</td>
<td>Female Wistar rats</td>
<td>High-AGE diet vs low-AGE diet (12 wk)</td>
<td>58:1 CML</td>
<td>High-AGE diet resulted in: ↑ Glucose, ↑ insulin, ↓ testosterone, ↓ estradiol, and ↓ progesterone in serum ↓ RAGE expression in PBMCs ↓ GLO-1 activity in ovarian tissue Low-AGE diet resulted in: ↓ Macrophage infiltration of remnant kidney, ↓ MCP-1, ↑ glutathione peroxidase activity</td>
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<td>Leung et al. (2014)</td>
<td>Male Sprague-Dawley rats</td>
<td>High-AGE, high-fat Western diet vs standard diet (16 wk)</td>
<td>5:1 CML</td>
<td>High-AGE diet resulted in: ↑ RAGE and ↑ MIF expression in kidney, ↓ plasma MIF</td>
</tr>
<tr>
<td>Lin et al. (2002)</td>
<td>apoE-deficient mice with femoral artery injury</td>
<td>High-AGE diet vs low-AGE diet (1 wk prior to artery injury and 4-wk post injury)</td>
<td>10:1 CML</td>
<td>Low-AGE diet resulted in: ↓ Neointimal formation, ↓ macrophage infiltration of neointimal lesions, ↔ plasma cholesterol</td>
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(continued)
### Table 1 Continued

<table>
<thead>
<tr>
<th>Reference</th>
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<tr>
<td>Matafome et al. (2012)108</td>
<td>Wistar-wild type rats with GK-type 2 diabetes</td>
<td>Drinking water supplemented with MG vs regular drinking water (14 wk)</td>
<td>MG-supplemented water contained MG at 50–75 mg/kg/d</td>
<td>MG supplementation resulted in: ↑ Plasma NEFAs, ↓ serum adiponectin, ↑ urinary 8-isoprostanes, ↑ adipose hypoxia, ↑ macrophage infiltration of adipose tissue, ↑ TGF-β and ↑ MCP-1 expression in adipose tissue</td>
</tr>
<tr>
<td>Patel et al. (2012)81</td>
<td>Mice</td>
<td>High-AGE diet vs regular AGE diet (39 wk)</td>
<td>3:1 AGE</td>
<td>High-AGE diet resulted in: Liver neutrophil infiltration present at week 26, in the absence of steatosis. Neutrophil infiltration had resolved at week 39, and steatosis was present</td>
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<tr>
<td>Peppa et al. (2003)187</td>
<td>Mice with diabetes (1-cm full-thickness skin wound)</td>
<td>High-AGE diet vs low-AGE diet (12 wk)</td>
<td>5:1 CML</td>
<td>Low-AGE diet resulted in: ↓ Time to full wound closure, ↓ inflammatory cell infiltration of wound at day 21</td>
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<tr>
<td>Sena et al. (2012)188</td>
<td>Wistar wild-type rats with GK-type 2 diabetes</td>
<td>Drinking water supplemented with MG vs standard drinking water (12 wk)</td>
<td>MG-supplemented water provided MG at 50–75 mg/kg/d</td>
<td>MG supplementation resulted in: ↑ RAGE expression in vascular wall and ↑ MCP-1 expression in aorta in both wild type and diabetic rats</td>
</tr>
<tr>
<td>Shangari et al. (2007)66</td>
<td>Rats</td>
<td>High-AGE diet vs regular-AGE diet (10 wk)</td>
<td>9:1 AGE</td>
<td>High-AGE diet resulted in: ↓ Glutathione, ↓ thiamin, ↑ macrophage infiltration of the colon, ↑ nitrotyrosine present in colon, plasma, and liver</td>
</tr>
<tr>
<td>Tikellis et al. (2008)189</td>
<td>Wild-type RAGE knockout mice</td>
<td>High-AGE, high-fat Western diet vs standard diet (16 wk)</td>
<td>3:1 AGE</td>
<td>High-AGE diet resulted in: ↑ IL-6, ↑ TNF-α, ↑ ICAM-1, ↑ MCP-1, ↑ p65 expression in cardiac tissue. Expression was reduced in RAGE knockout mice on high-AGE diet</td>
</tr>
<tr>
<td>Tikellis et al. (2014)111</td>
<td>apoE knockout mice (RAGE/ apoE double knockout)</td>
<td>Drinking water supplemented with MG vs standard drinking water (6 wk)</td>
<td>MG-supplemented water provided MG at 10 mg/kg/d</td>
<td>MG supplementation resulted in: ↑ MCP-1, ↑ ICAM-1 in circulation, ↑ ICAM-1, ↑ tetherin expression in aortic endothelial cells, ↑ macrophage activation in aorta</td>
</tr>
<tr>
<td>Zhu et al. (2011)190</td>
<td>Wild-type mice (5-mm burn wound)</td>
<td>Diets supplemented with high-AGE food vs diets not supplemented with high-AGE foods (8 d post burn)</td>
<td>High-AGE diet contained 205 more AU of AGES per day than low-AGE diet</td>
<td>High-AGE diet resulted in: ↓ Wound healing, ↑ HMGB1 expression in WBC, ↑ plasma HMGB1</td>
</tr>
</tbody>
</table>

