JULIANA FERREIRA TAVARES

DIETARY ADVANCED GLYCATION END PRODUCTS INTAKE AND CARDIOMETABOLIC RISK IN OVERWEIGHT ADULTS

Dissertação apresentada à Universidade Federal de Viçosa, como parte das exigências do Programa de Pós-Graduação em Ciência da Nutrição, para obtenção do título de *Magister Scientiae.*

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(Orientadora)

Aos meus pais.

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SUMMARY

1. LIST OF ABREVIATIONS AND SYMBOLS

AGEs	Advanced glycation end products
BMI	Body mass index
CAT	Catalase
CEL	Carboxyethyl lysine
CML	Carboxymethyl lysine
CRP	C-reactive protein
DBP	Diastolic blood pressure
DeHS	Descriptors in health sciences
DEXA	Dual energy X-ray absorptiometry
eNOS	Endothelial nitric oxide synthase
FRAP	Total plasma antioxidant activity
GFR	Glomerular filtration rate
GLP	Glucagon-like peptide
GLUT	Glucose transporter
H2O2	Hydrogen peroxide
HDL-c	High-density-lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
ICAM	Intracellular adhesion molecule
IL	Interleukin
IPAQ	International physical activity questionnaire
IRS-1	Insulin receptor substrate 1
JAK-STAT	Janus kinase signal transducer of activation
JNK	Jun N-terminal kinase
KEGG	Kyoto Encyclopedia of Genes and Genomes
kU	Kilounits
LDL-c	Low-density lipoprotein cholesterol
MAP	Mean arterial pressure
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte-1 chemoattractive protein
MDA	Malondialdehyde
MeSH	Medical subject headings
MG	Methylglyoxal
MIF	Macrophage migration inhibitory factor

NFκB	Nuclear factor kappa B
NO	Nitric oxide
PICOS	Participants, intervention comparators, outcomes, and study design
PP	Pulse pressure
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PYY	Peptide YY
QFFQ	Quantitative food frequency questionnaire
RAGE	Receptor for advanced glycation end products
RCS	Reactive carbonyls species
ROS	Reactive oxygen species
$\mathbf{S_{i0,120}}$	Insulin sensitivity index
SBP	Systolic blood pressure
SD	Standard deviation
SOD	Superoxide dismutase
sRAGE	Soluble receptor for advanced glycation end products
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TG/HDL-c	Triglyceride to high-density lipoprotein cholesterol ratio
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TyG	Triglyceride-glucose index
VCAM	Vascular cell adhesion molecule
VLDL-c	Very-low-density-lipoprotein cholesterol
WC	Waist circumference
↔	Unchanged
↑	Increase
↓	Reduction

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4. ABSTRACT

TAVARES, Juliana Ferreira, M.Sc., Universidade Federal de Viçosa, September, 2018. **Dietary advanced glycation end products intake and cardiometabolic risk in overweight adults.** Adviser: Rita de Cássia Gonçalves Alfenas.

Obesity has reached epidemic proportions worldwide and it is considered a severe public health problem. Overweight is associated with inflammation and oxidative stress, leading to chronic diseases manifestation. The results of recent studies suggest that advanced glycation end products (AGEs), in turn, may favor inflammation and oxidative stress occurrence. Therefore, the consumption of diets rich in AGEs may be involved in the pathogenesis of chronic diseases. Although the effect of the consumption of dietary AGEs has been investigated in animals and humans with diabetes and impaired renal function, studies in overweight healthy subjects are scarce. Therefore, we conducted a systematic review in which we critically analysed clinical studies that evaluated the effects of dietary AGEs on overweight related complications. We also conducted a cross-sectional study to explore the associations between dietary AGEs versus cardiometabolic risk markers in healthy overweight adult subjects. In our systematic review we verified that dietary AGEs restriction seems to improve anthropometric, glycemic, cardiometabolic and inflammatory markers, suggesting that it may be a therapeutic strategy to promote health and prevent chronic diseases. In our cross-sectional study, we estimated the habitual dietary AGEs intake using a Quantitative Food Frequency Questionnaire to assess our subject's previous six months food intake. We also assessed blood pressure, biochemical variables, homeostatic model assessment for insulin resistance (HOMA-IR), besides the concentrations of inflammatory, and oxidative stress markers. Dietary AGEs consumption was positively associated with malondialdehyde concentrations, an oxidative stress and lipid peroxidation marker, regardless of habitual physical activity, sex, body mass index, energy intake and macronutrients intake. Since oxidative stress is a condition implicated in chronic diseases pathogenesis and overweight subjects are already at high risk of developing such conditions, it is imperative to establish a safe recommendation on dietary AGEs intake and to further explore the molecular mechanisms underlying dietary AGEs and chronic diseases development.

5. RESUMO

TAVARES, Juliana Ferreira, M.Sc., Universidade Federal de Viçosa, setembro de 2018. **Consumo de produtos finais de glicação avançada e risco cardiometabólico em adultos com excesso de peso.** Orientadora: Rita de Cássia Gonçalves Alfenas.

A obesidade atingiu proporções epidêmicas em todo o mundo e é considerada um grave problema de saúde pública. O excesso de peso se associa à inflamação e ao estresse oxidativo, levando à manifestação de doenças crônicas. Os resultados de estudos recentes sugerem que os produtos finais de glicação avançada (AGEs), por sua vez, podem favorecer a ocorrência de inflamação e estresse oxidativo. Logo, o consumo de dietas ricas em AGEs pode estar envolvido na patogênese das doenças crônicas. Embora o consumo de AGEs tenha sido investigado em animais e em indivíduos com diabetes e comprometimento da função renal, os estudos conduzidos em indivíduos com sobrepeso saudáveis são escassos. Por este motivo, realizamos uma revisão sistemática em que nós analisados criticamente os estudos clínicos que avaliaram os efeitos dos AGEs dietéticos em complicações relacionadas ao excesso de peso. Além disso, realizamos um estudo transversal para explorar as associações entre o consumo de AGEs e os marcadores de risco cardiometabólico em adultos saudáveis com excesso de peso. Em nossa revisão sistemática nós verificamos que a restrição de AGEs na dieta melhora marcadores antropométricos, glicêmicos, cardiometabólicos e inflamatórios e, portanto, sugerindo que esta pode ser uma estratégia terapêutica para promover a saúde e prevenir doenças crônicas. No estudo transversal, nós estimamos a ingestão de AGEs usando um Questionário Quantitativo de Frequência Alimentar pra avaliar a ingestão alimentar nos seis meses anteriores. Nós também avaliamos pressão arterial, variáveis bioquímicas sanguíneas, homeostatic model assessment for insulin resistance (HOMA-IR), além da concentração de marcadores inflamatórios e de estresse oxidativo. O consumo de AGEs na dieta se associou positivamente às concentrações de malondialdeído, um marcador de estresse oxidativo e peroxidação lipídica, independentemente da atividade física habitual, sexo, índice de massa corporal, consumo de calorias e ingestão de macronutrientes. Como o estresse oxidativo é uma condição implicada na patogênese das doenças crônicas e os indivíduos com sobrepeso já estão em maior risco de desenvolver tais condições, é imperativo estabelecer uma recomendação segura sobre a ingestão de AGEs e explorar os mecanismos moleculares relacionados ao consumo de AGEs no desenvolvimento de doenças crônicas.

6. GENERAL INTRODUCTION

The prevalence of obesity nearly tripled in the past decades and reached epidemic proportions worldwide. According to the World Health Organization, in 2016, 39% of the adult population were overweight and 13% obese (WHO, 2017). Overweight is a risk factor for cardiovascular and metabolic diseases (ABBASI et al., 2013; JUNG; CHOI, 2014). Furthermore, inflammation and oxidative stress are overweight associated complications and are considered essential mechanisms involved in chronic diseases genesis (BONDIA-PONS et al., 2012; FERNÁNDEZ-SÁNCHEZ et al., 2011; DE HEREDIA et al., 2012; FURUKAWA et al., 2017).

Advanced glycation end products (AGEs) are a group of prooxidants that are highly reactive compounds formed from non-enzymatic reactions between reactive sugars and free amino acid groups in proteins, lipids, and nucleic acids (URIBARRI et al., 2010a). These compounds are formed endogenously as a normal consequence of metabolism, but under hyperglycemia and elevated oxidative stress their formation is accelerated (SINGH et al., 2009; URIBARRI et al., 2010a). AGEs can also be originated from diet (TESSIER; BIRLOUEZ-ARAGON, 2012). In modern western diets, high amounts of sugar, fat, and protein are widely consumed, resulting in high AGEs concentrations in the blood (YAMAGISHI; OKUDA, 2007; DI PINO et al., 2016; VLASSARA et al., 2016). Although the nutrient composition of the consumed diet is a key factor in AGEs formation, the reaction that leads to AGEs formation depends directly in the temperature and the time applied in food preparation and processing. AGEs formation is mainly increased during frying, roasting, grilling, and baking (AMES, 1998; DELGADO-ANDRADE et al., 2010, 2012). The Maillard reaction, a process that leads to browning of food, widely used by industry to enhance sensorial characteristics of foods, is well known to increase AGEs formation (TESSIER; BIRLOUEZ-ARAGON, 2012).

High circulating AGEs concentrations have been implicated in chronic diseases pathogenesis (YAMAGISHI; OKUDA, 2007; VLASSARA et al., 2016). It is estimated that 10-30% of the dietary AGEs consumed are readily absorbed into the bloodstream, and only one third of it is excreted in urine and feces, contributing significantly to the total of pool AGEs in the body (GOLDBERG et al., 2004; DI PINO et al., 2016; EJTAHED et al., 2016; BOTROS et al., 2017). The clinical relevance of AGEs is related to their capacity to activate inflammatory pathways and induce oxidative stress by binding to their specific membrane bound receptors (RAGE) (GUGLIUCCI et al., 2009; BRIX et al., 2012).

Observational studies involving impaired renal function and diabetes subjects demonstrated associations between high dietary AGEs intake versus oxidative stress and inflammation biomarkers, besides endothelial dysfunction, hyperglycemia, and hyperlipidemia (URIBARRI et al., 2003; CHAO et al., 2010). However, the associations between the consumption of AGEs and cardiometabolic risk factors in healthy overweight subjects have not been explored yet. Since this population its already at a increased risk of developing chronic diseases it is imperative to explore and identify modifiable risk factors for chronic diseases pathogenesis.

The results of human clinical trials suggest that the consumption of AGEs restricted diets leads to beneficial effects on health in overweight subjects (HARCOURT et al., 2011; POULSEN et al., 2014; MARK et al., 2014; MACÍAS-CERVANTES et al., 2015; DE COURTEN et al., 2016; BAYE et al., 2017). Nonetheless, in none of these studies the actual dietary AGEs consumption was assessed, which may impair the reliability of the results obtained in these studies.

