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Can advanced glycation end-products and their receptors be affected by weight loss? A systematic review

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Summary

Advanced glycation end products (AGEs) have been implicated in the pathogenesis of most chronic diseases. Therefore, identification of treatments that can attenuate the effects of these compounds and prevent cardiometabolic complications is of extreme public health interest. Recently, body weight management interventions showed positive results on reducing serum AGE concentrations. Moreover, the soluble receptor for advanced glycation end products (sRAGE) is considered to be a novel biomarker to identify patients with obesity most likely to benefit from weight management interventions. This systematic review aimed to critically analyze papers evaluating the effects of weight loss on serum AGEs and its receptors in adults with excess body weight. MEDLINE, Cochrane, Scopus, and Lilacs databases were searched. Three studies evaluating the response of AGEs to energy-restricted diets and six assessing sRAGE as the primary outcome were included. Energy-restricted diets and bariatric surgery reduced serum AGE concentrations, but effects on endogenous secretory RAGE (esRAGE) and sRAGE concentrations are conflicting. These results may be associated with mechanisms related to changes in dietary intake and limiting endogenous AGE formation. Therefore, the role of energy-restricted diets and bariatric surgery on lowering serum AGE concentrations, as well as its effects on AGEs receptors, deserves further investigation.

KEYWORDS
advanced glycation end product, bariatric surgery, caloric restriction, overweight, sRAGE

1 | BACKGROUND

Obesity prevalence has nearly tripled in the past decades, and it has reached epidemic proportions worldwide. According to the World Health Organization in 2016, 39% of the adult population had overweight, and 13% had obesity.[1] Being overweight is a significant risk factor for cardiovascular and metabolic diseases.[2,3] Furthermore, inflammation and oxidative stress are complications associated to

Abbreviations: AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products; NF-kB, nuclear factor kappa B; sRAGE, soluble receptor advanced glycation end products; PRISMA, preferred reporting items for systematic reviews and meta-analyses; MeSH, medical Subject Headings; DeHS, descriptors in Health Sciences; HOMA-IR, homeostatic model assessment of insulin resistance; HbA1c, glycated hemoglobin; OGTT, oral glucose tolerance test; CRP, C-reactive protein; SD, standard deviation; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-c, low density lipoprotein cholesterol; HDL-c, high density lipoprotein cholesterol; Kcal, calorie; BMI, body mass index; Kg, kilogram; m, meter; ADF, alternate day fasting; cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous receptor for advanced glycation end products; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; ROS, reactive oxygen species; FL-RAGE, full-length isoform receptor for advanced glycation end products.

overweight, and they consist in essential mechanisms involved in chronic diseases genesis.[4-7]

Advanced glycation end products (AGEs) are a group of prooxidant compounds mainly formed through nonenzymatic reactions between reactive sugars and proteins.[8] These compounds are produced endogenously as part of the normal aging metabolism, although their formation is exacerbated by hyperglycemia and elevated oxidative stress.[9] AGEs can also be originated from the diet, by intestinal absorption of free or protein bound AGEs.[10] In modern western diets, high amounts of sugar, fat, and protein are widely consumed, resulting in high AGE concentrations in the bloodstream.[11,12] Moreover, the Maillard reaction, a process that leads to browning of food, commonly used by industry to enhance sensorial characteristics of foods, is well known to increase AGE formation.[10]

A robust body of evidence have implicated the consumption of AGEs as a risk factor for the development of chronic diseases.[13-15] The pathological effects of these compounds are due to their capacity to activate inflammatory and oxidative stress pathways through interactions with the specific membrane-bound receptor for advanced glycation end products (RAGE).[16,17] AGEs-RAGE interaction activates the proinflammatory NF-κB transcription factor in the cellular nucleus, leading to a higher production of proinflammatory cytokines, adhesion molecules, and RAGE itself.[18] This upregulated feedback mechanism seems to explain the link between AGEs and the pathogenesis of cardiometabolic diseases.[19,20] Moreover, individuals with obesity have a higher expression of RAGE protein in adipose tissue than lean individuals with similar age.[21] Similarly, evidence from animal models demonstrated that RAGE deficiency results in lower adipose cells hypertrophy, better glycemic control, and lower inflammatory marker concentrations.[22-24] On the other hand, the soluble form of RAGE receptor (sRAGE), present in the circulation, acts as a decoy preventing the interaction between AGE-RAGE and its mediated damage.[25,26] Therefore, treatments that can attenuate RAGE signaling pathway and prevent obesity-related complications are of extreme public health interest.