**Abbreviations:** AGE, advanced glycation end product; AGER1, advanced glycation end product receptor 1; apoE, apolipoprotein E; AU, arbitrary units; CML, carboxymethyllysine; DSS, dextran sulfate sodium; GK, Goto-Kakizaki (nonobese model of type 2 diabetes); GLO-1, glyoxalase 1; GSH, reduced glutathione; GSSG, oxidized glutathione; HDL, high-density lipoprotein; HMGB1, high-mobility group box 1; ICAM-1, intracellular adhesion molecule 1; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein 1; MG, methylglyoxal; MIF, macrophage migration inhibitory factor; MPG, myeloperoxidase; MRP, Maillard reaction product; NEFAs, nonesterified fatty acids; PBMCs, peripheral blood mononuclear cells; PKCa, protein kinase Ca; RAGE, receptor for advanced glycation end products; SIRT-1, sirtuin 1; STZ, streptozotocin; TG, triglyceride; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule 1; WBC, white blood cells; ↓, significantly lower than comparison diet group post intervention; ↑, significantly higher than comparison diet group post intervention; ↔, no significant difference between low-AGE and high-AGE diet groups post intervention.
highlights the need for cautious interpretation of data from animal studies. Moreover, when assessing the numerous cross-sectional studies, further caution is required not to attribute data to the primary cause of pathology. The initiation of pathology would need to be investigated by studies specifically profiling disease progression. There are also major limitations associated with providing heat-treated food to represent a high-AGE diet during feeding studies, because heating may destroy both antioxidants and heat-labile vitamins, and generate other toxic components within food. In order to demonstrate a causal relationship between dietary AGEs and disease, future research should involve the dietary administration of individual synthetically generated AGEs of known molecular weights.191

Dietary AGE restriction in mice prone to atherosclerosis demonstrated significant reductions in the inflammation of vascular lesions and reduced endothelial migration of monocytes due to the downregulation of VCAM-1 and MCP-1 expression, likely related to the reduced expression of RAGE.185,186 These changes occurred in the absence of any differences in serum cholesterol, triglycerides, high-density lipoprotein, or glucose between low-AGE and high-AGE diet groups. This suggests a role for excessive dietary AGEs very early in the vascular inflammatory process, whereby atherosclerosis is enhanced and vascular repair is inhibited well before changes in circulating lipids or glucose occur. Dietary methylglyoxal was found to be equally detrimental to the vasculature in a rat model of diabetes.188 AGEs are well known to mediate damage to both antioxidants and heat-labile vitamins, and glucose between low-AGE and high-AGE diet groups. This suggests a role for excessive dietary AGEs very early in the vascular inflammatory process, whereby atherosclerosis is enhanced and vascular repair is inhibited well before changes in circulating lipids or glucose occur. Dietary methylglyoxal was found to be equally detrimental to the vasculature in a rat model of type 2 diabetes.188 AGEs are well known to mediate damage in the diabetic kidney,192 with high-AGE diets in rats182 and mice42 increasing renal inflammation, macrophage recruitment, and RAGE expression. A low-AGE diet increased antioxidant activity to provide a protective function.

Wounded mice consuming a low-AGE diet exhibited faster healing times than those receiving a high-AGE diet,187,190 and wounds showed reduced macrophage infiltration. Expression of high-mobility group box-1 was increased in the animals consuming the high-AGE diet, implying that AGEs may participate in the perpetuation and amplification of inappropriate inflammatory signals. The effects of dietary AGEs on intestinal inflammation are contradictory. One study in rats found a high AGE intake to be associated with increased colonic oxidative stress and inflammation, along with reduced antioxidant capacity.66 In contrast, a high-AGE diet in mice with colitis appeared to be protective of the colon and was associated with reduced intestinal inflammation.50

