Special Article

Effect of reducing dietary advanced glycation end products on obesity-associated complications: a systematic review

Priscila V.M. Ribeiro, Juliana F. Tavares, Mirian A.C. Costa, Jéssica B. Mattar, and Rita C.G. Alfenas

Context: *Consumption of dietary advanced glycation end products (AGEs) is associated with oxidative stress, inflammation, and other chronic conditions commonly associated with obesity.* ***Objective:*** *To analyze the effects of dietary AGEs on complications associated with obesity.* ***Data sources:*** *This systematic review was conducted and reported according to PRISMA guidelines. The PubMed, Cochrane, and Scopus databases were searched, using the terms "advanced glycation end products," "overweight," and "obesity." The last search was performed in October 2018.* ***Data extraction:*** *Six studies that evaluated the effects of low-AGE and high-AGE diets were included in the review. The duration of the studies ranged from 1 day to 12 weeks. A comparison of all the compiled data was conducted by the authors.* ***Data analysis:*** *Circulating and urinary AGE markers, besides soluble receptor for AGEs, were considered as the primary outcomes. The secondary outcomes were cardiometabolic, inflammatory, glycemic, anthropometric, and renal markers.* ***Conclusions:*** *AGE-RAGE interactions can activate the NF-κB (nuclear factor kappa B) signaling pathway and inhibit the PI3K-AKT pathway in adipocytes, which may explain their association with chronic diseases. This interaction can be considered as a novel explanation for the pathogenesis of obesity. AGEs can also be used as a biomarker for monitoring responses to dietary interventions in overweight and obese people.* ***Systematic Review Registration:*** *PROSPERO registration no. CRD42018082745.*

INTRODUCTION

Obesity has reached epidemic proportions worldwide and has become a serious public health problem. The World Health Organization estimated that in 2016 more than 1.9 billion adults were overweight, and of these, over 650 million were obese.[1] Obesity is a risk factor for the development of chronic diseases, such as cardiovascular diseases, diabetes, and kidney disease.[2–4] Inflammation and oxidative stress are complications associated with obesity, which in turn are related to the genesis of chronic diseases.[5,6]

Changes in lifestyle, especially in dietary patterns, play a central role in the prevention and control of obesity. Recent studies have revealed that the consumption of foods rich in advanced glycation end products (AGEs) are thought to play a fundamental role in the pathogenesis of chronic disease.[7,8] Since dietary AGEs increase obesity, oxidative stress, and inflammation, a reduced intake of AGEs appears to be beneficial,

Affiliation: *P.V.M. Ribeiro, J.F. Tavares, M.A.C. Costa, J.B. Mattar, and R.C.G. Alfenas* are with Department of Nutrition and Health, Universidade Federal de Viçosa, Viçosa, Minas Gerais, Brazil.

Correspondence: *P.V.M. Ribeiro*, Department of Nutrition and Health, Universidade Federal de Viçosa, Ave PH Rolfs s/n, Viçosa, Minas Gerais 36570-900, Brazil. E-mail: priscilavazdemelo@yahoo.com.br.

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independently from the consumption of standard energy-restricted diets.

Moreover, some studies have detected a positive association between visceral fat and elevated serum concentration of AGEs, suggesting a causal role of exogenous AGEs in metabolic syndrome, which in turn is independent from energy balance.[9] AGE formation results from nonenzymatic reactions between reactive sugars and proteins (the Maillard reaction), and the formation depends directly on the temperature and the time used for food preparation. This reaction is activated during frying, roasting, grilling, and baking.[10–12] Therefore, the consumption of AGE-rich foods should be restricted.[7]

The consumption of low-AGE diets decreases circulating and urinary AGE markers and improves anthropometric, glycemic, cardiometabolic, inflammatory, and renal function markers in overweight and obese people.[13–18] However, the mechanism of action of molecular AGEs in obesity-associated complications remains unclear. The amount of AGEs considered safe for consumption also needs to be established. Therefore, a systematic review was carried out according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) model,[19] to analyze the effects of dietary AGEs on complications associated with obesity, as well as to discuss the molecular mechanisms linked to the effects of these compounds on the progression of chronic diseases, and to establish a safe recommendation for AGE consumption.

METHODS

Protocol and registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) model[19] (Annex I Checklist) and was registered in the PROSPERO database (registration number: CRD42018082745).

Literature search

The participants, intervention comparators, outcomes, and study design (PICOS) criteria adopted in this study are shown in Table 1. Four authors (PVMR, JFT, MACC, and JBM) independently searched for original articles that investigated the effects of dietary advanced glycation end products on obesity complications, using the following electronic databases: MEDLINE (PubMed, www.pubmed.com), Cochrane (www.cochrane.org), and Scopus (www.scopus.com). Keywords were chosen from MeSH (Medical Subject Headings) terms and Descriptors in Health Sciences (DeHS) using the following search terms: ("glycosylation end products, advanced" OR "advanced glycation end products" OR "dietary advanced glycation end products" OR "circulating advanced glycation end products") AND (overweight OR obesity) NOT review*.

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criterion
Participants	Overweight and obese adults
Intervention or exposure	Consumption of a low-AGE diet
Comparison	Consumption of a high-AGE diet
Outcome	Circulating and urinary AGEs; cardiometabolic, inflammatory, glycemic, renal, and anthropometric markers
Study design	Clinical trials

Abbreviation: AGEs, advanced glycation end products.

The search strategy was not restricted by date and language. The last search was conducted on October 9, 2018. A reverse manual-search was also performed to identify relevant articles cited in the selected studies.

Study selection

The study selection was performed by five authors (PVMR, JFT, MACC, JBM, and RCGA) in three phases: analysis of titles, abstracts, and full texts. Included in the selection were all clinical trials that assessed the effects of reducing intake of dietary advanced glycation end products on markers of obesity complications in overweight and obese individuals.

Comments, reviews, letters, case reports, abstracts, and unpublished articles were excluded, along with animal studies, in-vitro studies, and epidemiological studies involving subjects with overweight- or obesity-related diseases (eg, metabolic syndrome, diabetes, and polycystic ovary syndrome).