Individuals with higher body fat have higher caloric and dietary AGE consumption, mainly due to the adoption of a western dietary pattern, rich in simple sugars, saturated fats, and preference for highly processed foods.[27] Moreover, overeating can also promote oxidative stress and as a result increase endogenous AGE formation.[28,29] Therefore, weight management interventions, such as energy-restricted diets and bariatric surgery, could play a role in decreasing serum AGE concentrations, both by reducing intake and endogenous formation.[30-32] Additionally, recent studies[33-36] have suggested that sRAGE concentrations could be a novel biomarker to identify patients with obesity that would most likely benefit from weight management interventions, but the results are still conflicting[37,38] and further research is warranted.

Nevertheless, the mechanisms involved in serum AGE concentration reduction, likewise the discrepancies in sRAGE response to a weight loss intervention, have not yet been clarified. Therefore, this systematic review aimed to critically analyze papers evaluating the effects of weight loss on serum AGEs and its receptor concentrations in adults with overweight and obesity, and to explore the underlying molecular mechanisms involved in that.

2 | METHODS

2.1 | Protocol and registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[39] and was registered in PROSPERO (registration number: CRD42018099916).

2.2 | Literature search

Five authors (J.F.T., P.V.M.R., O.G.L.C., L.E.S., and R.C.G.A.) independently searched for original articles that investigated the effects of weight loss on serum AGEs and its receptor concentrations using the following electronic databases: MEDLINE (PubMed, www.pubmed.com), Cochrane (www.cochrane.org), Scopus (www.scopus.com), and Lilacs (www.lilacs.bvsalud.org). Keywords were chosen from the Medical Subject Headings (MeSH) and Descriptors in Health Sciences (DeHS) using the following search strategy: ("obesity" AND "overweight") AND ("advanced glycation end products" OR "glycation end products, advanced") AND ("weight loss").

The search strategy was not restricted by date and language. The last search was done on September 3, 2019. A reverse handsearch was also performed to identify relevant articles cited in all selected studies.

2.3 | Studies selection

The authors (J.F.T., P.V.M.R., O.G.L.C., L.E.S., and R.C.G.A.) performed the studies selection in three phases: titles analyses, abstracts reading, and full texts reading and comprehension. We included all detected studies that assessed the effects of weight loss, through dietetic interventions or bariatric surgery, on advanced glycation end products (AGEs) and their receptors concentrations in individuals with overweight or obesity.

Comments, reviews, letters, case reports, transversal studies, abstracts, unpublished articles, as well as animal and in vitro studies were not included.

2.4 | Data extraction

After reading the selected studies, a comparison of the compiled data was conducted by the authors (J.F.T., P.V.M.R., O.G.L.C., L.E.S., and R.C.G.A.) 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 (energy-restricted diets or bariatric surgery), and study duration. Additionally, results regarding serum AGEs and sRAGE concentrations were extracted.

2.5 | Assessment of risk of bias

The authors assessed the data reported in each study to analyze potential risk of selection, performance, attrition, detection, and reporting biases. The studies were classified to present low, moderate, or high risk, according to predefined criteria described by the Agency for Healthcare Research and Quality "Methods Guide for Effectiveness and Comparative Effectiveness Reviews",[40] using questions specified in the RTI Item Bank.[41] The methodology is specifically designed to assess the risk of bias in different types of studies, and it is composed of 12 questions for RCT and 13 for cohort.[40] Most of the studies regarding the topic of interested were designed as single arm pre-post studies, or with no comparative/control groups. Therefore, when evaluating these studies, we decided to not consider questions regarding random allocation sequence, allocation concealment, blinding of participants and staff, and the blindness of outcome evaluation. Studies were classified as having a low risk of bias when >80% questions were answered as "yes (low risk)," a moderate risk of bias when 50% to 79% of the questions were answered as "yes (low risk)," and a high risk of bias when <50% questions were answered as "yes (low risk)".[42] Different opinions between the authors were settled by consensus.

2.6 | Data analyses

The characteristics presented by the selected studies are summarized in Tables 1, 2, and 3. The studies were organized chronologically by year of publication, starting with the first published study. Serum AGEs and sRAGE were considered as the primary outcomes, as well as how changes in these markers correlate with cardiometabolic and anthropometric markers.

Conducting a statistical meta-analysis was not justified due to the heterogeneity between the included studies. Therefore, in accordance with Cochrane handbook, the authors performed a systematic review.[43]

3 | RESULTS

3.1 | Study selection

We identified 442 studies after searching the PubMed, SCOPUS, Cochrane, and Lilacs databases. A total of 26 duplicate studies were removed, resulting in 416 unique records. Then, we excluded 146 nonoriginal studies, 251 studies were considered irrelevant to the topic of interest and one animal study. After reading the full text of the remaining 18 studies, nine met all criteria adopted for this systematic review. The reasons for exclusion of the other studies are indicated in Figure 1.