Tikellis et al.189 compared the effect of a 16-week high-AGE Western diet on cardiac dysfunction in wild-type mice with the effect of standard chow in controls. Mice receiving the Western diet showed significant upregulation in the myocardial expression of inflammatory cytokines IL-6 and TNF-α, chemokines ICAM-1 and MCP-1, and the NF-κB subunit p65. Expression of inflammatory proteins was significantly reduced in RAGE knockout mice on the Western diet compared with that in the wild-type mice, implicating the AGE-RAGE axis as the primary mediator of cardiac inflammation in response to a high-AGE, high-fat diet. In many of the animal studies performed, high-AGE diets contained large quantities of fat, suggesting that the pathogenic endpoints observed might also relate to the fat content rather than to the AGE content alone. Indeed, high-fat feeding in mice has been shown to upregulate proinflammatory cytokine and Toll-like receptor production in white adipose tissue,193 and the saturated fatty acid palmitate is known to activate NF-κB.194,195

Due to their preferential accumulation in the liver and their contribution to RAGE activation, AGEs are thought to induce hepatic injury and contribute to the progression from steatosis to nonalcoholic fatty liver disease.196 A high-AGE dietary intervention in mice was associated with increased hepatic neutrophil accumulation in the absence of steatosis,1 implicating food-derived AGEs in the early pathogenesis of liver inflammation. Leung et al.184 reported that a high-AGE diet increased hepatic AGE accumulation in rats, stimulated NADPH-dependent oxidative stress, and induced liver inflammation and fibrosis. These effects were mediated by RAGE and ROS, as the blockade of NADPH oxidase and RAGE prevented hepatic cellular injury.

Mice consuming a high-AGE diet exhibited impaired insulin action in skeletal muscle prior to any increase in fasting glucose,179 which was potentiated by an AGE-induced upregulation of protein kinase Cδ activity. High-AGE diets in androgenized female rats were associated with hormonal dysregulation181 and reduced ovarian glyoxalase 1 activity, lending support to the hypothesis that excess dietary toxins might contribute to polycystic ovarian syndrome and its sequelae.

A low-AGE diet supplemented with methylglyoxal induced adipose tissue expansion and insulin resistance and reduced AGER1 expression over 4 generations of mice,149 suggesting a role not only forAGEs but also for dicarbonyls in the perpetuation of inflammatory stress.

**DIETARY ADVANCED GLYcation ENd PRODUCTS AND INFLAMMATION: HUMAN INTERVENTION STUDIES**

Population studies examining the relationship between dietary AGE intake and chronic inflammatory diseases are limited, primarily because there are currently no...
validated survey tools available to assess long-term dietary AGE consumption. A cross-sectional study in humans with type 2 diabetes found positive correlations between habitual high dietary AGE consumption and biomarkers of inflammation such as interleukin 1α (IL-1α), TNF-α, and MCP-1.197 Another study of healthy adults found associations between elevated dietary AGE consumption and increased levels of high-sensitivity C-reactive protein and VCAM-1.198

Dietary intervention trials exploring the effects of dietary AGE restriction on inflammatory markers in humans are summarized in Table 2.42,151,198–212 These studies have been performed in healthy overweight individuals, women with polycystic ovarian syndrome, people with types 1 and 2 diabetes, and patients with chronic kidney disease or end-stage renal failure. Dietary interventions involving a single high-AGE meal or beverage showed no change in NF-κB DNA-binding activity in peripheral blood mononuclear cells from healthy adults,206 increased circulating plasminogen activator inhibitor 1 in healthy adults and people with diabetes,211 and increased serum VCAM-1 and ICAM-1 in people with type 2 diabetes.202–204,213 These results suggest that a single high-AGE meal could potentially activate certain inflammatory processes. A 2-week low-AGE dietary intervention improved inflammatory markers in overweight males42 and in overweight people with type 1 or 2 diabetes.212 A high-AGE diet was capable of influencing the oxidative status of young healthy volunteers within only 4 weeks.199 Excessive AGE consumption increased oxidative stress and reduced the levels of vitamins and fatty acids known for their anti-inflammatory effects. However, apart from differences in AGE intake, there were also considerable differences in macro- and micronutrient intakes between the study groups.