Data extraction

After reading the selected studies, a comparison of all the compiled data was conducted by the authors (PVMR, JFT, MACC, JBM, and RCGA) to guarantee their integrity and reliability. Differences in decisions regarding the studies selected were settled by consensus. For each included study, the following information was extracted: title, author name(s), year of publication, study purpose, subjects' characteristics, sample size, study design, intervention (low/high AGE consumption), and study duration; also extracted were the main results regarding circulating and urinary AGEs as well

as cardiometabolic, inflammatory, glycemic, renal, and anthropometric markers.

Assessment of risk of bias

Risk of bias was assessed using the Cochrane Collaboration method.[20] The studies were judged on three levels of bias: high risk, low risk, and unclear (when the information provided was not sufficient to make a clear judgment). The authors considered the following biases: random sequence generation and allocation concealment (selection bias), blinding of participants and staff (performance bias), blinding of results evaluation (detection bias), and selective reporting (notification bias).[20]

Data analyses

All studies reviewed in this article are summarized in Table 2 according to their main characteristics and findings concerning obesity-associated markers. The studies were organized chronologically by year of publication, starting with the first published study. Circulating and urinary advanced glycation end products N€-(carboxymethyl)lysine (CML), N€-(carboxyethyl)lysine (CEL), methylglyoxal (MG), and the soluble receptor for the advanced glycation end product (sRAGE) were considered as the primary outcomes. The secondary outcomes were cardiometabolic markers (lipid profile and systemic arterial pressure), inflammatory markers (TNF-α, IL-6, MCP-1, PCR, NFκB), glycemic markers (insulin sensitivity, HOMA-IR [homeostasis model assessment of insulin resistance], glycemia, fasting insulin), anthropometric markers (body mass index, waist circumference, waist-hip ratio), and renal markers (GFR, albumin, creatinine). In addition, the interaction between dietary AGE intake and the study duration was analyzed.

RESULTS

Study selection

The PubMed, SCOPUS, and Cochrane database searches identified 679 studies. After the removal of 224 duplicates,455 articles remained, of which 445 studies were excluded based on their titles since they were considered irrelevant to the topic of interest. After reading the summary of the remaining 10 studies, 6 met all the criteria for the systematic review. The reasons for the inclusion of studies are shown in Figure 1.

Description of the included studies

A total of 172 healthy overweight and obese (mean BMI $31.7 \pm 2.3\,kg/m^2$) subjects participated in the 6 studies included in this review (Table 2).[13–18] All studies included both overweight and obese participants.[13–18] The sample sizes in these studies varied from 11[13] to 73[15] participants. The mean age was 36 ± 7.7 years for healthy overweight and obese subjects. All studies were randomized and controlled, 4 were crossovers,[13,14,17,18] and 2 were parallel studies,[15] with a duration varying from 1 day[14] to 12 weeks.[16] The content of the AGEs in the test diets ranged from 10.7 mg/day[15] to 43 mg/day[17,18] and 3302 kU/day[13] to 7306 kU/day[16] in the chronic studies and 2.8 mg/meal in the acute study.[14] In the control diets, consumption of AGEs varied from 24.6 mg/day[15] to 59 mg/day[17,18] and 11 223 kU/day to 14 090 kU/day[16] and 5 mg in the acute study[14] (Table 2). In all studies, a normocaloric diet was prescribed to participants and a food menu (low-AGE vs high-AGE content) was provided to accommodate the participants' preferences and dietary habits. In addition, the test and control diets were similar in macronutrient content and total energy, differing only in relation to the AGE content.

Main results of the studies

The main results obtained in this study were related to the effects of dietary AGEs on urinary and circulating AGEs, inflammation and oxidative stress, insulin resistance, and chronic disease markers. Analyzing the AGE consumption between the groups, it was observed that low-AGE diets have an average AGE content of 5304 kU/d[13,16] or 32.23 mg/d[14,15,17,18] and that high-AGE diets average a content of 12 656 kU/d[13,16] or 43.53 mg/d.[14,15,17,18]

The consumption of low-AGE diets was found to reduce the urinary excretion of CML,[15] methylglyoxal-derived hydroimidazolone (MG-H1),[15,17] and CEL.[17] Similarly, there was a reduction in circulating AGEs (CML and MG)[16] in the participants consuming a low-AGE diet. Regarding metabolic markers, low-AGE diets reduced plasma triglyceride levels and increased high-density lipoprotein (HDL),[16] reduced plasma glucose levels after an oral glucose tolerance test, and reduced fasting insulin and HOMA-IR levels,[15] while insulin sensitivity increased.[15,16] Moreover, a restriction in AGE intake also reduced body weight,[15,16] waist circumference,[15] waist-hip ratio,[15] body mass index (BMI),[15,16] and urinary albumin/creatinine ratios,[13] but increased the estimated glomerular filtration rate (eGFR).[17]

In contrast, the consumption of high-AGE diets reduced plasma CML levels, increased urinary CML[13] and postprandial plasma glucose peak,[14] and increased urinary 8-isoprostans[13] and F2-isoprostanes,[14] monocytic chemotactic protein-1 (MCP-1), plasma cystatin C,[13] and vascular cell adhesion molecule-1 (marker of endothelial activation),[14] but reduced levels of macrophage migration inhibitory factor (MIF).[13]

Table 2 **Studies conducted to assess the effect of reducing dietary advanced glycation end products on overweight- and obesity-associated complications**