3.2 | Description of included studies

The nine studies included in this review (Tables 1 and 2) contained data from 455 subjects. Sample sizes of the studies ranged from 22[38] to 85[33] subjects. One study included only women,[31] the other eight studies included participants of both sexes (female: 76.9%, n = 350; male: 23.1%, n = 105).[30,32-38] The mean ± SD age of the participants from seven studies was 46.2 ± 8.6 years.[30-35,37] In the other two studies, the age (median and interquartile range) was 44.0 (35.0-55.0)[36] and 43.5 (33-55).[38] Three studies (33.3%) included only healthy overweight subjects,[30,31,36] three studies (33.3%) included subjects with morbid obesity,[33,37,38] two studies (22.2%) included patients with type 2 diabetes mellitus (T2DM),[34,35] and one study (11.2%) included healthy overweight and participants with T2DM or impaired glucose tolerance (IGT).[32] Three studies (33.4%) evaluated the response of AGEs to energy-restricted diets,[30-32] and six (66.6%) evaluate sRAGE as the primary result to the weight management intervention, bariatric surgery (22.2%),[33,37] energy-restricted diet (22.2%),[36,38] or both (22.2%).[34,35] Among the included studies, there is one longitudinal study,[33] five clinical trials,[31,32,34,36,38] and three cohort studies,[30,35,37] with a duration varying from 2[30] to 36 months.[35] In the present review, we only included data from participants who underwent a weight management intervention. Regarding the geographic distribution, most studies were conducted in the United States and Europe (United States, n = 3; France, n = 1; Austria, n = 1; and Germany, n = 1).[33-38] The other studies were conducted in Chile (n = 1),[31] Japan (n = 1),[30] and Australia (n = 1)[32] (Table 3).

3.3 | Bias risk assessment

Four (44.4%) studies were classified as low risk of bias[30,31,33,34], four (44.4%) as moderate risk of bias,[35-38] and only one (11.2%)[32] had high risk of bias (Table 3). The major limitations were in the selection bias, with the design or analyses accounting for relevant confounding variables (four studies, 50%), in the performance bias when the researchers were not able to discard any impacts from concurrent interventions or unintended exposures (six studies, 75%), and regarding the detection bias for outcomes assessors lack of blindness (two out of two studies where these evaluation biases where applicable) and control or adjustment for confounding variables (four out of four studies where these evaluation biases where applicable, 100%).

TABLE 1 Characteristics of the studies in which the response of advanced glycation end products to weight management interventions was assessed

Reference	Sample	Intervention	Duration	Main results
Gugliucci et al, 2009[30]	37 healthy overweight individuals 42.8.0 ± 9.3 years old Sex: 30 female and 7 male BMI: 28.3 ± 3.2 kg/m^2	Low calorie diet (~1200 kcal/day - 20% average reduction in calorie intake)	2 months	Primary outcomes: ↓ AGEs (7.21%) The decrease in serum AGE concentrations was positively correlated with changes in triglycerides, waist circumference, and BMI
Rodríguez et al, 2014[31]	37 premenopausal woman with overweight or obesity 33 ± 5 years old BMI: 28.1 ± 2.0 kg/m^2	Low calorie Mediterranean type diet (20 kcal/kg initial weight)	3 months	Primary outcomes: ↓ AGEs (33.3%)
Deo et al, 2017[32]	49 overweight individuals (with and without DM2 or IGT) 57 ± 9 years old Sex: 18 female and 31 male BMI: 32.7 ± 6.8 kg/m^2	Healthy overweight individuals: Low-fat, energy-restricted diet (~1700 kcal/day) either high in protein or carbohydrate Overweight individuals with DM2 or IGT: Two energy-restricted diets (~1400 to 1700 kcal/day) differing in cholesterol content (590 mg or 213 mg)	3 months	↓ AGEs (14.3%) Changes in serum AGE concentrations did not correlate with cardiometabolic markers.

Abbreviations: AGEs, Advanced glycation end products; BMI, body mass index; CML, Nϵ-(carboxymethyl)lysine; DBP, diastolic blood pressure; HC, hip circumference; HDL, high density lipoprotein; HOMA-IR, Homeostasis model assessment of insulin resistance; IGT, impaired glucose tolerance; LDL, low density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; WC, waist circumference.
Legend: ↔ Unchanged.