The inability to avoid significant differences in fat and carbohydrate consumption between low-AGE and high-AGE groups may have also been a potential confounder in a 4-week study involving overweight women, in whom dietary AGE restriction improved insulin sensitivity.201 A 6-week intervention study that provided isocaloric, nutrient-equivalent diets to healthy individuals on a high-AGE or low-AGE diet found no differences between groups in circulating markers of endothelial function or inflammation.207 An 8-week high-AGE diet increased insulin resistance, testosterone levels, and oxidative stress in women with polycystic ovarian syndrome.208 These abnormal parameters subsequently improved after the women were changed to an 8-week low-AGE diet, indicating the potential contribution of dietary AGEs to the hormonal and metabolic pathology associated with polycystic ovarian syndrome. Longer-term studies of 16 weeks’ duration in people with diabetes151 and in healthy individuals198 favored a low-AGE diet for reducing the production of proinflammatory cytokine TNF-α, reducing the expression of RAGE, and upregulating the anti-inflammatory proteins AGER1 and SIRT-1 in peripheral mononuclear cells. It is thought that low-molecular-weight AGEs do not interact with RAGE,57,214 so it is uncertain how consumption of a high-AGE meal (during which only low-molecular-weight AGEs are absorbed) can result in a subsequent increase in RAGE activation. It is possible that dicarbonyls could form high-molecular-weight complexes in the circulation immediately following a high-AGE meal, but this requires confirmation by future research.

It has recently been hypothesized that dietary AGEs might increase appetite and energy intake due to enhanced sensory-stimulating properties of MRPs in food.215 Sebekova et al.,216 in a recent study in rats, showed that consumption of a diet high in MRPs (in the form of bread crust) for 3 weeks led to increases in food intake and circulating leptin and adiponectin, along with increased expression of hypothalamic and olfactory bulb leptin receptor in the context of an increase in neuronal activity in brain areas involved in the central regulation of food intake and energy homeostasis.216 Other research, however, fails to support this theory, with a single high-AGE meal having no effect on hunger, appetite hormone responses, or subsequent food intake in overweight individuals.205 More research is required to determine whether dietary AGEs modulate the processes driving food consumption, with the effects of food-derived AGEs on central appetite regulation and energy homeostasis at the level of the hypothalamus being an exciting new area of investigation. It is possible that the addictive qualities of highly processed foods are mediated by MRPs through effects on the reward centers of the brain.