Reference	Sample	Intervention	Study design	Duration	Main results
Harcourt et al (2011)[13]	11 healthy overweight and obese men 30±9 years old BMI: 31.8±4.8 kg/m^2	Test: low-AGE diet (3302 kU/d) Control: high-AGE diet (14,090 kU/d)	Randomized, controlled, and crossed	2 weeks (4 weeks washout)	Test group: ↓ urinary albumin/creatinine ratios Control group: ↑ plasma cystatin C, ↓ plasma CML, ↑ urinary CML, ↑ urinary 8-isoprostanes, ↑ plasma MCP-1, ↓ plasma MIF
Poulsen et al (2014)[14]	19 healthy overweight and obese individuals 34.8 ± 10.0 years old Sex: 16 women and 3 men BMI: 31.3 ± 5.1 kg/m^2	Test: low-AGE diet (2.8 mg/meal) Control: high-AGE diet (5.0 mg/meal)	Randomized, single-blind, controlled, and crossover	1 day (2 weeks washout)	Test group: ↓ plasma ghrelin after intervention, and ↔ GLP-1 and PYY, compared to the control group Control group: ↑ peak of postprandial plasma glucose, plasma VCAM-1, and urinary F2-isoprostane after intervention compared to the test group
Mark et al (2014)[15]	73 healthy overweight and obese women 39.6±1.4 years old BMI: 32.7±0.7 kg/m^2	Test: low-AGE diet (10.7 mg/d) Control: high-AGE diet (24.6 mg/d)	Randomized, double-blind, controlled, and parallel	4 weeks	Test group: ↓ weight, BMI, WP, waist-hip ratio, urinary excretion of CML and MG-H1, 2h glucose, fasting insulin, and HOMA-IR, and ↑ Si0(120), after intervention compared to the control group
Macías-Cervantes et al (2015)[16]	29 healthy overweight and obese men 43.9±6.2 years old BMI: 28.6±2.0 kg/m^2	Test: low-AGE diet (7306 ± 2811 kU/d) Control: habitual food intake (11, 223 ± 4147 kU/d)	Randomized, controlled, and parallel	12 weeks	Both groups: ↓ weight, BMI, and WC Test group: ↓ triglycerides and circulating AGEs (CML and MG) and ↑ HDL-C
de Courten et al (2016)[17]	20 healthy overweight and obese individuals 34.0±10.0 years old Sex: 6 women and 14 men BMI: 31.3±3.8 kg/m^2	Test: low-AGE diet (43 [36–51] mg/d) Control: high-AGE diet (59 [49–68] mg/d)	Randomized, double-blind, controlled, and crossed	2 weeks (4 weeks washout)	Test group: Sensitivity to insulin, MG-H1, and urinary CEL, eGFR ↔ Serum concentrations of CML, MG-H1, CEL, sRAGE, urinary CML, body weight, and insulin secretion between diets
Baye et al (2017)[18]	20 healthy overweight and obese individuals 34.0±10.0 years old Sex: 6 women and 14 men BMI: 31.3±3.8 kg/m^2	Test: low-AGE diet (43 [36–51] mg/d) Control: high-AGE diet (59 [49–68] mg/d)	Randomized, double-blind, controlled, and crossed	2 weeks (4 weeks washout)	Test group: ↔ SBP, DBP, MAP, PP, TC, LDL, HDL, triglycerides, IL-6, MCP-1, TNF-α, PCR, and NFκB compared to the control

Abbreviations: AGEs, advanced glycation end products; BMI, body mass index; CEL, N€-(carboxyethyl)lysine; CML, N€-(carboxymethyl)lysine; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GLP-1, glucagonlike-peptide-1; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment of insulin resistance; ICAM-1, intracellular adhesion molecule-1; IL-6, interleukin-6; LDL, low-density lipoprotein; MAP, mean arterial pressure; MCP-1, monocyte chemoattractant protein-1; MG-H1, methylglyoxal-derived hydroimidazolidine; MIF, macrophage migration inhibitory factor; NFκB, nuclear factor kappa B; PP, pulse pressure; PYY, peptide YY; SBP, systolic blood pressure; Si0(120), insulin sensitivity index; sRAGE, soluble receptor for advanced glycation end product; TC, total cholesterol; TNF-α, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1; WC, waist circumference; ↔ , unchanged.

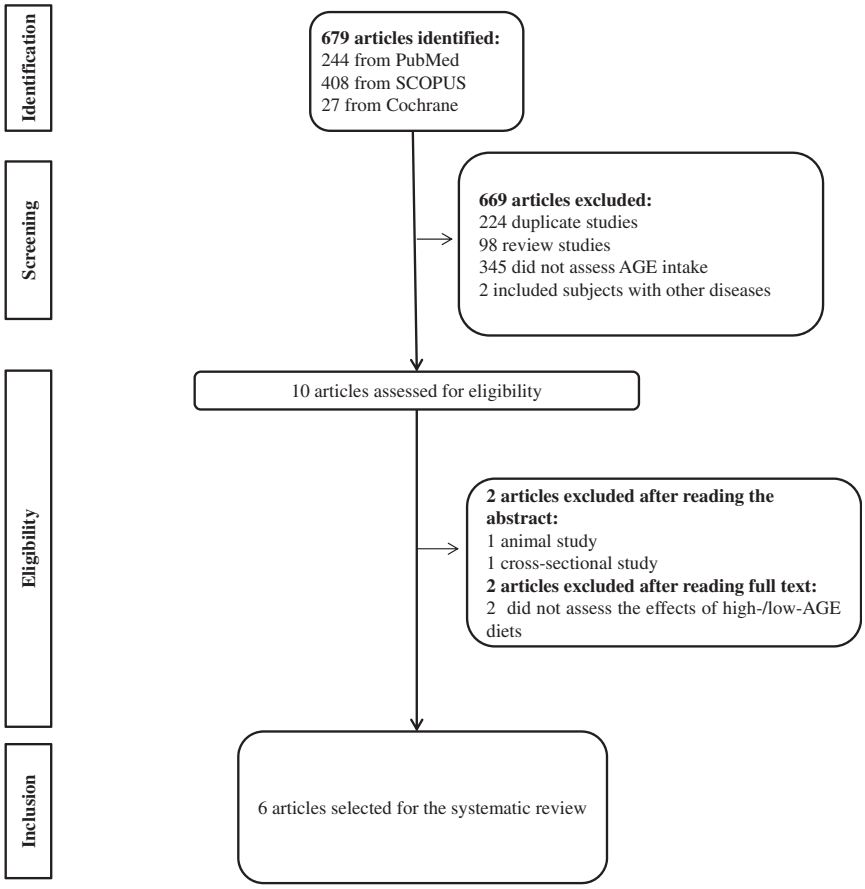

Figure 1 **Flowchart of the study selection process.**

Assessment of risk of bias

The major domains evaluated in the present study were the random generation allocation sequences and the data concerning incomplete results; most of the studies presented a low risk of bias, and only 2 studies were unclear as to how their random allocation sequences were generated.[13,15] All studies were randomized; the missing data were balanced between the intervention groups, and the ratios between the groups were similar. However, blinding of treatment allocations was not clearly presented in 2 studies.[13,15] Only studies by Harcourt et al[13] and Macías-Cervantes et al[16] presented an unclear risk of bias due to the blinding of the participants or staff and the method used to evaluate the results. In addition, Mark et al[15] did not clearly define their selective results report (Figure 2).[13–18]