However, in case the negative effects of dietary AGEs on health is confirmed in well-designed studies, the establishment of the amount of dietary AGEs intake considered to be safe must be defined (URIBARRI et al., 2010b). Besides, recommendation on AGEs restriction consumption could be a relatively simple, but effective approach for obesity and chronic diseases prevention and control (YAMAGISHI; OKUDA, 2007; ANGOORANI et al., 2016).

7. OBJECTIVE

General objective

To assess the associations between dietary advanced glycation end products intake versus cardiometabolic risk markers in healthy overweight adults subjects.

Specific objectives

- Perform a critical review of the current literature about the effects of dietary advanced glycation end products on overweight related complications, and propose the molecular mechanisms related to the effects of these compounds in chronic diseases;
- Characterize the subjects habitual dietary advanced glycation end products intake;
- Evaluate the associations between the habitual dietary advanced glycation end products intake versus:
    - Anthropometry and body composition;
    - Systemic blood pressure;
    - Lipid profile, glucose and insulin serum concentrations;
    - Insulin resistance;
    - Oxidative stress and inflammation serum markers concentrations.

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9. REVIEW ARTICLE: Effect of dietary advanced glycation end products on overweight associated complications: a systematic review

(Artigo submetido à revista Nutrition Reviews, aguardando aceite final)

9.1 ABSTRACT

Context: The consumption of advanced glycation end products (AGEs) is related to oxidative stress, inflammation and the development of chronic diseases.

Objective: This systematic review was designed to analyze the effects of dietary AGEs on overweight complications.

Data sources: The terms 'advanced glycation end products' and 'overweight' were searched on the PubMed, Cochrane and Scopus databases. The last search was performed in September, 2017.

Data extraction: Six studies that tested the effect of low and high-AGE diets consumed from one day to 12 weeks were included. A comparison of all the compiled data was conducted by the authors.

Results: The studies reported an improvement in circulating and urinary AGEs and in anthropometric, glycemic, cardiometabolic, inflammatory and renal markers when a low-AGE diet was consumed. High consumption of AGEs leads to increases in oxidative stress and inflammation.

Conclusions: AGE-RAGE interactions can activate the NF-κB signaling pathway and can inhibit the adipocytes PI3K-AKT pathway, which may explain their association with chronic diseases. This interaction can be considered as a novel explanation for obesity pathogenesis. AGEs can also be used as a biomarker for monitoring responses to dietary interventions in overweight people.

PROSPERO Registration number: CRD42018082745

Keywords: Advanced glycation end product**,** RAGE, insulin resistance, NF-κB, ROS, pathway PI3K-AKT, dietary recommendations, dietary AGEs, obesity, renal injury and endothelial dysfunction.

9.2. INTRODUCTION

Obesity has reached epidemic proportions worldwide and has become a serious public health problem. The World Health Organization estimates that in 2016 more than 1.9 billion adults were overweight and that over 650 million of them were obese.[1] Overweight 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 overweight, 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 obesity prevention and control. Recently, the consumption of foods rich in advanced glycation end products (AGEs) has been considered to play a fundamental role in chronic disease pathogenesis.[7,8] AGEs formation results from non-enzymatic 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.[9–11] Therefore, the consumption of AGEs-rich foods should be restricted.[7] The consumption of low-AGEs diets decreases circulating and urinary AGEs markers and improves anthropometric, glycemic, cardiometabolic, inflammatory and renal function markers in overweight people.[12–17]

However, the mechanism of action of molecular AGEs in overweight subjects and the complications remain unclear. The amount of AGEs that is considered to be safe for consumption also needs to be established. Therefore, the purpose of this systematic review is to analyze the studies that have evaluated the effects of dietary AGE consumption on overweight people complication markers, to investigate the molecular mechanisms related to the effects of these compounds in chronic diseases, and to suggest a safe recommendation for AGEs ingestion based on the results of the published studies.

9.3. METHODS

Protocol and Registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[18] (Supplementary Table I - Checklist) and was registered in PROSPERO (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 independently searched for original articles that investigated the effects of dietary advanced glycation end products on overweight complications using the following electronic databases: MEDLINE (PubMed, www.pubmed.com), Cochrane (www.cochrane.org), and Scopus (www.scopus.com). Keywords were chosen from the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeHS) using the following search strategy: ("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*.

The search strategy was not restricted by date and language. The last search was done in September 13, 2017. A reverse hand-search was also performed to identify relevant articles cited in all selected studies.

Table 1: PICOS criteria for inclusion of studies

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

AGEs: Advanced glycation end products.

Study Selection

The study selection was performed by five authors in three phases: analysis of titles, abstracts and full texts. All clinical trials that assessed the effects of dietary advanced glycation end products on overweight complications were included.

Comments, reviews, letters, case reports, abstracts and unpublished articles were not included. Animal studies, *in vitro* studies, and epidemiological studies involving people with diseases other than being overweight (e.g., metabolic syndrome, diabetes, and polycystic ovary syndrome) were excluded.

Data Extraction

After reading the selected studies, a comparison of all the compiled data was conducted by the authors to guarantee its integrity and reliability. Divergent decisions were settled by consensus. For each study included, the following information was extracted: title, author's name, year of publication, study purpose, subjects' characteristics, sample size, study design, intervention (low/high AGEs consumption), and study duration; in addition, the main results were extracted regarding circulating and urinary advanced glycation end products 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.[19] 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), and blinding of results evaluation (detection bias) and selective reporting (notification bias).[19]

Data Analyses

All studies reviewed in this article were summarized in a table according to their main characteristics and results concerning overweight-associated markers. The studies were organized chronologically by year of publication, starting with the first published study. Circulating and urinary advanced glycation end products carboxymethyl lysine (CML), carboxyethyl lysine (CEL), methylglyoxal (MG) and the soluble receptor for the advanced glycation end product (sRAGE) were considered as the primary outcomes. The secondary results were cardiometabolic (lipid profile and systemic arterial pressure),

inflammatory (TNF-α, IL-6, MCP-1, PCR, NFκB), glycemic (insulin sensitivity, HOMA-IR, glycemia, fasting insulin), anthropometric (body mass index, waist circumference, waist-hip ratio) and renal (GFR, albumin, creatinine) markers. In addition, the interaction of dietary AGEs intake versus the study duration was analyzed.

9.4. RESULTS

Study Selection

After searching the PubMed, SCOPUS and Cochrane databases, 584 studies were identified. A total of 191 duplicates were identified among the databases and were removed, resulting in 393 articles. Then, 383 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 criteria for the systematic review. The reasons for exclusion of the other studies are indicated in Figure 1.

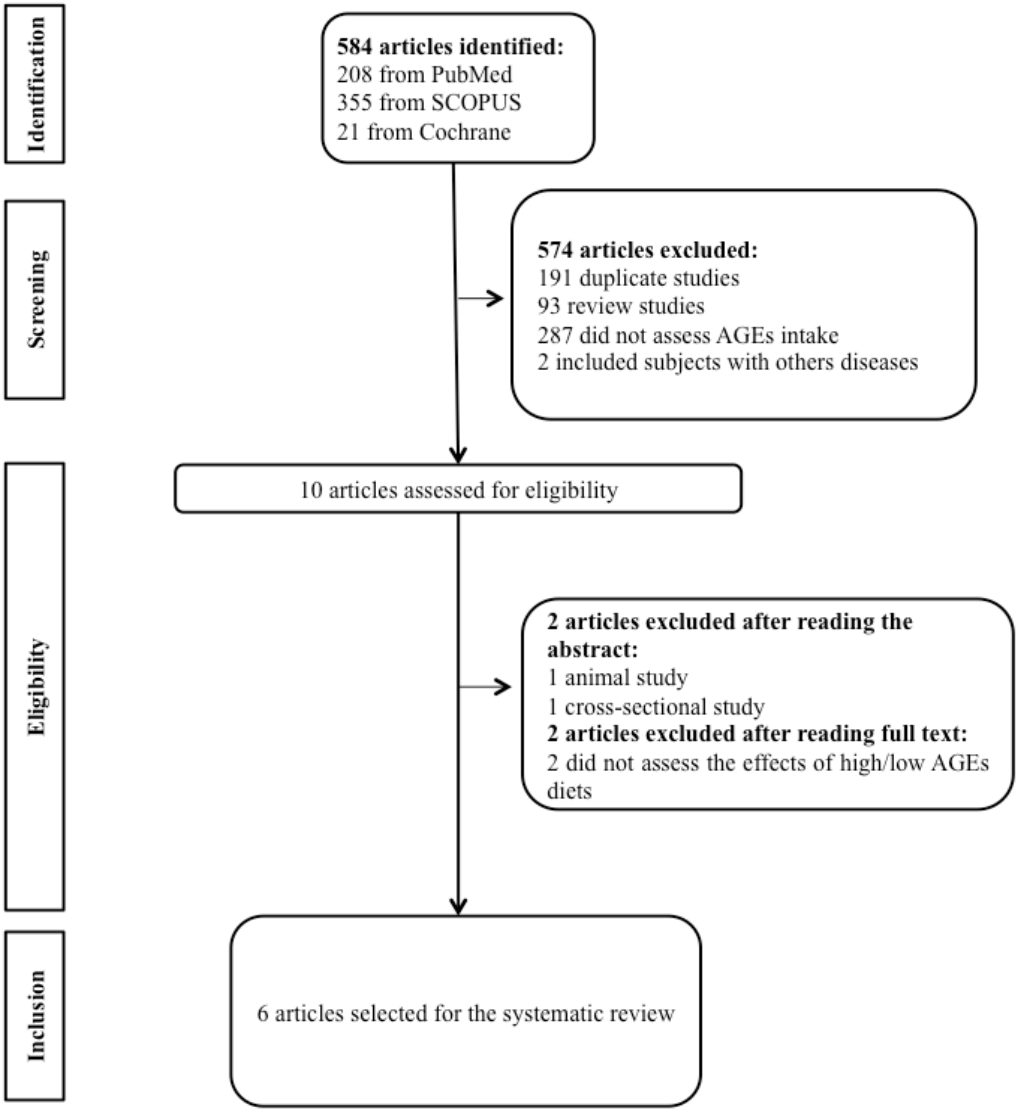


Figure 1: Flowchart of the studies selection process.