**LIMITATIONS OF DIETARY ADVANCED GLYCATION END PRODUCT STUDIES IN HUMANS**

The results of human dietary AGE intervention studies must be interpreted with caution. Humans consume foods rather than individual nutrients, and the proinflammatory effects attributed to AGEs in food may be the result of other detrimental food components generated during the cooking process. A variety of food components commonly found in the Western diet have been shown to correlate with biomarkers of inflammation and endothelial dysfunction.69,217 and AGEs are likely to be only one of many dietary factors capable of adversely affecting human health. The simple act of eating has been shown to activate NF-κB, regardless of the AGE content of the food consumed.206 Additionally,
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<td>Birlouez-Aragon et al. (2010)&lt;sup&gt;199&lt;/sup&gt;</td>
<td>France, n=64 healthy volunteers, 32 M and 32 F (mean age, 19 y; mean BMI, 21.8 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Crossover Not blinded</td>
<td>Random assignment to 4-wk low-MRP diet (2.2 ± 0.9 mg CML/d) or 4-wk standard MRP diet (5.4 ± 2.3 mg CML/d) before crossover</td>
<td>GC–MS/MS to CML</td>
<td>High-AGE diet resulted in: ↓ vitamin C, ↓ vitamin E, ↓ total n-3 fatty acids, ↑ ubiquinol</td>
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<td>Harcourt et al. (2011)&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Australia, n=11 healthy overweight or obese males (mean age, 30 y; mean BMI, 31.8 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Crossover Outcome assessors blinded</td>
<td>Random assignment to 2-wk low-AGE diet (3302 kU CML/d) or 2-wk high-AGE diet (14 090 kU CML/d) before crossover</td>
<td>AGE database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: ↓ cystatin C, ↓ MCP-1, ↑ MIF</td>
</tr>
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<td>Luevano-Contreras et al. (2013)&lt;sup&gt;200&lt;/sup&gt;</td>
<td>Mexico, n=26 nonsmoking patients with type 2 DM, 3 M and 23 F (mean age, 47.3 y; mean BMI, 29.3 kg/m&lt;sup&gt;2&lt;/sup&gt;; mean HbA1c, 8.6%; mean DM duration, 5.2 y)</td>
<td>Parallel Participants instructed on food choices and preparation methods Outcome assessors blinded</td>
<td>Random assignment to 6-wk low-AGE diet (n=13; 396 kU CML/d) or 6-wk high-AGE diet (n=13; 12 214 kU CML/d)</td>
<td>AGE database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: ↓ TNF-α, ↔ CRP</td>
</tr>
<tr>
<td>Mark et al. (2014)&lt;sup&gt;201&lt;/sup&gt;</td>
<td>Denmark, n=73 women aged 20-50 y with BMI 25-40 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Parallel Participants instructed on food choices and preparation methods Some food provided Outcome assessors blinded</td>
<td>Random assignment to 4-wk low-AGE diet (n=36) or 4-wk high-AGE diet (n=37). AGE content of diets not reported</td>
<td>LC–MS/MS to CML</td>
<td>High-AGE diet resulted in: ↑ Fasting insulin, ↑ HOMA-IR, ↔ fasting glucose, ↔ postprandial glucose, ↔ GLP-1</td>
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<td>Negrean et al. (2007)&lt;sup&gt;202&lt;/sup&gt;</td>
<td>Germany, n=20 patients with type 2 DM, 14 M and 6 F (mean age, 55.9 y; mean BMI, 29.5 kg/m&lt;sup&gt;2&lt;/sup&gt;; mean HbA1c, 89%; mean DM duration, 8.7 ± 1.7 y)</td>
<td>Crossover Outcome assessors blinded</td>
<td>Random assignment to single low-AGE meal (27 500 kU CML) or single high-AGE meal (15 100 kU CML) before crossover. Measurements at 2, 4, and 6 h postprandial</td>
<td>ELISA to CML</td>
<td>Low-AGE meal resulted in: ↑ Adiponectin, ↑ leptin, ↓ VCAM-1, ↔ CRP, ↔ TNF-α, ↔ IL-6</td>
</tr>
<tr>
<td>Stirban et al. (2007)&lt;sup&gt;203&lt;/sup&gt;, (2008)&lt;sup&gt;204&lt;/sup&gt;, (2008)&lt;sup&gt;213&lt;/sup&gt;</td>
<td>Denmark, n=19 overweight subjects, 3 M and 16 F (mean age, 34.8 y; mean BMI, 31.3 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Crossover Outcome assessors blinded</td>
<td>Assignment to either a single low-AGE meal (2.8 mg CML) or a single high-AGE meal (5.0 mg CML) before crossover to the alternative meal 2 wk later. Measurements at 45, 90, 180, and 300 min postprandial</td>
<td>LC–MS/MS to CML</td>
<td>High-AGE meal resulted in: ↑ Urinary isoprostanes, ↑ VCAM-1, ↔ CRP, ↔ TNF-α, ↔ IL-6, ↔ ICAM-1</td>
</tr>
<tr>
<td>Poulsen et al. (2014)&lt;sup&gt;205&lt;/sup&gt;</td>
<td>Germany, n=9 healthy nonsmoking male volunteers (mean age, 32 y; mean BMI, 24 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Crossover Not blinded</td>
<td>Assignment to single low-AGE meal (250 g minimally AGE-modified casein, 104.2 ± 23.3 mg CML/mg casein) before crossover to single high-AGE meal (250 g highly AGE-modified casein, 301.7 ± 49.2 mg CML/mg casein). Measurements at 2 h postprandial</td>
<td>ELISA to CML</td>
<td>High-AGE meal resulted in: ↔ NF-kB activation</td>
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<td>Schiekofer et al. (2006)&lt;sup&gt;206&lt;/sup&gt;</td>
<td>USA, n=24 healthy volunteers (mean age, 59 y; mean BMI, 26 kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>Parallel Outcome assessors blinded</td>
<td>Random assignment to 6-wk low-AGE diet (n=12) or 6-wk high-AGE diet (n=12). AGE content of diets not reported</td>
<td>Database based on ELISA to CML</td>