DISCUSSION

Dietary recommendations

Although some studies have indeed examined the effects of low- or high-AGE diets, owing to the differences between the methods used to determine the AGE content and the limited number of studies, the authors of such studies were unable to suggest a cutoff point to classify the AGE consumption as high or low. A low-AGE diet was associated with positive effects on health (improves anthropometric, glycemic, cardiometabolic, inflammatory, and renal function markers) and better outcomes compared with a high-AGE diet. Despite the fact that the subjects of the studies included in this review were prescribed isocaloric diets, a reduction in body weight was observed[14,15]. However, since the actual food intake was not evaluated, possible unintended modifications on the caloric or macronutrient intake cannot be ruled out. Moreover, the results of the studies suggest a link between a high-AGE diet and adverse impacts on health, evidencing the need to establish the recommended safe dietary AGE intake.[21]

Harcourt et al[13] and Macías-Cervantes et al[16] calculated the consumption of AGEs listed in a database of almost 550 foods. In that report, AGE content was assessed as CML, a chemical type of AGE commonly used for that purpose, and expressed as AGE kU/100 g of food.[21–23] Conversely, the other 4 studies included in this review expressed the AGE content in

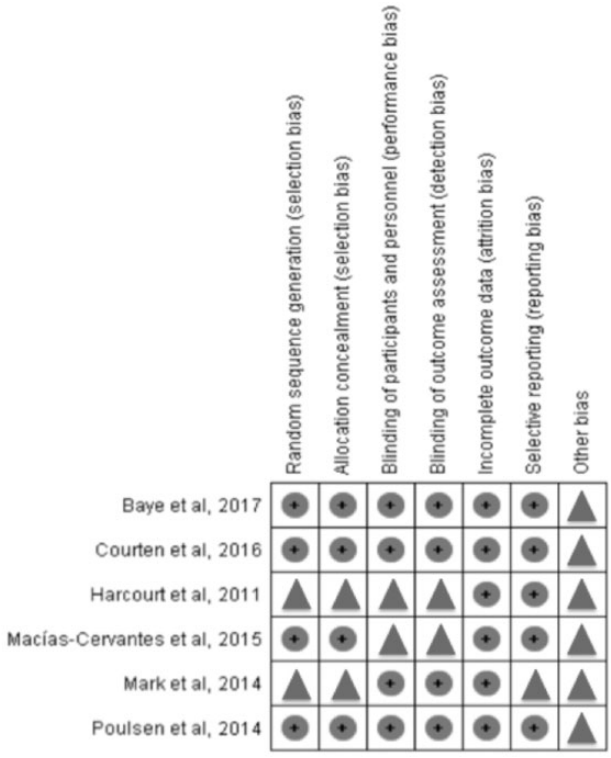

Figure 2 **Risk of bias summary: authors' judgments about each risk of bias item for each included study.** Circle, low risk; triangle, unclear

milligrams.[14,15,17,18] This difference in units of AGE content did not allow a comparison of AGE consumption between the studies. Thus, establishing a standard unit that allows determination of cutoffs for low- and high-AGE diets is recommended. The results of the studies suggest that restricting dietary intake of AGEs may be a therapeutic strategy to promote health. Therefore, it is fundamental to replace AGE-rich foods with low-AGE foods.

In addition to the concentration of reactants, the formation of AGEs in foods is influenced by the preparation technique used.[21,24] Meat, high-sugar/high-fat foods, and highly processed foods are likely to develop a high AGE content.[21,25] High temperatures, low humidity, and alkaline pH contribute to the formation of new AGEs – conditions associated with grilling, searing, roasting, and frying methods of cooking.[21,24]

In contrast, dairy products, fruits, and vegetables have a lower AGE content. Higher humidity, lower temperatures, and low pH make a minor contribution to the formation of AGEs. Thus, steaming, stewing, boiling, and poaching should be the preferred techniques used to prepare foods.[21,24] Before cooking, the use of lemon juice and vinegar may reduce the formation of AGEs.[21] Table 3 shows the differences between food groups and cooking methods that contribute to a lower or higher AGE content.[21–23]

Table 3 **Factors that influence AGE content of foods**

Food characteristic		Cooking method	
High AGEs	Low AGEs	High AGEs	Low AGEs
Processed food	Grains	High temperature	Low temperature
Meat group	Vegetables	Grilling	Steaming
Fat group	Fruits	Searing	Stewing
Bakery products	Fat-free dairy	Roasting	Boiling
Dairy	Soups	Frying	Poaching
		Low humidity	High humidity
		Alkaline pH	Low pH

Source: Uribarri et al (2010)[21]; Barbosa et al (2016)[22]; Tessier and Birlouez-Aragon (2012).[23]
Abbreviation: AGEs, advanced glycation end products.