Description of the Included Studies

A total of 172 healthy overweight subjects participated in the six studies included in this review (Table 2).[12–17] These studies had sample sizes varying from 11[12] to 73[14] participants. Two studies included only men,[12,15] one included only women,[14] and three included participants of both sexes (female: 47.46%, n = 28; male: 52.54%, n = 31).[13,16,17] The mean age was 36.05 ± 7.77 years. All studies were randomized and controlled, four were crossovers,[12,13,16,17] and two were parallel studies,[14] with a duration varying from 1 day[13] to 12 weeks.[15] The content of the AGEs in the test diets ranged from 10.7 mg/day[14] to 43 mg/day[16,17] and 3302 kU/day[12] to 7306 kU/day[15] in the chronic studies and 2.8 mg/meal in the acute study.[13] In the control diets, consumption of AGEs varied from 24.6

mg/day[14] to 59 mg/day[16,17] and 11223 kU/day to 14090 kU/day[15] and 5 mg in the acute study[13] (Table 2). In all studies, a food menu (low-AGEs versus high-AGEs content) was provided to meet the participants' preferences and dietary habits. In addition, the test and control diets were similar in macronutrient content and total energy, differing only in terms of the AGEs content.

Table 2: Studies in which the effect of dietary advanced glycation end products in overweight complications was assessed

Reference	Sample	Intervention	Study Design	Duration	Main results
Harcourt et al., 2011	11 healthy overweight men 30.0±9.0 years old BMI: 31.8±4.8 kg/m^2	Test: Low AGEs diet (3302 kU / day) Control: High AGEs diet (14090 kU / day)	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-isoprostantes, ↑ plasma MCP-1, ↓plasma MIF
Poulsen et al., 2014	19 healthy overweight subjects 34.8 ± 10.0 years old Sex: 16 women and 3 men BMI: 31.3 ± 5.1 kg/m^2	Test: Low AGEs diet (2.8 mg / meal) Control: High AGEs diet (5.0 mg / meal)	Randomized, single blind, controlled and crossover	1 day (2 weeks washout)	Test group: ↓ plasma ghrelin after intervention ↔ GLP-1 e PYY compared to the control group Control group: ↑ peak of postprandial plasma glucose; plasma VCAM-1; urinary F2-isoprostane after intervention compared to the test group
Mark et al., 2014	73 healthy overweight women 39.6±1.4 years old BMI: 32.7±0.7 kg/m^2	Test: Low AGEs diet (10.7 mg/day) Control: High AGEs diet (24.6 mg/day)	Randomized, double-blind, controlled and parallel	4 weeks	Test group: ↓ weight, BMI, WP, hip waist ratio, urinary excretion of CML and MG-H1, 2h glucose, fasting insulin, HOMA-IR and ↑ $S_{i0,120}$ after intervention in comparison to the control group

Macías-Cervantes et al., 2015	29 healthy overweight men 43.9±6.2 years old BMI: 28.6±2.0 kg/m²	Test: Low AGEs diet (7306 ± 2811 kU/day) Control: habitual food intake (11223 ± 4147 kU/day)	Randomized, controlled and parallel	12 weeks	Both groups: ↓ weight, BMI e WP Test group: ↓ triglycerides and circulating AGEs (CML e MG) e ↑ HDL-c
Courten et al., 2016	20 healthy overweight subjects 34.0±10.0 years old Sex: 6 women and 14 men BMI: 31.3±3.8 kg/m²	Test: Low AGEs diet (43 (36–51) mg/day) Control: High AGEs diet (59 (49–68) mg/day)	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	20 healthy overweight subjects 34.0±10.0 years old Sex: 6 women and 14 men BMI: 31.3±3.8 kg/m²	Test: Low AGEs diet (43 (36–51) mg/day) Control: High AGEs diet (59 (49–68) mg/day)	Randomized, double-blind, controlled and crossed	2 weeks (4 weeks washout)	Test group: ↔ SBP, DBP, MAP e PP, TC, LDL, HDL, triglycerides, IL-6, MCP-1, TNF-α, PCR, NFκB compared to the control

AGEs: Advanced glycation end products; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein; IL-6: interleukin -6; MCP-1: monocytic chemotactic protein -1; TNF- α: tumor necrosis factor α; PCR: C-reactive protein; NFκB: nuclear factor kappa B; BMI: body mass index; WP: waist perimeter; CEL: N_{ϵ} -(carboxyethyl)lysin; MG-H1: methylglyoxal-derived hydroimadazolidine; CML: Nє -(carboxymethyl)lysine; sRAGE: soluble receptor for advanced glycation end product; $S_{i0,120}$: insulin sensitivity index; VCAM-1: vascular cell adhesion molecule-1; ICAM-1: Intracellular adhesion molecule-1; HOMA-IR: Homeostasis model assessment of insulin resistence; MIF: macrophage migration inhibitoy factor; eGFR: estimated glomerular filtration rate; GLP-1: glucagonlike-peptide-1; PYY: peptide YY; ↔ Unchanged.

Main Results of the Studies

The consumption of a low-AGEs diet (10.7 mg/day of N € (carboxymethyl) lysine (CML)) for 4 weeks reduced the urinary excretion of CML and methylglyoxal-derived hydroimidazolone (MG-H1).[14] On the other hand, 43 mg/ day of CML (a diet low in AGEs) also reduced the urinary excretion of MG-H1 and N €–(carboxyethyl) lysine (CEL). However, the serum concentrations of CML, MG-H1, CEL, sRAGE and urinary CML remained unchanged.[16] In another randomized clinical study, the authors observed a reduction in circulating AGEs (CML and MG) in response to the intake of 7306 kU/day of AGEs over the 12 weeks of intervention.[15] On the other hand, the consumption of a high-AGEs diet (14090 kU/day) for two weeks reduced plasma CML and increased urinary CML.[12]

For the cardiometabolic markers, the consumption of a low-AGEs diet (7306 kU / day) for 12 weeks reduced plasma triglycerides and increased high density lipoprotein (HDL). However, physical exercise was associated with the test and control group concentrations.[15] Total cholesterol, low density lipoprotein (LDL), HDL and triglycerides concentrations remained unchanged when compared to the control group.[17] In addition, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and pulse pressure (PP) were similar in the test and control groups.[17] Blood glucose was reduced 2 h after an oral glucose tolerance test, and the fasting insulin, HOMA-IR, and insulin sensitivity index (Si0,120) increased 4 weeks after a low-AGEs diet.[14] Insulin sensitivity also increased in a randomized, crossover study in which a low-AGEs diet (43 mg / day) was consumed for 2 weeks. On the other hand, the consumption of 5.0 mg of AGEs (a high-AGEs diet) in a single meal promoted an increase in postprandial plasma glucose peak compared to the test group (low-AGEs diet).[13]

With regards to the anthropometric markers, the consumption of 10.7 mg / day of CML for 4 weeks reduced body weight, waist circumference, waist-hip ratio and body mass index (BMI) compared to the high-AGEs diet group.[14] In the study by Macías-Cervantes et al.,[15] there was a reduction of body weight, BMI and CP in both groups. However, the subjects were encouraged to increase their physical activity level in both the test and control group. In a randomized, 2-week crossover study, the participants' body weight remained unchanged.[16]

Plasma ghrelin, glucagonlike-peptide-1 (GLP-1) and peptide YY (PYY) remained unchanged after the consumption of a low-AGEs meal (2.8 mg) compared to the control group.[13]

Finally, a high-AGEs dietary intake (14090 kU / day) for two weeks increased urinary 8-isoprostans, monocytic chemotactic protein-1 (MCP-1), and plasma cystatin C and resulted in a macrophage migration inhibitory factor (MIF) reduction.[12] The consumption of a single high-AGEs meal (5.0 mg) increased urinary F2-isoprostanes and vascular cell adhesion molecule-1 (markers of endothelial activation).[13] On the other hand, low-AGEs dietary intake reduced urinary albumin/creatinine ratios[12] and increased the estimated glomerular filtration rate (eGFR).[16] However, consumption of 43 mg / day (the low-AGEs diet) for 2 weeks did not affect MCP-1, tumor necrosis factor α (TNF-α), C-reactive protein (CRP), nuclear factor kappa B NFκB), or interleukin-6 (IL-6) compared to the control group.[17]

Risk Assessment of Bias

The major domains evaluated in the present study were the random generation allocation sequence and the incomplete results data; most of the studies presented a low risk of bias, and only two studies were unclear as to their random sequence generation of allocation.[12,14] 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 two studies.[12,14] Only studies by Harcourt et al.[12] and Macías-Cervantes et al.[15] presented a risk of unclear bias due to the blinding of the participants, staff and evaluation of the results. In addition, Mark et al.[14] did not clearly define the selective results report (Figure 2).[12–17]

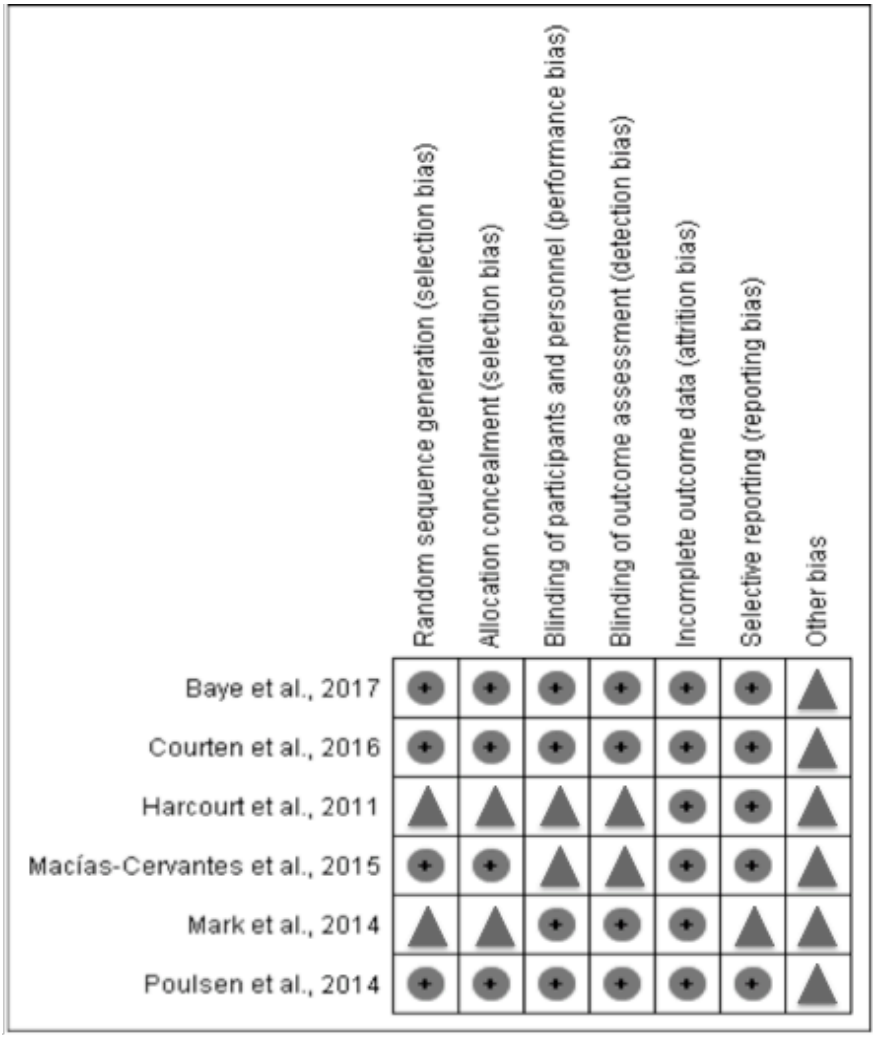


Figure 2: Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Circle: low risk; Triangle: unclear.