<td>High-AGE diet resulted in: ↔ VCAM-1, ↔ hsCRP, ↔ TNF-α receptors, ↔ IL-6</td>
</tr>
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<tr>
<td>Tantakali et al. (2014)(^{208})</td>
<td>Greece, (n=23) women with polycystic ovarian syndrome (mean age, 24 y; mean BMI, 26.2(\text{kg/m}^2))</td>
<td>Crossover</td>
<td>Assignment to an 8-wk high-AGE diet (16,000 KU CML/d) followed by an 8-wk low-AGE diet (5,700 KU CML/d). No washout</td>
<td>Database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: ↓ Oxidative stress (lipid peroxide concentration)</td>
</tr>
<tr>
<td>Urribarri et al. (2003)(^{199}) Peppa et al. (2004)(^{210})</td>
<td>USA, (n=18) patients with non-diabetic end-stage renal failure on peritoneal dialysis (mean age and BMI not reported)</td>
<td>Parallel</td>
<td>Random assignment to either 4-wk low-AGE diet (5,500 KU CML/d) or 4-wk high-AGE diet (17,000 KU CML/d</td>
<td>Database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: ↓ CRP, ↓ PAI-1, ↓ TNF-(\alpha), ↓ VCAM-1</td>
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<td>Urribarri et al. (2007)(^{211})</td>
<td>USA, (n=44) subjects with DM, 36 M and 8 F (mean age, 51 y; mean HbA1c, 8.6%), and (n=10) healthy subjects, 5 M and 5 F (mean age, 43 y)</td>
<td>Pre and post test</td>
<td>Single oral challenge of a high-AGE beverage containing 1800 KU CML. Measurements taken before and 90 and 150 min after beverage consumption</td>
<td>ELISA to CML</td>
<td>High-AGE oral challenge resulted in: DM and healthy subjects: ↑ PAI-1, ↓ VCAM-1</td>
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<tr>
<td>Urribarri et al. (2011)(^{212})</td>
<td>USA, (n=36) subjects, 18 with type 2 DM and 18 without DM (mean age, 64 y; mean BMI, 29.8 kg/m(^2)); HbA1c in patients with DM not reported</td>
<td>Parallel</td>
<td>Random assignment to 16-wk standard diet (&gt;20,000 KU CML/d) or 16-wk AGE-restricted diet (&lt;10,000 KU CML/d)</td>
<td>Database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: Type 2 DM subjects: ↑ adiponectin, ↓ leptin, ↓ TNF-(\alpha) in circulation, ↑ AGER1 mRNA, ↑ SIRT-1 mRNA, and ↓ RAGE mRNA in MNCs Healthy subjects: ↓ TNF-(\alpha) in circulation</td>
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<tr>
<td>Vlassara et al. (2002)(^{212})</td>
<td>USA, (n=11) subjects, 2 with type 1 DM and 8 with type 2 DM (mean age, 52 y; mean HbA1c, 7.8%; mean BMI, 28.2 kg/m(^2))</td>
<td>Crossover</td>
<td>Random assignment to 2-wk low-AGE diet (3670 KU CML/d) or 2-wk high-AGE diet (16,300 KU CML/d) before crossover</td>
<td>Database based on ELISA to CML</td>
<td>High-AGE diet resulted in: ↑ TNF-(\alpha), ↑ VCAM-1, ↔ CRP</td>
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<tr>
<td>Vlassara et al. (2002)(^{212})</td>
<td>USA, (n=13) subjects, 4 with type 1 DM and 9 with type 2 DM (mean age, 62 y; mean HbA1c, 7.2%; mean BMI, 30 kg/m(^2))</td>
<td>Parallel</td>
<td>Random assignment to either 6-wk low-AGE diet (3670±1200 KU CML/d) or 6-wk high-AGE diet (16,300±3700 KU CML/d)</td>
<td>Database based on ELISA to CML</td>
<td>High-AGE diet resulted in ↑ CRP, ↓ TNF-(\alpha), ↓ CRP, ↓ VCAM-1</td>
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<tr>
<td>Vlassara et al. (2009)(^{206})</td>
<td>USA, (n=30) healthy subjects and 9 patients with CKD</td>
<td>Parallel</td>
<td>Healthy subjects: random assignment to 16-wk regular diet (&gt;13,000 KU CML/d) or 16-wk low-AGE diet (&lt;5500 KU CML/d). CKD patients: random assignment to these same groups, but duration of intervention was 4 wk</td>
<td>Database based on ELISA to CML</td>
<td>Low-AGE diet resulted in: Healthy subjects: ↓ AGER1 mRNA, ↓ RAGE mRNA in MNCs, ↓ TNF-(\alpha), ↓ VCAM-1, ↔ CRP in circulation CKD subjects: ↓ TNF-(\alpha), ↔ VCAM-1 in circulation, ↑ AGER1 mRNA, ↔ RAGE mRNA in MNCs</td>
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**Abbreviations and symbols:** AGE, advanced glycation end product; AGER-1, advanced glycation end product receptor 1; BML, body mass index; CKD, chronic kidney disease; CML, carbonyllysine; CRP, C-reactive protein; DM, diabetes mellitus; ELISA, enzyme-linked immunosorbent assay; GC–MS/MS, gas chromatography coupled to tandem mass spectrometry; GLP-1, glucagon-like peptide 1; HbA1c, hemoglobin A1c; HOMA-IR, homeostatic model assessment – insulin resistance; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; kU, kilounits; LC–MS/MS, liquid chromatography coupled to tandem mass spectrometry; MCP-1, monocyte chemoattractant protein 1; MIF, macrophage migration inhibitory factor; MNGs, mononuclear cells; mRNA, messenger ribose nucleic acid; MRP, Maillard reaction product; NF-\(\kappa\)B, nuclear factor-\(\kappa\)B-p; PAI-1, plasminogen activator inhibitor 1; RAGE, receptor for advanced glycation end products; SIRT-1, sirtuin 1; TNF-\(\alpha\), tumor necrosis factor \(\alpha\); VCAM-1, vascular cell adhesion molecule 1; ↓, significantly lower than comparison diet group postintervention; ↔, no significant difference between low-AGE and high-AGE diet groups postintervention.
the benefits associated with a low-AGE diet may be more closely related to a higher antioxidant concentration in the food (which would have otherwise been destroyed during the cooking process) rather than a reduced AGE content.