Effect of dietary AGEs on inflammation and oxidative stress

Obesity is an inflammatory condition[26] associated with an imbalance between the production of reactive oxygen species and their detoxification through biological systems that remove or repair the damage caused by them.[27] Oxidative stress and low-grade inflammation precede the manifestation of chronic diseases such as diabetes and cardiovascular diseases.[5,28] Since obese people are already at increased risk of developing chronic diseases, it is imperative to explore and identify modifiable risk factors for the pathogenesis of chronic diseases. Food is the major environmental factor in direct contact with host defenses. It is currently suggested that AGE-producing substances from processed foods are a source of reactive oxygen species entering the body.[29–31]

AGEs constitute a class of pro-oxidant foods, and their content is increased by processing food at high temperatures.[32,33] Pro-oxidant AGEs also act as "appetite enhancer" agents that simultaneously stimulate excessive food intake and inflammation and increase the risk of obesity and diabetes mellitus.[34]

Approximately 10% of dietary AGEs are absorbed by humans, of which only one-third are excreted in urine and feces. Plasma concentrations of AGEs appear to be directly influenced by diet and the ability of the body to eliminate AGEs.[29] Recent evidence suggests that AGEs can also be formed intraluminally in the bowel through reactions between unabsorbed excess free fructose and partially digested proteins.[35]

AGEs can increase oxidative stress through the receptor for AGEs (RAGE). Activation of RAGE induces a signaling cascade event involving p38 and JNK MAPK (p38 and Jun N-terminal mitogen-activated protein kinase), JAK-STAT (Janus kinase–signal transducer and activator of transcription), and Cdc42/Rac pathways, many of which are the result of, and cause of further,

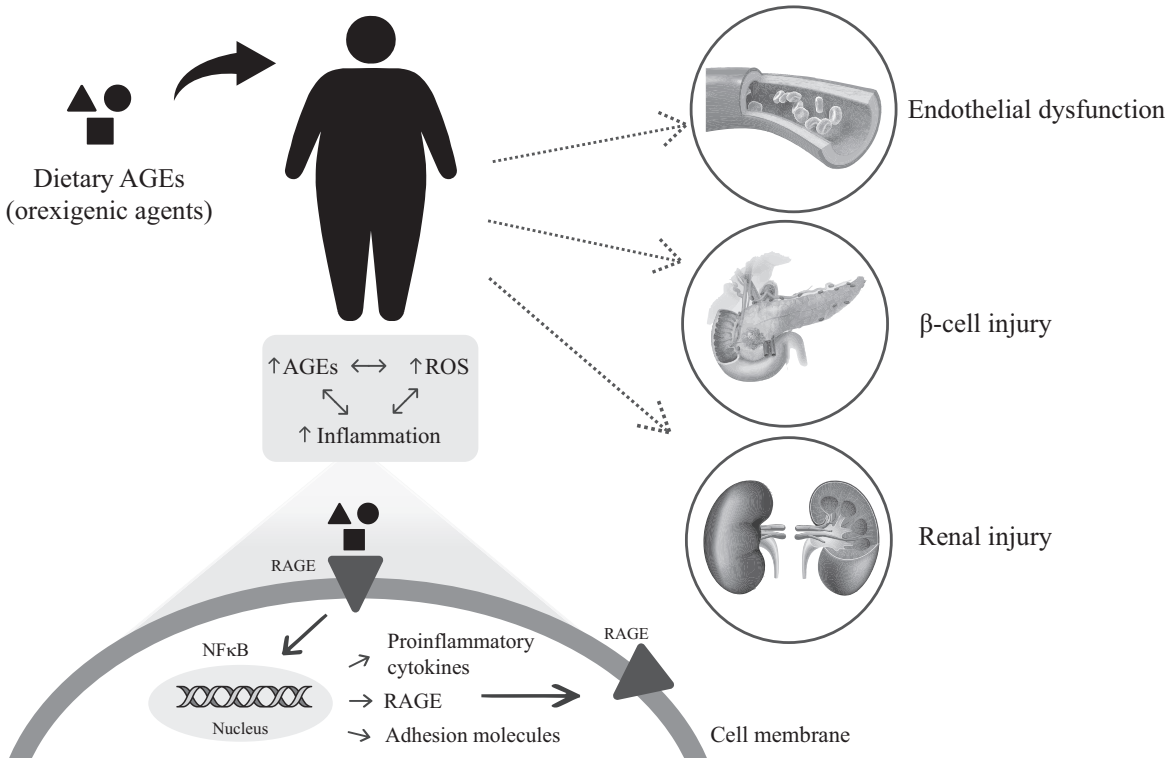

Figure 3 **The effect of dietary AGEs on overweight complications, through the increase in RAGE expression and activation of the NF-κB signaling pathway.** *Abbreviations:* AGEs, advanced glycation end products; NFκB, nuclear factor kappa B; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species

oxidative stress. Thus, they modulate global cellular responses to various stress conditions and increase cellular damage.[36] However, the RAGE-ligand interaction may activate several signaling cascades, which implies that different RAGE-ligands may induce different pathways (especially in different cell types). The consequences of such mechanisms can be critical in negative feedback pathways responsible for the return of cellular behavior to equilibrium.[37]

Some authors observed that a restriction in dietary intake of AGEs led to a reduction in oxidative stress and suppression of RAGE mRNA levels and protein concentrations in people and rats with diabetes.[38,39] Similarly, restricting intake of AGEs reduced RAGE concentrations in healthy human peripheral blood mononuclear cells and in people with diabetes to below their baseline, indicating that RAGE is regulated by AGEs in the external environment.[31,40]

Oxidative stress is an inflammatory mediator. Thus, the binding of AGEs to RAGE during intracellular signaling leads to the activation of the proinflammatory NF-κB (nuclear factor-κB) transcription factor.[41] In turn, NF-κB activates the transcription of target genes, such as proinflammatory cytokines, adhesion molecules, and RAGE.[41–43] Therefore, the expression of RAGE is induced by NF-κB, and continuous NF-κB activation results in positive receptor regulation and guarantees the maintenance and amplification of the signal[43] (Figure 3).