9.5. DISCUSSION

9.5.1. Dietary Recommendations and Effects Associated with AGEs Content of Food

A low-AGEs diet was associated with positive effects on health and better outcomes compared with a high-AGEs diet. Moreover, the results of the studies suggest a link between a high-AGEs diet and adverse impacts on health, evidencing the need for establishing safe dietary intake recommendations.[20]

Analyzing the AGEs consumption between the groups, it was observed that low-AGEs diets had an average of 5.304 kU/d or 32.23 mg/d and that high-AGEs diets an average of 12.656 kU/d or 43.53 mg/d. However, due to the differences between the methods used to determine the AGEs content and the limited number of studies, we were unable to suggest a cutoff point to classify AGEs consumption as high or low.

Harcourt et al.[12] and Macías-Cervantes et al.[15] calculated the AGEs consumption considering a database of almost 550 foods. In that report, the AGEs content was assessed as carboxymethyllysine, a chemical type of AGEs commonly used for that purpose, and expressed as AGEs kilounits/100 grams of food.[20–22] Conversely, the other four studies included in this review expressed the AGEs content in milligrams/100 grams of food. This difference in units of AGE content does not allow a comparison of AGEs consumption between the studies. Thus, establishing a standard unit that allows determination of cutoffs for low- and high-AGEs diets is recommended.

The formation of AGEs in foods is also influenced by the preparation technique used.[20,23] Meat and high-sugar, high-fat, and highly processed foods are prone to develop a high AGEs content.[20,24] High temperatures, low humidity and alkaline pH contribute to new AGEs formation, which includes grilling, searing, roasting, and frying methods.[20,23]

The results of the studies suggest that dietary AGEs restriction may be a therapeutic strategy to promote health. Therefore, it is fundamental to replace AGEs-rich foods with low-AGEs foods. Dairy products, fruits and vegetables have lower AGEs contents. Higher humidity, lower temperatures and low-pH have a minor contribution to AGEs formation. Thus, steaming, stewing, boiling and poaching should be the preferred techniques used to prepare foods.[20,23] Before cooking, the use of lemon juice and vinegar may reduce AGEs formation.[20] Table 3 shows differences between food groups and cooking methods that contribute to a lower or higher AGEs content.[20–22]

Table 3: Factors that influence food AGEs content

Food characteristics		**Cooking methods**	
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

AGEs: Advanced glycation end products
Source: Uribarri et al., 2010; Tessier, Aragon, 2012; Barbosa et al., 2016

9.5.2. Effect of Dietary AGEs on Overweight-Associated Undesirable Outcomes

Obesity is an inflammatory condition[25] and is associated with an imbalance between reactive oxygen species (ROS) production and their detoxification through biological systems that remove or repair the damage caused by them.[26] In turn, food is the major environmental factor in direct contact with host defenses. It is currently suggested that substances producing AGEs from processed foods are a source of reactive oxygen species entering the body.[27–29]

AGEs are a class of pro-oxidant foods, and their content is increased by processing the food at high temperatures.[30,31] 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.[32]

Approximately 10% of dietary AGEs are absorbed by humans, with only one-third of them being excreted in urine and feces. The plasma concentration of AGEs appears to be directly influenced by diet and the ability of the body to eliminate them.[27]

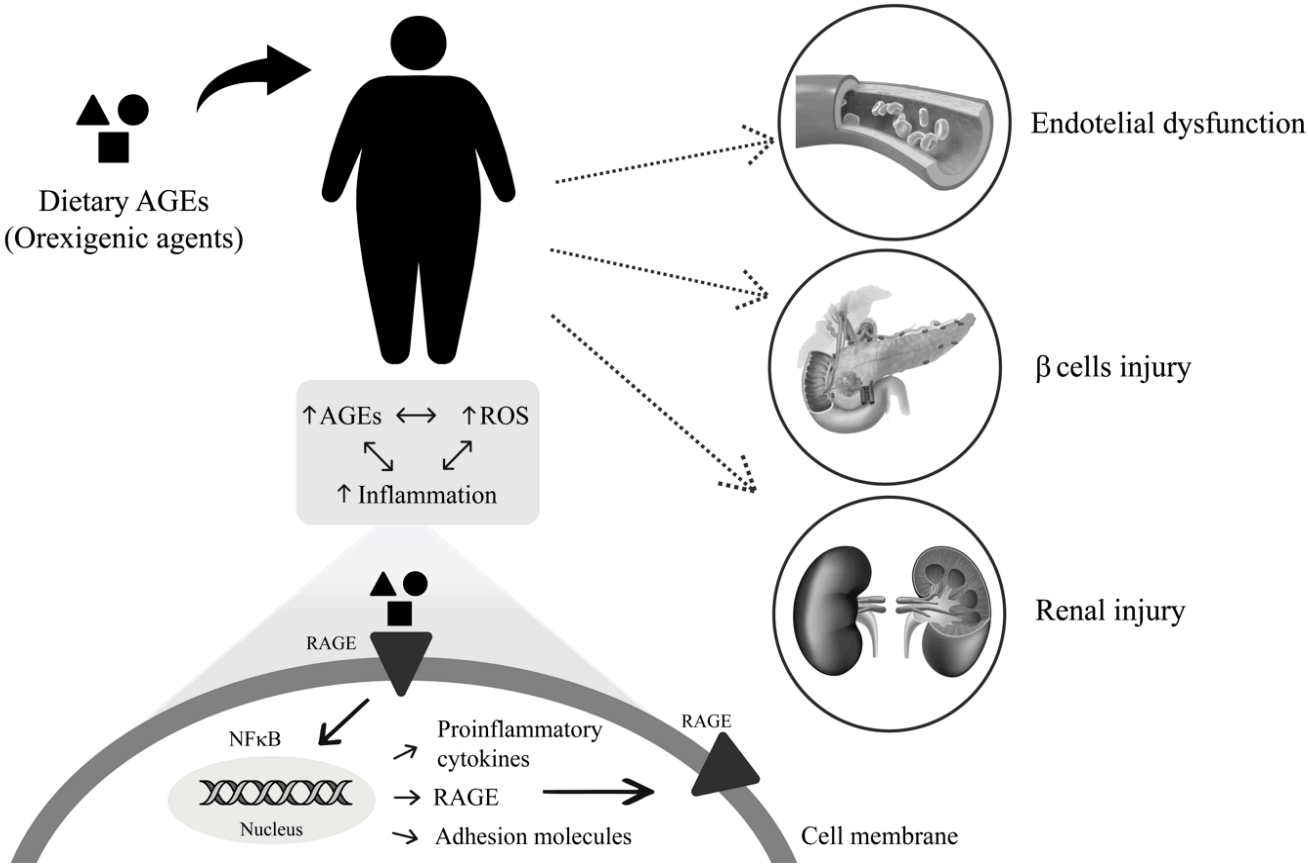
AGEs can increase oxidative stress through the receptor for AGEs (RAGE). Activation of RAGE induces a signaling cascade event, including MAPK p38-JNK, JAK-STAT and CDC42-RAC, many of which are the result and cause of oxidative stress. Thus, they modulate global cellular responses to various stress conditions and increase cellular damage.[33] 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.[34]

Some authors observed that the restriction of dietary AGEs led to oxidative stress reduction and suppression of RAGE mRNA levels and protein concentrations in people and rats with diabetes.[35,36] Similarly, AGEs restriction reduced RAGE concentrations in healthy human peripheral blood mononuclear cells and in people with diabetes, indicating that RAGE is regulated by AGEs from the external environment.[29,37]

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 transcription factor.[38] In turn, NF-κB activates the transcription of target genes, such as proinflammatory cytokines, adhesion molecules and RAGE.[38–40] 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[40] (Figure 3).

Figure 3: Mechanism related to the effect of dietary AGEs in overweight



complications, through the increase of RAGE expression and activation of the NF-κB signaling pathway.

AGEs: advanced glycation end products; ROS: reactive oxigen species; RAGE: receptor for advanced glycation end products.

9.5.3. AGEs and Chronic Diseases

Once host defenses are compromised and increased oxidative stress occurs, AGEs-RAGE may increase and perpetuate the inflammation condition, leading to obesity, diabetes mellitus and cardiovascular and kidney diseases.[38,41] The consumption of an AGE-s rich diet appears to lead to pathological consequences, such as weight gain, obesity and, consequently, metabolic syndrome.[42–44]

The kidney is the major organ for AGEs detoxification, both by filtration and active secretion and absorption, two processes that result in the net excretion of urine AGEs.[27,45] The kidneys are directly exposed to a greater circulating AGEs concentration than many other organs, a fact that may make them vulnerable to circulating lesions of reactive carbonyls and ROS.[46] A diet rich in AGEs can lead to renal damage by inducing proteinuria and/or high formation of pro-fibrotic transforming growth factor β1 (TGF-β1), accelerating atherosclerosis (through lipid peroxidation).[42,44] It has been shown that chronic ingestion of high-AGEs foods may predispose the kidney to chronic injury in the absence of diabetes mellitus, suppressing local anti-AGEs defenses, and inducing oxidative stress and inflammatory responses.[28,29]

Furthermore, AGEs-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. On the other hand, the bioavailability and activity of the endothelium-derived vasodilator, nitric oxide (NO), has been shown to be reduced by AGEs.[47] The role of AGEs in endothelial dysfunction was verified in type 2 diabetics, in which serum AGEs were negatively associated with the degree of endothelium-independent vasodilatation.[48] Some mechanisms have been suggested to explain these associations. One of these is the induction of AGE-s related oxidative stress and NO inactivity.[49] In addition, eNOS 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.[50] Additionally, AGEs may impair endothelial balance by reducing the endothelial prostacyclin (PGI2) production and increasing endothelin-1 expression.[51]