Dietary AGEs are thought to exert their negative effects over many years, thereby limiting the conclusions that can be drawn from short-term human intervention trials that range in length from a single meal to 16 weeks. Longer-term studies might be problematic because many individuals will find it difficult to adhere to a low-AGE diet, which may be less palatable than the high-AGE Western diet to which they are accustomed. Many of the trials contained very low numbers of participants, and most were likely to be underpowered. A number of the trials did not provide participants with food throughout the study, but instead provided instructions to each subject about appropriate food choices and cooking methods. Reduced dietary compliance may have been an issue during these studies, particularly during the later stages of the trials. Some trials administered dietary AGEs at concentrations that far exceeded normal physiological intake, so the results should be interpreted with caution.

Twelve of the 15 dietary AGE intervention studies listed in Table 2 either utilized an ELISA technique to measure the CML content of food or referred to an AGE database that was developed using this technique. While this database was very useful when information about the potential toxicity of food-derived AGEs was still in its infancy, more accurate and validated methods of AGE measurement are now available and should be utilized where possible. To date, most studies have focused on the assessment of CML in food, body fluids, and tissue. CML is only one of many AGEs, most of which have not yet been fully characterized. More information about dietary AGEs other than CML is required, as other AGE moieties are likely to have a variety of different effects on human health. Some AGEs in the body may merely be markers of inflammation rather than causal agents, and others might be capable of exerting beneficial antioxidant activity.

**REDUCING ADVANCED GLYCAION END PRODUCT INTAKE**

There is currently insufficient evidence to recommend reducing dietary AGE intake as a therapeutic strategy for the prevention and/or management of inflammatory conditions in humans. However, a variety of agents that inhibit the formation or action of AGEs have been identified. Exposure to AGEs could be minimized by substances that prevent the generation of AGEs (by reducing glucose and/or ROS, acting as dicarbonyl traps, or chelating metal ions), interfere with the action of AGEs (by putative crosslink breakers or RAGE antagonists), or prevent exposure to AGEs (by AGE detoxification or reduced environmental contact with AGEs), as suggested in a recent review. A mitochondria-targeted reagent, MitoG, that assesses the levels of mitochondrial dicarbonyls has recently been developed. Since this compound sequesters methylglyoxal, it may hold promise for targeting intracellular AGE formation.

Strategies to limit the intake of diet-derived AGEs have been previously discussed. The phosphate binder sevelamer carbonate is frequently used in patients with chronic kidney disease and, in addition to phosphate, is known to bind to a number of compounds in the gut, such as bile acids, bacterial endotoxins, and AGEs, thus preventing their absorption. Independent of its phosphate-lowering ability, sevelamer is thought to attenuate coronary artery calcification, atherosclerosis, and endothelial damage in chronic kidney disease patients by reducing serum glucose, cholesterol, ROS, and inflammatory markers. Exploratory studies indicate that sevelamer’s capacity to sequester intestinal AGEs is sufficient to reduce circulating AGEs and may prove to be a useful tool in reducing the absorption of dietary AGEs.

Although the absolute content of individual AGE moieties in food is the subject of controversy, there is a general consensus that bakery products, fried meats, and other highly heated foods contain a high proportion of AGEs. Limiting the dietary intake of foods that have undergone browning by the application of intense heat, particularly food and beverages containing high levels of protein or carbohydrate derived from simple sugars, would significantly reduce AGE consumption (see Figure 2). Modification of cooking methods, such as the replacement of frying and baking (where food is exposed to intense, dry heat) with steaming, boiling, and stewing (where food has a higher water content and is cooked at lower temperatures), reduces the formation of AGEs, though achieving maximum palatability and desired texture may be problematic. Alternatively, the addition of natural products (such as green tea extract, garlic, or vitamin C) known to inhibit AGE formation during the cooking process may offer a solution. Previous studies have suggested that acidic ingredients such as lemon juice or vinegar reduce AGE formation by lowering the pH of the food. Thiamin (vitamin B₆) and its derivatives are able to scavenge dicarbonyl compounds, thereby inhibiting AGE formation. Rutin (a flavonoid) and α-tocopherol (vitamin E) are powerful antioxidants capable of neutralizing ROS and reducing AGE production associated with oxidative stress. The Mediterranean diet has been suggested as a potential dietary strategy in the prevention of AGE toxicity because it...
is lower in AGEs and higher in antioxidants than the typical Western diet.\textsuperscript{79,231}