AGEs and insulin resistance

The effects of AGEs and their receptors on adipose tissue remain unknown. In vitro and experimental evidence suggests that AGE-RAGE interactions can attenuate insulin sensitivity in adipocytes.[44,45] In one in-vitro study conducted on 3T3-L1 adipocytes, the presence of AGEs inhibited glucose uptake in both the presence and absence of insulin, and increased the generation of intracellular reactive oxygen species (ROS) and the expression of monocyte-1 chemoattractive protein (MCP-1).[44]

Monden et al[45] demonstrated that increased RAGE expression is associated with adipocyte hypertrophy, suppression of glucose transporter type 4 (GLUT-4), attenuation of insulin-stimulated glucose uptake, and reduction of IRS-1 (insulin receptor substrate-1) phosphorylation. The authors confirmed their results in cells and rats by demonstrating that RAGE deficiency is associated with obesity resistance, increased expression of GLUT-4 and adiponectin, and decreased expression

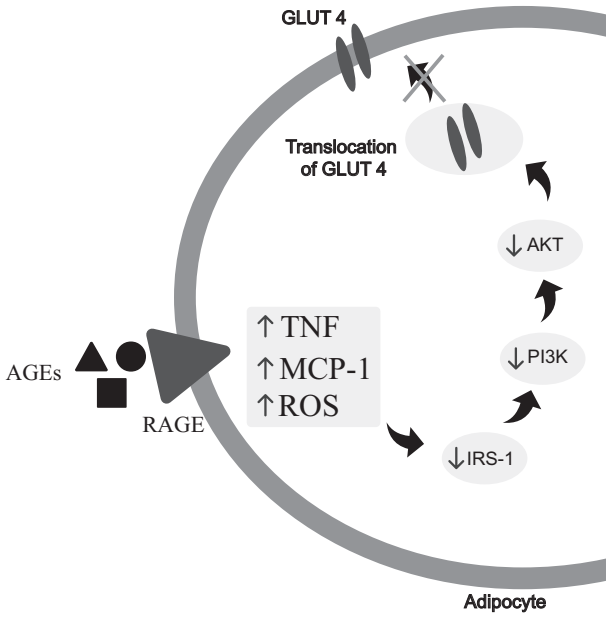

Figure 4 **Proposed AGE-RAGE interaction mechanism associated with increased oxidative stress and inflammation, inducing insulin resistance via the PI3K-AKT signaling pathway in adipocytes.** *Abbreviations:* AGEs, advanced glycation end products; GLUT 4, glucose transporter type 4; IRS-1, insulin receptor substrate-1; MCP-1, monocyte chemoattractant protein-1; PI3K, phosphatidylinositol-3 kinase; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; TNF, tumor necrosis factor

of MCP-1, resulting in increased insulin sensitivity in adipose tissue.[45]

The results of these studies suggest that AGE-RAGE interactions in adipocytes inhibit glucose uptake via the increased production of ROS, cytokines, and other inflammatory molecules, as well as via the decreased phosphorylation of IRS-1, thereby inhibiting the PI3K-AKT signaling pathway.[44–48]

Thus, based on data gathered from the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database, together with in-vitro and experimental evidence,[44,45] the authors hypothesize that AGE-RAGE interactions may be involved in insulin resistance in adipose tissues through downregulation of the insulin signaling pathway (PI3K-AKT) (Figure 4).

Finally, owing to the use of thermal processes by the food industry, the increased consumption of processed foods in the last 50 years has favored a greater consumption of dietary AGEs. Therefore, it is hypothesized that this change in dietary pattern is likely to have contributed to an increase in obesity, oxidative stress, and inflammation, which may explain the increase in the manifestation of overweight-associated complications (diabetes mellitus, cardiometabolic disorders, and renal diseases) due to a higher consumption of AGEs.[34] Thus, this review provides new insights into the role of dietary AGEs in the pathogenesis of obesity and associated complications.

AGEs and chronic diseases

Once host defenses are compromised and increased oxidative stress occurs, AGE-RAGE interactions may increase and perpetuate the inflammation condition, leading to obesity, diabetes mellitus, and cardiovascular and kidney diseases.[41,49] The consumption of an AGE-rich diet appears to lead to pathological consequences, such as weight gain, obesity, and, consequently, metabolic syndrome.[50–52]

The kidney is the major organ for AGE detoxification, by both filtration and active secretion and absorption – two processes that result in the net excretion of urinary AGEs.[29,53] The kidneys are directly exposed to a greater concentration of circulating AGEs than many other organs – a fact that may render them vulnerable to circulating lesions of reactive carbonyls and ROS.[54] A diet rich in AGEs can lead to renal damage by inducing proteinuria and/or high formation of profibrotic transforming growth factor β1 (TGF-β1), accelerating atherosclerosis (through lipid peroxidation).[50,52] It has been shown that chronic ingestion of high-AGE foods may predispose the kidney to chronic injury in the absence of diabetes mellitus, suppressing local anti-AGE defenses, and inducing oxidative stress and inflammatory responses.[30,31]

Furthermore, AGE-RAGE interactions are active in pathogenic pathways involved in the development and progression of atherosclerosis. The endothelium neutralizes the effects of different chemical or physical stimuli to maintain homeostasis. When this balance is disturbed, the endothelium becomes susceptible to invasion by leukocytes and lipids, representing the key steps in the formation of atherosclerotic plaque. However, the bioavailability and activity of the endothelium-derived vasodilator, nitric oxide (NO), have been shown to be reduced by AGEs.[55] The role of AGEs in endothelial dysfunction has been verified in type 2 diabetics, in which serum AGEs were negatively associated with the degree of endothelium-independent vasodilatation.[56] Some mechanisms have been suggested to explain these associations. One of these is the induction of AGE-related oxidative stress and NO inactivity.[57] In addition, NO synthase can be used to reduce the activity of endothelial NOS (eNOS) through receptor-mediated phosphorylation of serine residues in eNOS and to increase the degradation of eNOS mRNA.[58] Additionally, AGEs may impair endothelial balance by reducing the production of endothelial prostacyclin (PGI2) and increasing the expression of endothelin-1.[59]

Regarding the association between AGEs and diabetes, the consumption of an AGE-rich diet for 6 months increased body weight, visceral fat, and 8-isoprostane and decreased insulin and adiponectin sensitivity, leading to the development of diabetes in animals.[50] In another study, T-cell activation occurred, increasing oxidative stress, which led to pancreatic β-cell injury. Therefore, high-AGE consumption favors the occurrence of insulin resistance, visceral obesity, diabetes, and metabolic syndrome.[60]

Limitations

The papers included in this review present strong points. Calorie and macronutrient consumption were controlled in both the test and control groups, decreasing the risk of biases. However, the papers also had several limitations: (1) the duration of the interventions varied among the studies, which may have been insufficient to obtain a real conclusion about the effects of AGEs on health outcomes; (2) the variables analyzed differed among the studies; (3) none of the studies presented the actual dietary AGE content – only the mean values were tested; and (4) the AGE units used differed among the studies. All these factors rendered it difficult to compare the results obtained by the studies and to draw up recommendations about AGE consumption.