Regarding the association between AGEs and diabetes, the consumption of an AGE-s rich diet for 6 months increased body weight, visceral fat and 8-isoprostane and

decreased insulin and adiponectin sensitivity, leading to diabetes development in animals.[42] In another study, T cell activation occurred, increasing oxidative stress that led to pancreatic β-cell injury. Therefore, high AGEs consumption favors the occurrence of insulin resistance, visceral obesity, diabetes and metabolic syndrome.[52]

9.5.4. AGEs and Insulin Resistance in Adipocytes

The AGEs-RAGE interaction plays a central role in obesity and chronic disease pathophysiology. However, the effects of AGEs and their receptors on adipose tissue are still unknown. *In vitro* and experimental evidence suggests that AGEs-RAGE interactions can attenuate insulin sensitivity in adipocytes.[53,54]

In an *in vitro* study conducted in 3T3-L1 adipocytes, the presence of AGEs inhibited glucose uptake both in the presence and absence of insulin as well as increased the generation of intracellular reactive oxygen species (ROS) and the expression of monocyte-1 chemoattractive protein (MCP-1).[53]

Monden and colleagues[54] 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 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 adiponectins, and decreased expression of MCP-1, resulting in increased insulin sensitivity in adipose tissue.[54]

The results of these studies suggest that AGEs-RAGE interactions in adipocytes inhibit glucose uptake through increased ROS, cytokines and other inflammatory molecules production as well as decreased phosphorylation of IRS-1, thereby inhibiting the PI3K-AKT pathway.[53–57]

Thus, based on the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway associated with the *in vitro* and experimental evidence,[53,54] the authors hypothesize that interactions between AGEs-RAGE may be involved in insulin resistance in adipose tissues through insulin signaling pathway downregulation (PI3K-AKT) (Figure 4).

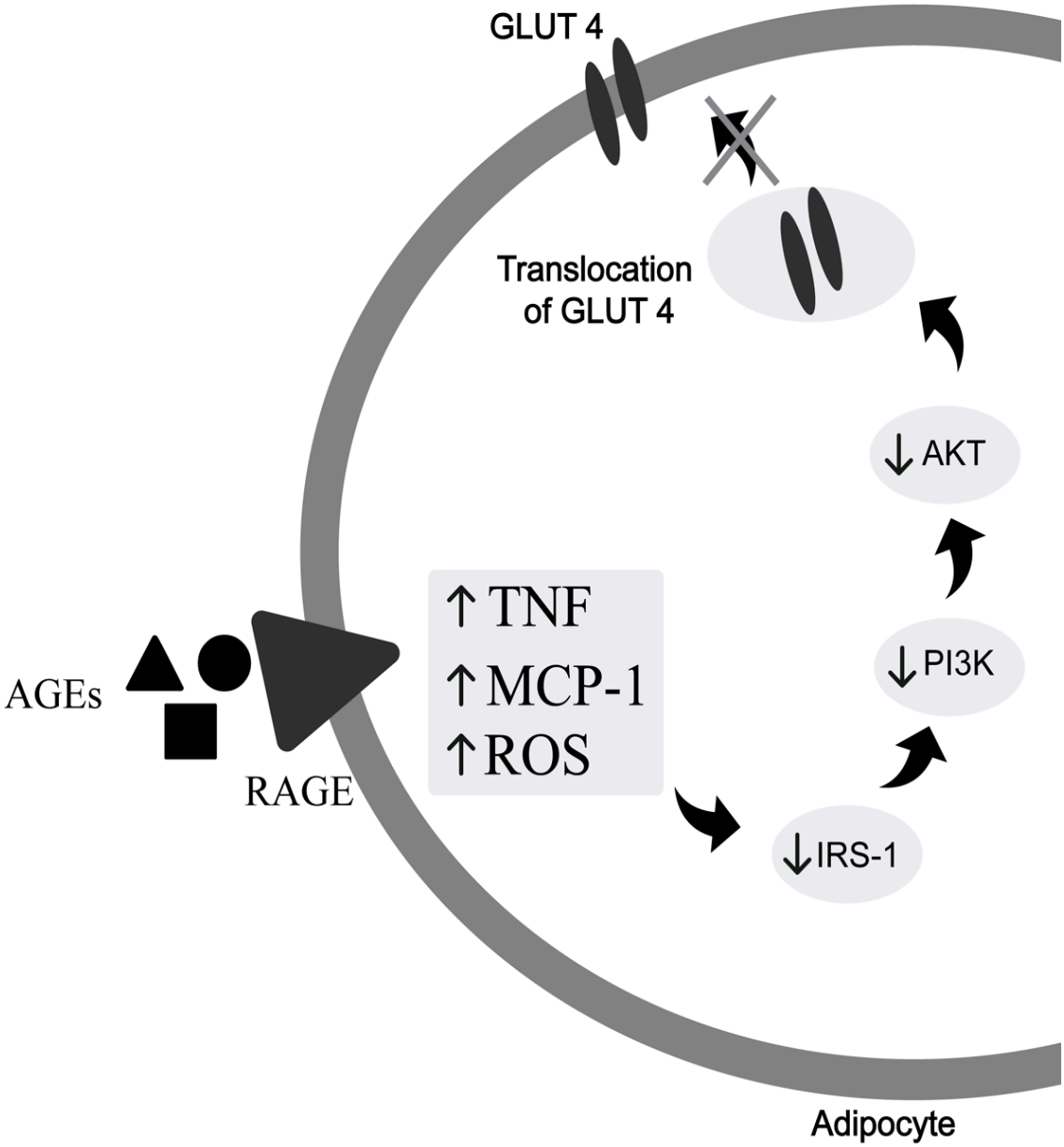


Figure 4: Proposed AGEs-RAGE interaction mechanism associated with increased oxidative stress and inflammation, inducing insulin resistance via PI3K-AKT signaling pathway in adipocytes.

Finally, due 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 dietary pattern change probably contributed to an increase in obesity, oxidative stress and inflammation, which can explain an increase in the manifestation of overweight-associated complications

(diabetes mellitus, cardiometabolic disorders, and renal diseases) due to higher AGEs consumption.[32] Thus, this review provides new insights into the role of dietary AGEs in the pathogenesis of obesity and associated complications.

9.6. LIMITATIONS

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 were different among the studies; (3) none of the studies presented the actual dietary AGEs content, only the mean value tested; and (4) the AGEs units used were different among the studies. All these factors make it difficult for us to compare the results obtained by the studies and to state recommendations about AGEs consumption.

Several AGEs are formed in food during preparation processes. However, it is difficult to quantify the total dietary AGEs content since there is not a standard quantification method. Although we know the types of foods that may contain the highest AGEs content and the food processing methods that are capable of increasing the AGEs content, we cannot be sure of the type of foods that contribute the most to total dietary AGEs consumption.

9.7. CONCLUSIONS

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

The association between a high-AGEs diet and the manifestation of overweight complications is due to the increase in ROS, which in turn leads to inflammation through activation of the NF-κB signaling pathway. This finding may explain the association among being overweight with diabetes mellitus, cardiometabolic disorders, and renal diseases. In addition, it seems that AGEs-RAGE interactions can inhibit the insulin signaling pathway (via PI3K-AKT), resulting in decreased glucose uptake in

adipocytes, and consequently lead to insulin resistance. This inflammatory action of dietary AGEs-RAGE binding can be considered as a new key point in obesity pathogenesis. AGEs can also be used as promising biomarkers to monitor the response to dietary interventions in overweight people.

Considering the scarcity of studies that portray the effect of diet on RAGE modulation, an investigation into how AGE-s rich foods modulate RAGE activity and function should be conducted with the objective of identifying effective therapeutic strategies to be used in the prevention and control of obesity.

9.8. CONFLICT OF INTEREST

The authors declare no conflict of interest.

9.9. ACKNOWLEDGMENTS

The authors thank Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG, Brazil), Coordenação de Aperfeiçoamento de Pessoal de Ensino Superior (CAPES, Brazil), and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) for financial support.

Supplementary Table I: PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Pg. 9 Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pg. 10 Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pg. 10 Yes
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Pg. 10 Yes
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pg. 11 Yes
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pg. 11 Yes
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Pg. 11 Yes
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pg. 12 Yes
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pg. 12 Yes

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Pg. 12 - 13 Yes
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pg. 12 Yes
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Not applicable

Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pg. 19 - 20 Yes
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pg. 13 - 14 Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pg. 15 - 17 Yes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pg. 19 - 20 Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Pg. 18 - 19 Yes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pg. 19 - 20 Yes
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pg. 20 - 25 Yes
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pg. 27 Yes
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pg. 27 - 28 Yes
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Pg. 28 Yes

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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10. ORIGINAL ARTICLE: Dietary advanced glycation end products consumption is associated with oxidative stress in overweight adults

10.1. ABSTRACT

Background/Objectives

The consumption of diets rich in dietary advanced glycation end products may be a novel explanation for overweight related complications manifestation, and for chronic diseases pathogeneses. Oxidative stress and low-grade inflammation precedes the manifestation of chronic diseases associated with overweight. Although the effect of the consumption of advanced glycation end products (AGEs) on cardiometabolic risk factors has been studied in animals, and humans with diabetes and impaired renal function, the association between AGEs consumption versus inflammatory and oxidative stress markers in healthy overweight adults has not been investigated yet. Therefore, to better understand the impacts of AGEs on inflammation and oxidative stress, in this study we explored the associations between habitual AGEs consumption and cardiometabolic risk markers in healthy overweight adults.

Subjects/ Methods

A total of 192 subjects (men: n = 75 or 39.06%; women: n = 117 or 60.94%, age: 27.63 ± 6.63 y, body mass index: 29.89 ± 2.66 kg/m^2) were evaluated. Anthropometry, blood pressure, blood biochemical variables, homeostatic model assessment for insulin resistance (HOMA-IR), inflammatory, and oxidative stress markers were assessed. Moreover, we estimated the atherogenic index by triglyceridemia to HDL-c ratio (TG/HDL-c) and the triglyceride-glucose index (TyG). A food frequency questionnaire validated for the Brazilian population was used to assess habitual food intake. Dietary advanced glycation end products intake was adjusted by daily energy intake (kU/1000kcal/day).

Results

AGEs consumption was associated with malondialdehyde concentrations regardless of habitual physical activity, sex, body mass index (kg/m^2), energy intake (kcal/day) and carbohydrate intake (g/day). Although AGEs consumption presented an inverse association with plasma insulin, the model lost significance after carbohydrate intake adjustment.

Conclusions

AGEs intake is associated with increased malondialdehyde concentrations, an oxidative stress marker, in healthy overweight adults.