Interestingly, Nagai et al.\textsuperscript{232} demonstrated that citrate (a derivative of citric acid) also inhibited the formation of CML and \(N\varepsilon\)-carboxyethyllysine in the lens of diabetic rats. Citric acid is a dietary chelator found in citrus fruits and drinks, and the authors suggested that it may inhibit AGE formation, possibly by limiting the uptake or promoting the excretion of metal ions through chelating activity. Diabetic rats fed n-3 polyunsaturated fatty acids while receiving a high-fat thermolyzed diet demonstrated increased antioxidant superoxide dismutase activity and reduced lipoperoxidation and AGE levels in the liver compared with controls.\textsuperscript{233} However, the high fat content of the diets may have contributed to the liver toxicity observed. Physical activity has also been hypothesized to reduce AGE formation by increasing the body’s capacity to detoxify methylglyoxal. Exercise increases activation of the Nrf2/ARE pathway and stimulates glutathione synthesis, which may attenuate the accumulation of dicarbonyls.\textsuperscript{234} However, much of the research involving AGE-inhibiting compounds is limited to in vitro or animal studies, and therefore it is not yet known whether these interventions will have clinical applications.

Additionally, in the small number of human trials specifically designed to determine the effectiveness of AGE-reducing agents, serum AGE levels have been measured as the primary endpoint. This is problematic because it has not yet been fully established whether a reduction in circulating AGEs translates into improved health outcomes. At this time, it appears that adherence to a diet based on current dietary guidelines and maintenance of a healthy body weight, avoidance of cigarette smoking, and engaging in regular physical activity offers the best strategy to minimize the effects of AGEs.

Current evidence indicates that, in order to limit dietary intake of dicarbonyl compounds such as 3-deoxyglucosone and methylglyoxal, consumption of a diet based on fresh fruits, vegetables, and milk products would be advantageous.\textsuperscript{10} Increased consumption of sugar-rich products such as sugar beet syrup and high fructose corn syrup, together with the consumption of fruit juices and beer, may increase dicarbonyl intake. However, as discussed earlier, the paucity of knowledge regarding bioavailability and intestinal absorption of dicarbonyl compounds prevents conclusions about the impact of excess dicarbonyl consumption in humans.

**FUTURE DIRECTIONS**

Long-term dietary studies are required to more accurately determine the effect of food-derived AGEs on chronic
low-grade inflammatory conditions. As adherence to a low-AGE diet might be challenging for many individuals, the use of agents that sequester dietary AGES in the intestine in order to reduce their absorption from food may have future therapeutic potential for the inhibition of inflammatory pathways.\(^{222}\) The effect of dietary AGES on the composition and function of the gut microbiota and its metabolites requires intensive research. Diets aimed at favorably altering the bacterial composition within the colon could potentially reduce intestinal precursors to MRPs, decrease MRP absorption, or minimize pathogenic microorganisms in the gut able to generate and secrete AGES.

The transient postprandial hyperglycemia induced by food intake (independent of its AGE content) has been shown to induce microinflammatory processes within the body.\(^{235}\) The use of short-term intermittent fasting requires further exploration, as it may be more beneficial than dietary AGE restriction for the attenuation of inflammation. An additional advantage of intermittent fasting is the increased likelihood of weight reduction, which has been shown to reduce circulating AGE levels.\(^{236}\) In a society where many individuals continuously “graze” rather than maintain specific mealtimes, there may be benefits in simply limiting the number of eating occasions on any given day. Consumption of a low-glycemic-index diet is associated with reductions in postmeal blood glucose and insulin excursions as well as lower levels of circulating inflammatory markers and advanced glycation end products.\(^{237}\) High-glycemic-index diets in mice are associated with a 3-fold increase in pathological AGE accumulation in tissue,\(^{238}\) supporting further exploration of low-glycemic-index diets for attenuation of AGES in humans.

### CONCLUSION

It is clear that the role of AGES in the pathogenesis of chronic inflammatory conditions requires more research. AGES and their precursors are ubiquitous in the highly processed foods characteristic of typical Western diets, and it is plausible that AGES may contribute significantly to the inflammatory milieu associated with many chronic noncommunicable diseases, though the potential of diet-derived AGES to facilitate inflammation is still unresolved. AGE accumulation can be manipulated via a number of nutritional components to reduce protein glycation, alter dietary metabolites, or enhance dicarbonyl detoxification systems. However, additional targeted research is required to determine the long-term consequences of chronic AGE overconsumption and the optimal strategies for minimizing AGE-related pathology.

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