Several AGEs are formed in food during preparation processes. However, it is difficult to quantify the total AGE content since no standard quantification method exists. Although the foods with the highest AGE contents and the food processing methods capable of increasing AGE content are well known, more studies are needed to identify the food groups that may contribute the most to total dietary AGE intake.

CONCLUSION

The consumption of low-AGE diets was found to reduce the concentration of circulating and urinary excretion of AGE markers, improve metabolic syndrome markers (reduced plasma triglycerides, blood glucose, fasting insulin, and HOMA-IR, but increased HDL), and reduce anthropometric variables (body weight, waist circumference, waist-hip ratio, BMI) and urinary albumin/creatinine ratios, but increased the estimated glomerular filtration rate. However, high-AGE diets reduced plasma CML and increased urinary CML, postprandial plasma glucose peak, and the concentration of urinary oxidative stress (8-isoprostanes and F2-isoprostanes), while negatively affecting inflammation (increased monocyte chemoattractant protein-1 [MCP-1]), renal function (plasma cystatin C [12]), and cardiovascular disease (vascular cell adhesion molecule-1: marker of endothelial activation) markers.

The results of the chronic studies selected for this review indicated that dietary intake of AGEs ranging from 3302 kU/day to 7306 kU/day and from 10.7 mg/day to 43 mg/day for 2–12 weeks positively affected the concentration of markers related to overweight complications. However, the uncertain contradictions related to dosage of AGEs in food make it difficult to establish a safe level of AGE consumption. Therefore, reducing the consumption of processed foods and changing food preparation methods are good strategies to promote health.

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REFERENCES

1. World Health Organization. Obesity and overweight. USA. Available at: http://www.who.int/mediacentre/factsheets/fs311/en/. Accessed December 7, 2017.
2. de Heredia FP, Gómez-Martínez S, Marcos A. Obesity, inflammation and the immune system. *Proc Nutr Soc*. 2012;71:332–338.
3. Abbasi F, Blasey C, Reaven GM. Cardiometabolic risk factors and obesity: does it matter whether BMI or waist circumference is the index of obesity? *Am J Clin Nutr*. 2013;98:637–640.
4. Jung UJ, Choi M-S. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci*. 2014;15:6184–6223.
5. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, et al. Inflammation, oxidative stress, and obesity. *Int J Mol Sci*. 2011;12:3117–3132.
6. Bondia-Pons I, Ryan L, Martinez JA. Oxidative stress and inflammation interactions in human obesity. *J Physiol Biochem*. 2012;68:701–711.
7. Yamagishi S, Ueda S, Okuda S. Food-derived advanced glycation end products (AGEs): a novel therapeutic target for various disorders. *Curr Pharm Des*. 2007;13:2832–2836.
8. Vlassara H, Cai W, Tripp E, et al. Oral AGE restriction ameliorates insulin resistance in obese individuals with the metabolic syndrome: a randomised controlled trial. *Diabetologia*. 2016;59:2181–2192.
9. Uribarri J, Cai W, Woodward M, et al. Elevated serum advanced glycation endproducts in obese indicate risk for the metabolic syndrome: a link between healthy and unhealthy obesity? *J Clin Endocrinol Metab*. 2015;100:1957–1966.
10. Ames JM. Applications of the Maillard reaction in the food industry. *Food Chem*. 1998;62:431–439.