Keywords

Dietary advanced glycation end products, cardiometabolic risk, inflammation, oxidative stress, dietary recommendations, obesity, chronic diseases, receptor for advanced glycation end products

10.2. INTRODUCTION

High body fat favor the development of oxidative stress and low grade inflammation, which in turn precedes the manifestation of chronic diseases such as diabetes and cardiovascular diseases in excess body weight subjects (1–4). According to some authors (5–9), the consumption of advanced glycation end products (AGEs) rich diets may negatively affect health, impairing cardiometabolic risk factors.

Advanced glycation end products (AGEs) are generated by reactions between reducing sugars or degradation products of carbohydrates and fats in the late stages of Maillard reaction (10). Their formation, in foods, is enhanced by thermal treatments with high temperatures and low humidity, such as frying, roasting grilling and baking (11–13). Evidence, from both animal and human studies, showed that high AGEs consumption can increase the total pool of circulating AGEs. It is estimated that 10% of the AGEs consumed is readily absorbed into the bloodstream (14–17).

The pathological effects of AGEs are related to their capacity to activate inflammatory pathways and induce oxidative stress by binding with cell surface receptors (18,19). The consumption modern western diets containing lots of processed AGEs rich foods has been considered to be a novel explanation for chronic disease pathogenesis (20,21). Thus, recommendation on the restriction of AGEs consumption could be a practical approach for obesity as well as for other chronic diseases prevention and control (20,22).

The results of human clinical trials suggest that the prescription of AGEs restricted diet leads to beneficial health effects in overweight subjects (23–28). However, the AGEs consumption during the intervention was not assessed in none of these studies. Observational studies involving subjects with impaired renal function and diabetes demonstrated associations between high dietary AGEs consumption versus endothelial dysfunction, hyperglycemia and hyperlipidemia, in addition to higher concentrations of oxidative stress and inflammation biomarkers (5,6). Nevertheless, the associations between the consumption of AGEs and cardiometabolic risk factors in healthy overweight subjects have not been explored yet. Since overweight is an independent risk factor for the development of chronic diseases it is imperative to explore and identify strategies to prevent the development of such conditions (29,30).

Therefore, to better understand the impacts of AGEs on inflammation and oxidative stress, in this study we explored the associations between habitual AGEs consumption and cardiometabolic risk markers in healthy overweight adults.

10.3. METHODOLOGY

Subjects

In this study we included subjects aged 18 to 50 years old, with a Body Mass Index (BMI) ranging from 25 to 34.9 kg/m² (31), and body fat of at least 20% for men and 30% for women (32). The exclusion criteria were the following: smokers, alcohol consumption higher than 15g/day, use of medications that can affect the biochemical variables evaluated (such as anti-inflammatories, antibiotics, corticosteroids and laxatives), history of cardiovascular diseases, diabetes, hypertension, liver and gastrointestinal diseases, eating disorders, food allergies or intolerances, as well as pregnant and lactating women.

The study protocol was approved by the Universidade Federal de Viçosa Ethics Committee (protocol number: 58027316.6.0000.5153). Subjects were clarified about the study protocol and signed a Consent Form previous to their participation.

Study Design

In this cross-sectional study, subjects were recruited through social media ads, pamphlets, and posters. At the first contact, subjects filled out a simplified recruitment questionnaire, containing questions regarding their age, smoking habits, history or presence of diseases, use of medications, and women-specific questions about pregnancy and lactation. Next, the subjects' habitual food intake, physical activity, height, body weight, and blood pressure were assessed. The subjects who meet the selection criteria were scheduled to return on an established day, for blood collection and body composition assessment. In a sub-sample of 84 women, we also evaluated inflammatory and oxidative stress markers.

Habitual food intake

A Quantitative Food Frequency Questionnaire (QFFQ) developed for the Brazilian population and validated by Ribeiro et al. (33) was used to assess the subjects dietary intake six months prior to the beginning of the study. For each food item in the questionnaire, subjects reported their habitual average frequency of consumption

(daily, weekly or monthly) and the portion size eaten (small, medium or large). To improve the quality of the information collected, a photographic album containing photos of different food portions was used (34). Each QFFQ was reviewed with the subjects to ensure accuracy and completeness.

Since food composition databases in Brazil have no data on foods AGEs content, we used a published Nothern American food CML–AGE (measured using a validated immunoassay method) database (35). Food AGE values were expressed in kUnit (kU) in 100 ml of liquid or 100 g of solid food for each of the 147 food items evaluated in the QFFQ.

The portions consumed by the participants were converted into grams/milliliters and the energy, macronutrients, fat type (cholesterol, saturated fatty acids, monounsaturated and polyunsaturated fatty acids), dietary fibers, as well as micronutrients (calcium, magnesium, manganese, phosphorus, iron, sodium, potassium, copper, zinc, retinol, thiamine, riboflavin, niacin, pyridoxine and vitamin C) contents was determinaded. The intake of each nutrient was evaluated by standard spreadsheet software (EXCEL 2010; Microsoft Corp, Redmond, WA). The Brazilian Food Composition Table (36), Nutrition Composition Chart of Instituto Brasileiro de Geografia e Estatísca (37) and the US Department of Agriculture's Food Composition Database (38) were used as references to quantify the nutrients intake.

Physical activity

Physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ) (39). Responses were converted to Metabolic Equivalent Task minutes per week (MET-min/wk), according to the IPAQ scoring protocol. MET scores across the sub-components (vigorous activity, moderate-intensity activity and walking) were summed to obtain overall physical activity.

Anthropometric, body composition, and blood pressure measurements

All anthropometric measurements were assessed according to Vasques et al. (40) recommendations and assessed by a single investigator. Body weight was assessed on a digital platform scale, with a resolution of 0.5 kg (Toledo®, Model 2096PP/2, São Paulo, Brazil), while subjects were barefoot and wearing lightweight clothing. Height was measured to the nearest 0.1 cm, using a wall-mounted stadiometer (Wiso, Chapecó, SC, Brazil). BMI was calculated from the weight(kg)/[height(m)]^2 ratio (41). Waist

circumference and sagittal abdominal diameter were measured in the narrowest waist using a flexible inelastic tape (38).

Body composition (lean mass, total body fat, and fat distribution) was assessed through Dual energy X-ray absorptiometry scan (DXA) (model Prodigy Advance, GE Healthcare Inc., Waukesha, WI), according to the manufacturer's instructions. Subjects were instructed to follow a protocol prior the evaluation: not take diuretics within seven days before, not to do intense exercise or to ingest caffeine-rich drinks the day before, and not to eat food or drink water in the previous 12 hours.

Blood pressure was assessed in both arms, according to Mancia et al. (42), using an automatic Omron HEM-7200 device (Omron Inc., Dalian, China).

Metabolic biomarkers

Antecubital blood samples were collected in the fasting state (12 h). Immediately after collection, serum (serum gel tubes) and plasma (EDTA tubes) samples were separated from whole blood by centrifugation (3,500 rpm, 4^0C, 15 min), and immediately stored at -80^0C until biochemical analyses. Glucose, insulin, triglycerides, total cholesterol and cholesterol fractions concentrations were assessed in all subjects. In a sub-sample of 84 women, we also evaluated inflammatory and oxidative stress markers.

Serum glucose, triglycerides (TG), total cholesterol, high-density-lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) concentrations were assessed using available commercial colorimetric assay kits (K802, K117, K083, K071, and K088, respectively; Bioclin®, Minas Gerais, Brazil) by an automated analyzer system (BS-200™ Chemistry Analyzer, Mindray). Serum insulin was quantified using eletroquimioluminescence method (Elecsys-Modular E-170, Roche Diagnostics Systems). Friedewald et al. equations were used to calculate serum very-low-density-lipoprotein cholesterol (VLDL-c) concentrations (34).

C-reactive protein (CRP) was quantified by ultrasensitive immunoturbidimetry, using the available commercial kit (K079, Bioclin®, Minas Gerais, Brazil). Insulin resistance was estimated by the Index of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) using the Matthews et al. equation (43). We also calculated the atherogenic index (TG/HDL-c ratio) (44) and triglyceride-glucose index (TyG index) (45,46).

Flow cytometry analysis was performed using a BD FACS Verse™ flow cytometer (BD Biosciences). Interleukin-8 (IL-8), interleukin-1β (IL-1β), interleukin-

6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor-α (TNF-α), and interleukin-12p70 (IL-12p70) plasma concentrations were measured using the commercial kit (Cytometric Bead Array CBA Human Inflammatory Cytokines Kit, BD Biosciences) according to the manufacturers' instructions. Data were analyzed using the FCAP Array Software v3.0 (BD Biosciences).

Catalase enzymatic activity was determined by the rate of hydrogen peroxide (H2O2) drop in spectrophotometer for 60 seconds at 240nm (47). SOD enzyme activity assessment, in turn, was based on the inhibition of the superoxide radical reaction with pyrogallol (48).

MDA determination was performed considering the product obtained from the reaction between MDA and thiobarbituric acid (TBA). The results were read in a spectrophotometric at 532 nm, according to Buege and Aust (49) method.

NO production was assessed determining the samples total nitrite, using the Griess reagent (50). Reading was carried out in a spectrophotometer at 540 - 570nm. Hydrogen peroxide (H2O2) production was determined according to a methodology adapted from Nourooz-Zadeh (51).

FRAP assay measures the sample's antioxidants capacity through the reduction of ferric 2,4,6-tripyridyl-s-triazine complex ([Fe(III)-(TPTZ)2] 3+) in an intense blue-colored ferrous complex [Fe(II)-(TPTZ)2] 2+, and was performed according to the methodology proposed by Benzie et al. (52).

Statistical Analyses

Data processing and analyses were performed using STATA software version 9.1 (Stata Corp., College Station, TX, USA), considering an α level of 5% as statistically significant. Data normality and homoscedasticity was determined by Shapiro-Wilk and Levene tests, respectively. The results are presented as mean ± standard deviation (SD).

Variables presenting non-parametric distribution were logarithmically transformed before the analyses. Participants were categorized into two groups according to their median of dietary advanced glycation end products intake adjusted by daily energy intake (kU/1000kcal/day). The comparison of mean between anthropometric, body composition, biochemical and food consumption markers among medians of dietary AGEs intake (kU/1000kcal/day) was performed by Student's T-test.

Multiple linear regressions adjusted by habitual physical activity, gender, BMI, daily energy intake (kcal/day), and carbohydrate intake (g/day) was used to evaluate

the association of dietary AGEs intake versus cardiometabolic risk predictors. A stepwise up multiple regression analysis was also used to identify which food groups consumed by the subjects explained dietary AGEs intake.

10.4. RESULTS

Subjects characteristics according to the energy-adjusted advanced glycation end products intake

One hundred and ninety-two subjects (men: *n* = 75 or 39.06%; women: *n* = 117 or 60.94%), 27.63 ± 6.63 years old, total body fat of 41.48 ± 8.04%, and BMI of 29.89 ± 2.66 kg/m^2 (overweight: *n* = 115 or 59.90%; obese: *n* = 77 or 41.10%) were included in this study. There were no significant differences between-groups across the medians of AGEs intake versus all anthropometric, body composition, blood pressure and metabolic variables assessed in this study, except for serum insulin concentrations (Table 1). Despite no significant differences in the concentrations of inflammatory cytokines, and of other oxidative stress markers, MDA concentrations were higher among subjects with higher AGEs intake (Table 2).

Dietary habits according to the energy-adjusted advanced glycation end products intake

Mean total AGEs intake was 21,752.06 kU (SD= 10,621.22 kU). Total AGEs intake was significantly higher in the second median than in the first median of energy-adjusted AGEs intake (kU/1000kcal/day). Energy, carbohydrate, dietary fiber, calcium, milk, dairy products, bread, and substitutes (crackers, biscuits and cakes) consumption decreased between medians of energy-adjusted AGEs intake (Table 3).

Energy-adjusted advanced glycation end products intake and cardiometabolic risk markers

Multiple linear regression model adjusted for habitual physical activity, sex, BMI, and energy intake showed a significant inverse association between advanced glycation end products intake and insulin, besides a positive association with MDA. The inclusion of carbohydrate intake in the model significantly affected the results, except for MDA concentration (Table 4).

Contribution of individual food groups to total advanced glycation end products consumption

Food groups described in Table 5 accounted for 73.3% of total variability in AGEs consumption. Meats and eggs (R^2 0.4467) were the main food group related to AGEs intake, which was followed by fat group, cereals, nuts, candies and soft drink/artificial juice groups (Table 5).

Table 1. Mean ± SD subjects anthropometric and clinical characteristics according to medians (M) of dietary advanced glycation end products (kU/1000Kcal/day) (n = 192)

Anthropometric and clinical variables	**M 1** 6981.1 ± 1218.7 (n=96)	**M 2** 11396.6 ± 2807.3 (n=96)	*P*-value
BMI (kg/m^2)	30.04 ± 2.67	29.75 ± 2.65	0.4393
Age (years)	27.83 ± 6.84	27.42 ± 6.44	0.6988
Body Weight (kg)	84.50 ± 13.04	84.57 ± 12.67	0.9413
Total body fat (%)	41.79 ± 8.04	41.18 ± 8.06	0.6267
Lean mass (kg)	46.15 ± 11.37	46.79 ± 11.50	0.7070
Waist circumference (cm)	98.54 ± 7.60	98.69 ± 7.51	0.8845
Hip circumference (cm)	111.12 ± 11.50	111.35 ± 0.75	0.7804
Waist-hip ratio	0.88 ± 0.06	0.88 ± 0.06	0.9577
Waist-height ratio	0.58 ± 0.04	0.58 ± 0.04	0.7025
SAD (cm)	21.47 ± 2.51	21.20 ± 2.74	0.4771
Total cholesterol (mg/dl)	175.52 ± 37.67	176.75 ± 39.06	0.9172
Triglycerides (mg/dl)	116.36 ± 63.65	116.98 ± 76.43	0.8339
HDL-c (mg/dl)	45.07 ± 12.14	46.92 ± 13.10	0.3215
LDL-c (mg/dl)	108.20 ± 32.69	106.02 ± 37.92	0.4156
VLDL-c (mg/dl)	22.58 ± 11.27	22.47 ± 11.38	0.8433
TG/HDL-c ratio	2.86 ± 2.23	2.80 ± 2.63	0.5498
TyG index	4.25 ± 0.66	4.34 ± 0.56	0.2751
Glucose (mg/dl)	72.43 ± 36.09	76.78 ± 30.00	0.2224
Insulin (µUI/ml)	10.80 ± 6.28	8.99 ± 4.72	0.0438*
HOMA-IR	1.82 ±1.52	1.73 ±1.25	0.7533
Uric acid (mg/dL)	4.45 ± 1.35	4.42 ± 1.43	0.7616
CRP (mg/dl)	4.83 ± 9.53	3.98 ± 4.87	0.4859
Systolic BP (mm Hg)	116.51 ± 15.76	114.47 ± 9.71	0.4433
Diastolic BP (mm Hg)	70.38 ± 10.98	69.41 ± 9.83	0.3664

BMI: body mass index; SAD: sagittal abdominal diameter; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol; VLDL-c: very low-density lipoprotein cholesterol TG/HDL-c ratio: ratio between triglycerides and HDL-c; TyG: triglyceride-glucose index; HOMA-IR: Index of Homeostasis Model Assessment of Insulin Resistance; CRP: C-reactive protein; BP: blood pressure. Variables were described as mean ± SD. *P*-value from T test. Non-normally distributed variables were log-transformed before analyses. (**P*-value<0.05).

Table 2. Mean ± SD subjects inflammatory and oxidative stress markers according to medians (M) of dietary advanced glycation end products (kU/1000kcal/day) (n = 84)

Inflammatory and oxidative stress markers	**M 1** 6981.1 ± 1218.7 (n=42)	**M 2** 11396.6 ± 2807.3 (n=42)	*P*-value
IL-12p70 (pg/mL)	6.91 ± 24.30	6.30 ± 18.66	0.7240
TNF-alpha (pg/mL)	3.01 ± 8.47	3.34 ± 10.36	0.8291
IL-10 (pg/mL)	2.87 ± 5.03	1.87 ± 3.36	0.3024
IL-6 (pg/mL)	4.62 ± 9.76	2.78 ± 4.72	0.0859
IL-1β (pg/mL)	4.20 ± 11.67	5.06 ± 13.95	0.4168
IL-8 (pg/mL)	11.40 ± 21.56	8.68 ± 3.43	0.6281
CAT (mm/ml/min)	2.92 ± 2.02	2.48 ± 2.14	0.1557
SOD (U/ml)	141.92 ± 66.66	139.44 ± 77.15	0.6012
MDA (µmol/ml)	3.08 ± 1.87	4.02 ± 2.20	0.0295*
NO (µmol/ml)	839.77 ± 2050.60	381.52 ± 479.15	0.2246
H2O2 (µmol/ml)	12.44 ± 5.86	10.16 ± 4.82	0.1871
FRAP (µmol/ml)	74825.78 ± 17298.17	75439.57 ± 15870.14	0.7890

TNF-alpha: tumor necrosis factor alpha; CAT: catalase; SOD: superoxide dismutase; MDA: malondialdehyde; NO: nitric oxide; H2O2: hydrogen peroxide; FRAO: total plasma antioxidant activity. Variables were described as mean ± SD. *P*-value from T test. Non-normally distributed variables were log-transformed before analyses. (**P*-value<0.05).

Table 3. Mean ± SD subjects energy, nutrients, and food-groups consumption according to medians (M) of dietary advanced glycation end products (kU/1000kcal/day) (n = 192)

Nutrients and food-groups comsumption	**Median 1** 6981.1 ± 1218.7 (n=96)	**Median 2** 11396.6 ± 2807.3 (n=96)	*P*-value
AGEs (kU/day)	18268.40 ± 8932.77	25235.72 ± 11067.36	<0.0001*
Energy (kcal/day)	2598.90 ± 1059.26	2217.51 ± 730.87	0.0140*
Carbohydrate (g/day)	363.19 ± 147.63	273.52 ± 91.11	<0.0001*
Fat (g/day)	82.11 ± 41.21	78.17 ± 36.64	0.7980
Protein (g/day)	109.04 ± 43.51	109.51 ± 32.29	0.4474
Cholesterol (mg/day)	315.869 ± 170.6633	337.8955 ±143.4534	0.0750
Dietary fiber (g/day)	36.02 ± 16.17	29.54 ± 12.97	0.0052*
Calcium (mg)	1007.15 ± 482.38	806.32 ± 364.15	0.0033*
Vitamin C (mg)	460.63 ± 1354.41	257.65 ± 457.66	0.0996
Milk, dairy products (g/day)	338.69 ± 263.05	237.49 ± 193.90	0.0099*
Breads, bread substitutes (g/day)	174.17 ± 132.38	126.26 ± 74.90	0.0026*
Fat group (g/day)	13.58 ± 16.05	16.16 ± 29.57	0.8899
Cereals (g/day)	333.84 ± 204.90	266.54 ± 123.33	0.0598
Fruits (g/day)	444.43 ± 395.90	320.64 ± 238.80	0.1050
Vegetables (g/day)	153.51 ± 135.22	134.61 ± 98.38	0.6832
Meats and eggs (g/day)	163.0121 ± 83.76	198.02 ± 72.63	0.0002*
Legumes (g/day)	146.63 ± 116.47	129.87 ± 113.69	0.5212
Soft drink, artificial juice (g/d)	398.91 ± 419.73	308.13 ± 285.49	0.5110
Candies (g/d)	56.60 ± 60.82	46.24 ± 41.37	0.8301
Nuts (g/day)	5.89 ± 11.49	3.76 ± 7.93	0.8433

P-value from T test. Non-normally distributed variables were log-transformed before analyses (**P*-value<0.05).

Table 4. Multiple linear regression models with dietary advanced glycation end products consumption (kU/1000Kcal/day) as the main independent variable

Dependent variables	β	95% CI	R^2	*P*-value
Insulin (log)				
Multivariate model 1†	-0.298	-0.547, -0.049	0.1266	0.019*
Multivariate model 2‡	-0.319	-0.571, -0.067	0.1321	0.013*
Multivariate model 2 + carbohydrate‡‡	-0.197	-0.505, 0.109	0.1414	0.206
MDA (log)				
Multivariate model 1†	0.889	0.396, 1.382	0.1875	0.001*
Multivariate model 2‡	0.877	0.384, 1.371	0.1990	0.001*
Multivariate model 2 + carbohydrate‡‡	1.129	0.492, 1.765	0.2147	0.001*

95% CI: confidence interval; MDA: malondialdehyde. †Multivariate model 1 was adjusted for habitual physical activity, sex and body mass index (kg/m^2); ‡ Multivariate model 2 was adjusted for the same variables as Multivariate model 1 plus energy intake (kcal/day); ‡‡ Multivariate model 2 plus carbohydrate intake. **P*-value<0.05

Table 5. Main food groups that contributed to dietary advanced glycation end products consumption

Food groups	R^2	Cumulative R^2
Meats and eggs (g/day)	0.4467	0.4467
Fat (g/day)	0.1129	0.5596
Cereals (g/day)	0.0572	0.6168
Nuts (g/day)	0.0580	0.6748
Candies (g/d)	0.0321	0.7069
Soft drink, artificial juice (g/d)	0.0267	0.7336

10.5. DISCUSSION

In this cross-sectional study involving overweight adults, we investigated the associations between advanced glycation end products (AGEs) consumption versus cardiometabolic risk markers. Since we included men and women in our study, we considered that adjusting dietary AGEs consumption by energy intake (kU/1000kcal) would be a reasonable way to present our data, and to avoid biases regarding the differences in total energy intake due to gender. Then we stratified our sample into medians of dietary AGEs intake adjusted by energy intake (kU/1000kcal).