11. Delgado-Andrade C, Seiquer I, Haro A, et al. Development of the Maillard reaction in foods cooked by different techniques. Intake of Maillard-derived compounds. *Food Chem*. 2010;122:145–153.
12. Delgado-Andrade C, Tessier FJ, Niquet-Leridon C, et al. Study of the urinary and faecal excretion of Nε-carboxymethyllysine in young human volunteers. *Amino Acids*. 2012;43:595–602.
13. Harcourt BE, Sourris KC, Coughlan MT, et al. Targeted reduction of advanced glycation improves renal function in obesity. *Kidney Int*. 2011;80:190–198.
14. Poulsen MW, Bak MJ, Andersen JM, et al. Effect of dietary advanced glycation end products on postprandial appetite, inflammation, and endothelial activation in healthy overweight individuals. *Eur J Nutr*. 2014;53:661–672.
15. Mark AB, Poulsen MW, Andersen S, et al. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. *Diabetes Care*. 2014;37:88–95.
16. Macías-Cervantes MH, Rodríguez-Soto JMD, Uribarri J, et al. Effect of an advanced glycation end product-restricted diet and exercise on metabolic parameters in adult overweight men. *Nutrition*. 2015;31:446–451.
17. de Courten B, De Courten MPJ, Soldatos G, et al. Diet low in advanced glycation end products increases insulin sensitivity in healthy overweight individuals: a double-blind, randomized, crossover trial. *Am J Clin Nutr*. 2016;103:1426–1433.
18. Baye E, Courten MPJ D, Walker K, et al. Effect of dietary advanced glycation end products on inflammation and cardiovascular risks in healthy overweight adults: a randomised crossover trial. *Sci Rep*. 2017;7:4123. doi:10.1038/s41598-017-04214-6
19. Moher D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement (Chinese edition). *J Chin Integr Med*. 2009;7:889–896.
20. Higgins JPT, Green S, Cochrane Collaboration, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Chichester, England, Hoboken, NJ: Wiley-Blackwell; 2008.
21. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. *J Am Diet Assoc*. 2010;110:911–916.e12.
22. Barbosa JHP, Souza IT, Santana AEG, et al. Determination of advanced glycation (AGEs) and lipoxidation (ALEs) end products in foods and biological systems: advances, challenges and perspectives. *Quím Nova*. 2016;39. doi:10.5935/0100-4042.20160048
23. Tessier FJ, Birlouez-Aragon I. Health effects of dietary Maillard reaction products: the results of ICARE and other studies. *Amino Acids*. 2012;42:1119–1131.
24. Goldberg T, Cai W, Peppa M, et al. Advanced glycoxidation end products in commonly consumed foods. *J Am Diet Assoc*. 2004;104:1287–1291.
25. Diamanti-Kandarakis E, Palimeri S, Palioura E. Current perspectives on the health risks associated with the consumption of advanced glycation end products: recommendations for dietary management. *Diabetes Metab Syndr Obes Targets Ther*. 2015;8:415–426. doi:10.2147/DMSO.S63089
26. Nathan C. Epidemic inflammation: pondering obesity. *Mol Med*. 2008;14:485–492.
27. Adachi T, Inoue M, Hara H, et al. Relationship of plasma extracellular-superoxide dismutase level with insulin resistance in type 2 diabetic patients. *J Endocrinol*. 2004;181:413–417.
28. Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in obesity and its impact on metabolic syndrome. *J Clin Invest*. 2004;114:1752–1761.
29. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci USA*. 1997;94:6474–6479.
30. Uribarri J, Cai W, Peppa M, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. *J Gerontol A Biol Sci Med Sci*. 2007;62:427–433.
31. Vlassara H, Torreggiani M, Post JB, et al. Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. *Kidney Int Suppl*. 2009;76(Suppl):S3–S11.
32. Pouillart P, Mauprivez H, Ait-Ameur L, et al. Strategy for the study of the health impact of dietary Maillard products in clinical studies: the example of the ICARE clinical study on healthy adults. *Ann N Y Acad Sci*. 2008;1126:173–176.
33. Ames JM. Determination of N epsilon-(carboxymethyl)lysine in foods and related systems. *Ann N Y Acad Sci*. 2008;1126:20–24.
34. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. *Nat Rev Endocrinol*. 2011;7:526–539.
35. Bains Y, Gugliucci A, Caccavello R. Advanced glycation endproducts form during ovalbumin digestion in the presence of fructose: inhibition by chlorogenic acid. *Fitoterapia*. 2017;120:1–5.
36. Yeh RF, Lim LP, Burge CB. Computational inference of homologous gene structures in the human genome. *Genome Res*. 2001;11:803–816.
37. Bierhaus A, Humpert PM, Morcos M, et al. Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med*. 2005;83:876–886.
38. Cai W, He JC, Zhu L, et al. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: association with increased AGER1 expression. *Am J Pathol*. 2007;170:1893–1902.
39. Cai W, He JC, Zhu L, et al. Oral glycotoxins determine the effects of calorie restriction on oxidant stress, age-related diseases, and lifespan. *Am J Pathol*. 2008;173:327–336.
40. Uribarri J, Cai W, Ramdas M, et al. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. *Diabetes Care*. 2011;34:1610–1616.
41. Bierhaus A, Schiekofer S, Schwaninger M, et al. Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes*. 2001;50:2792–2808.
42. Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997;336:1066–1071.
43. Li J, Schmidt AM. Characterization and functional analysis of the promoter of RAGE, the receptor for advanced glycation end products. *J Biol Chem*. 1997;272:16498–16506.
44. Unoki H, Bujo H, Yamagishi S, et al. Advanced glycation end products attenuate cellular insulin sensitivity by increasing the generation of intracellular reactive oxygen species in adipocytes. *Diabetes Res Clin Pract*. 2007;76:236–244.
45. Monden M, Koyama H, Otsuka Y, et al. Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice: involvement of toll-like receptor 2. *Diabetes*. 2013;62:478–489.
46. Chakraborty C. Biochemical and molecular basis of insulin resistance. *Curr Protein Pept Sci*. 2006;7:113–121.
47. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. *Nat Rev Mol Cell Biol*. 2006;7:85–96.
48. Chakraborty C, Roy SS, Hsu MJ, et al. Landscape mapping of functional proteins in insulin signal transduction and insulin resistance: a network-based protein-protein interaction analysis. *PLoS One*. 2011;6:e16388.
49. Basta G, Lazzerini G, Massaro M, et al. Advanced glycation end products activate endothelium through signal-transduction receptor RAGE: a mechanism for amplification of inflammatory responses. *Circulation*. 2002;105:816–822.
50. Hofmann SM, Dong H-J, Li Z, et al. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the db/db mouse. *Diabetes*. 2002;51:2082–2089.
51. Uribarri J, Peppa M, Cai W, et al. Restriction of dietary glycotoxins reduces excessive advanced glycation end products in renal failure patients. *J Am Soc Nephrol*. 2003;14:728–731.
52. Kaňková K, Šebeková K. Genetic variability in the RAGE gene: possible implications for nutrigenetics, nutrigenomics, and understanding the susceptibility to diabetic complications. *Mol Nutr Food Res*. 2005;49:700–709.
53. Makita Z, Radoff S, Rayfield EJ, et al. Advanced glycosylation end products in patients with diabetic nephropathy. *N Engl J Med*. 1991;325:836–842.
54. Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. *Lab Investig J Tech Methods Pathol*. 1994;70:138–151.
55. Bucala R, Tracey KJ, Cerami A. Advanced glycosylation products quench nitric oxide and mediate defective endothelium-dependent vasodilatation in experimental diabetes. *J Clin Invest*. 1991;87:432–438.
56. Tan KCB, Chow W-S, Ai VHG, et al. Advanced glycation end products and endothelial dysfunction in type 2 diabetes. *Diabetes Care*. 2002;25:1055–1059.
57. Xu B, Chibber R, Ruggiero D, et al. Impairment of vascular endothelial nitric oxide synthase activity by advanced glycation end products. *FASEB J*. 2003;17:1289–1291.
58. Rojas A, Romay S, González D, et al. Regulation of endothelial nitric oxide synthase expression by albumin-derived advanced glycosylation end products. *Circ Res*. 2000;86:E50–E54.
59. Yamagishi S, Fujimori H, Yonekura H, et al. Advanced glycation endproducts inhibit prostacyclin production and induce plasminogen activator inhibitor-1 in human microvascular endothelial cells. *Diabetologia*. 1998;41:1435–1441.
60. Peppa M, Uribarri J, Cai W, et al. Glycoxidation and inflammation in renal failure patients. *Am J Kidney Dis*. 2004;43:690–695.