Our results indicated that subjects with higher energy-adjusted AGEs consumption presented higher total AGEs intake, but lower energy and carbohydrate intake, besides having lower serum insulin and higher MDA concentrations, an oxidative stress marker. These results were independent of habitual physical activity, sex, BMI and energy intake. When we included carbohydrate intake in the adjusted models, the inverse association between energy-adjusted AGEs consumption versus insulin was no longer significant.

AGEs are a complex and heterogeneous group of compounds, formed endogenously through a nonenzymatic reaction between a carbonyl group of reducing sugars and free amino groups of proteins, lipids, or nucleic acids. Hyperglycemia and oxidative stress increase the rate in which that reaction occurs (35,53). AGEs can be formed endogenously, and it can be absorbed after the consumption of highly processed foods. The Maillard reaction, a process that leads to browning of food, which enhances sensorial quality, is well known for generating large quantities of AGEs (54).

Regarding the individual contribution of food groups to total AGEs intake, our data indicate that 55.96% of total AGEs intake derived from meats and eggs group alongside with fat group. Although fat tends to contain more AGEs per gram, meats are consumed in higher portions, hence having the major contribution to AGEs intake (16,22,35). Similarly, Ejtahed et al, in a longitudinal study, verified that the meats and fats group were accountable for the majority of total AGEs intake (85.5%) (16). On the other hand, food groups such as legumes, vegetables, fruits, and milk products present the lowest dietary AGEs (16,22). The higher water content in those foods and the higher concentration of vitamins and antioxidants may explain the diminished AGEs formation (22,35).

The results of animal studies suggest that high dietary AGEs intake correlates with higher plasma AGEs concentrations, and with the development of chronic diseases, such as kidney disease (55) and atherosclerosis (56). These compounds can

activate inflammatory pathways and induce oxidative stress through interactions with their specific membrane-bound receptors (RAGE) (57). On the other hand, dietary AGEs restriction may accelerate wound healing (58), improve insulin sensitivity (59,60), besides preventing chronic kidney disease (55,61) and diabetes development (62). In a two-week crossover study and a six-week randomized parallel study, the consumption of a low AGEs diet reduced inflammatory makers in type 1 and type 2 diabetes subjects (63).

Interactions between AGE-RAGE can induce ROS production via NADPH oxidase activation and different signalling cascade of events, including MAPK p38-JNK, JAK-STAT and CDC42-RAC, resulting in oxidative stress (64–66). Furthermore, increased ROS production and oxidative stress act as inflammatory mediators, activating the proinflammatory NF-κB transcription factor (67). In turn, NF-κB activation leads to a higher production of proinflammatory cytokines, adhesion molecules and RAGE itself (67–69), establishing a positive feedback mechanism and perpetuating the signal (69).

Besides the Maillard reaction, AGEs can be generated by other pathways, such as the peroxidation of lipids into dicarbonyls derivatives (70). This reaction occurs when fatty acids, attacked by ROS, produce peroxyl radicals that are highly reactive, leading to further oxidation and reactive carbonyls species (RCS) production, such as malondialdehyde (MDA) (71–73).

Further evidence suggests that MDA overproduction through AGEs oxidative stress-inflammation vicious cycle can lead to secondary oxidative damage to proteins (74). Therefore, MDA is frequently used as an indicator of lipid peroxidation and oxidative stress in vivo, and its concentration is elevated in T2DM subjects (75,76). In a randomized prospective study, T2DM adult subjects were randomly assigned to low AGEs or standard AGEs prescribed diets having the same macronutrients distribution. After six weeks, dietary AGEs restriction reduced MDA concentrations (77). Although the results of that study are quite interesting, the actual food intake and methods used to prepare the foods consumed by the subjects during the study were not accessed. Therefore, there is no guaranty that the results obtained in that study were due to dietary AGEs restriction.

Although food composition plays an essential role in AGEs formation, high cooking temperature for extended periods of time seems to be the most important modulating factor of the Maillard reaction in foods (10). Cooking methods, such as grilling, roasting, broiling, and, frying favors and accelerate the formation of the AGEs

like carboxy-methyl-lysine (CML) and methyl-glyoxal (MG) (15,35). On the other hand, boiled or steam foods are less prone to AGEs formation. Also, an alkaline pH can increase AGEs formation. Therefore, the use of acidic ingredients like lemon juice or vinegar could be a strategy to reduce AGE formation in food, especially in meat (35).

Few studies investigated the associations between dietary AGEs intake versus circulating AGEs concentration, cardiometabolic risk markers and chronic diseases complications. The results of two cross-sectional studies indicated a positive correlation between AGEs consumption and circulating AGEs concentration (78,79). Higher circulating AGEs were also correlated with increased CRP concentrations (79). However, in both studies (78,79), food intake was assessed based on a 3-day record, which may not reflect the habitual dietary AGEs consumption. Therefore, the authors of these studies used a non-validated method to estimate AGEs consumption that may either overestimate or underestimate the regular consumption.

The relationship between dietary AGEs intake of 85 subjects with arterial stiffness, and inflammation markers, was assessed by a 10-day food record (15) in a cross-sectional study. Subjects with high dietary AGEs intake showed a reduced arterial stiffness and increased CRP concentrations (15). Although food intake was assessed for a longer period of time than in the previously mentioned studies (76, 77), it still does not reflect the habitual food intake. In another cross-sectional study, involving a representative population sample (n=5848), including participants aged 19 to 70 years old, the authors investigated the associations between dietary AGEs and risk of metabolic syndrome (22). Similarly, to the present study, energy and carbohydrate consumption decreased in the subjects that had a higher AGEs intake. The results showed that the subjects in the highest quartile of AGEs intake had a higher risk of abdominal obesity and hypertriglyceridemia when compared to the ones in the lowest quartile. However, the associations became non-significant after adjustment for energy and macronutrients intake (22). Although the authors of that study assessed the habitual food intake using a validated food frequency questionnaire, the cooking methods used for food preparation once again was not considered.

To our knowledge, the present study is the first to investigate how dietary AGEs is associated with oxidative stress and inflammation in healthy overweight subjects. Considering the fact that oxidative stress and inflammation favors the manifestation of chronic diseases, such as diabetes and cardiovascular diseases (66,80–82), the identification of strategies capable to attenuate these undesirable condition prior to these diseases manifestation is highly desirable. In our study, no association between

dietary AGEs intake versus other cardiometabolic risk markers, such as hyperglycemia, hypertension, hypercholesterolemia and insulin resistance as well as inflammation markers was observed. However, the subjects with lower AGEs intake had lower MDA concentrations, an oxidative stress marker.

Although the role of dietary AGEs in cardiometabolic diseases, such as obesity and T2DM, seem to be supported by human (83) and animal studies (60), mechanisms underlying these associations still need to be clarified. For instance, a possible link to explain these associations may be the overproduction of ROS in the formation process of dietary AGEs during meats and fats cooking (14). Finally, further research is needed in order to establish safe dietary recommendations for AGEs consumption, as well as to explore the absorption mechanisms and metabolic effects of dietary AGEs. Meanwhile, changes on dietary partners, such as modification in cooking methods may be a simple, but promising approach to decrease AGEs intake and therefore prevent cardiometabolic diseases (35,77).

Our study has several strengths, including the use of a QFFQ specifically developed and validated for the Brazilian population. We used multiple statistical adjustments to minimize differences among the subjects and to control potential confounders and we identified the food groups that are the major contributors to total AGEs intake. Furthermore, the cooking methods were considered when the QFFQ was applied, so this allowed us to have a better estimation of AGEs intake. The study also has limitations. This was a cross-sectional study and it detected associations between variables. Therefore, we were not able to prove causation. We also used an American food-AGE database. Several Brazilian specific food items were not available in that database, and the dietary AGEs content was estimated from similar foods. Also, although diet was assessed by a validated QFFQ, potential measurement errors or recall bias are unavoidable. However, in order to increase data reliability, we used photo albums to better estimate food portions and to minimize survey errors.

10.6. CONCLUSION

Our findings indicate that a higher dietary AGEs intake is associated with elevated MDA concentrations, an oxidative stress and lipid peroxidation marker. Thus, the effects of lower dietary AGEs intake by humans must be better explored. Whether lower chronic dietary AGEs intake will reduce cardiometabolic risk and overweight associated complications through a reduction in ROS production and consequently in

the activation of inflammatory pathways in healthy overweight subjects warrants further clarification.

10.7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

10.8. ACKNOWLEDGMENTS

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11. GENERAL CONCLUSION

- Dietary advanced glycation end products (AGEs) seem to be implicated in the pathogenesis and progression of chronic diseases;
- The association between a high-AGEs diet and the manifestation of overweight complications seems to be caused by increased oxidative stress due to AGEs interactions with their membrane bound receptor (RAGE), which in turn can lead to the activation of the NF-κB signaling pathway and production of inflammatory cytokines;
- AGEs-RAGE interactions also seem to cause insulin resistance, in adipocytes, though inhibition of the insulin signaling pathway (via PI3K-AKT), resulting in decreased glucose uptake;
- Although the role of dietary AGEs in cardiometabolic diseases, such as diabetes and chronic kidney disease, seem to be supported by human and animal studies, the investigation of the effect of AGEs in healthy overweight subjects is still scarce. Besides, the mechanisms underlying the associations between dietary AGEs intake and the conditions that precedes chronic diseases development, such as oxidative stress and inflammation in that population, still need clarification;
- AGEs intake is associated with elevated MDA concentrations, an oxidative stress and lipid peroxidation marker, in overweight, but otherwise healthy subjects;
- Results of clinical studies suggest that AGEs intake restriction may positively affect the concentration of overweight related complications markers. However, the lack of a standard method to quantify AGEs in food makes it difficult to establish how much AGEs would be safe to consume. Therefore, reducing the consumption of processed foods and changing food preparation methods seem to be a good strategy to promote health and prevent chronic diseases in healthy overweight subjects;
- Future studies should be conducted to better explore the role of chronic dietary AGEs intake on cardiometabolic risk and overweight associated complications in healthy overweight subjects;
- Moreover, we recommend the creation of an AGEs content database based on commonly consumed Brazilian foods.