3.4 | Results of individual studies

3.4.1 | Effects of energy-restricted diets on serum AGE concentrations

The consumption of an energy-restricted diet (~1200 kcal/day) for 2 months reduced serum AGE concentrations by 7.21% in healthy individuals with excess body weight. These changes were correlated with changes in triglycerides, waist circumference, and BMI.[30] Likewise, the consumption of energy-restricted Mediterranean type diet (20 kcal/kg initial weight), for 3 months, reduced (33.3%) serum AGEs in premenopausal woman with overweight and obesity.[31] In another clinical trial, there was a 14.3% reduction in serum AGE concentrations in response to the consumption of energy-restricted diets (~1400 to 1700 kcal/day) differing in carbohydrate, protein, or cholesterol contents, for 3 months, in individuals with overweight and individuals with T2DM or IGT. No correlations between changes in serum AGEs and others cardiometabolic markers were observed.[32]

3.4.2 | Effects of weight loss management interventions on sRAGE concentrations

There is considerable variability in the responses of sRAGE concentrations to weight management interventions, such as bariatric surgery or energy-restricted diets. In a 24-month longitudinal study, bariatric surgery associated with a postoperative program increased sRAGE concentrations in individuals with morbid obesity (BMI: 45.4 ± 7.9 kg/m^2).[33] Moreover, at the end of the experimental period, changes in sRAGE correlated with changes in fasting insulin, 1 and 2-h postprandial glucose, HOMA-IR, triglycerides, and γ-glutamyl transferase (GGT).[33] In another 24-month energy-restriction based on alternate day fasting (ADF) trial, individuals with obesity (BMI: 29.7-36.8 kg/m^2) were randomized into intervention (consumption of 25% or 125% of caloric requirements in alternate days) or control group (maintenance of habitual diet).[36] In addition to sRAGE concentrations, the authors also investigated others isoforms of the receptor, such as cleaved receptor for advanced glycation end products (cRAGE) and

TABLE 2 Characteristics of the studies in which the response of soluble receptors for advanced glycation end products to weight management interventions was assessed

Reference	Sample	Intervention	Duration	Main results
Brix et al, 2012[33]	85 individuals with morbid obesity 41 ± 12 years old Sex: 75 female and 10 male BMI: 45.4 ± 7.9 kg/m^2	Bariatric surgery and postoperative-care follow-up program: RYGB 74.2% (n = 63) Sleeve gastrectomy 12.9% (n = 11) Gastric banding 12.9% (n = 11)	24 months	↑ sRAGE 1-h postprandial insulin was correlated with postsurgery sRAGE levels. ΔsRAGE levels were correlated with: Δ 1-h postprandial glucose, Δ 2-h postprandial glucose, Δinsulin fasting, Δinsulin 2-h postprandial, HOMA-IR, GGT, and triglycerides.
Lorenzi et al, 2014[37]	69 individuals with morbid obesity 37 ± 9 years old Sex: 48 female and 21 male BMI: 46.7 ± 9.9 kg/m^2	Bariatric surgery: RYGB 100% (n = 69)	12 months	↓ sRAGE The decrease in anti-sRAGE autoantibodies was correlated with an increase in high-density lipoprotein.
Parikh et al, 2014[34]	57 individuals with type 2 diabetes Bariatric surgery (n = 29): 53.9 ± 8.4 years old BMI: 32.4 ± 1.8 kg/m^2 Sex: 23 female and 6 male Medical weight management (n = 28): 46.8 ± 8.1 years old BMI: 32.8 ± 1.7 kg/m^2 Sex: 22 female and 6 male	Bariatric surgery: RYGB 74.2% (n = 7) Sleeve gastrectomy (n = 16) Gastric banding (n = 5) Medical weight management: Intensive lifestyle interventions, group and individual sessions of nutrition and physical activity counseling	6 months	↔ sRAGE in both groups ↑ sRAGE concentrations at baseline were associated with higher weight loss within the participants in the bariatric surgery group. No associations between sRAGE and antrhopometric and metabolic markers were observed pre-treatment and post-treatment.
Hagen et al, 2015[38]	22 individuals with morbid obesity 47.5 (39.0 – 52.0) years old Sex: 17 female and 5 male BMI: 48.5 kg/m^2 (38.1-45.4)	Very low calorie diet: 800 kcal/d (formula meals) for 12 weeks and a following 12 week weight maintenance phase (general meals)	6 months	↔ sRAGE Fold changes of sRAGE from baseline to week 24 were negatively correlated to fold changes of BMI.
Horwitz et al, 2016[35]	57 individuals with type 2 diabetes Bariatric surgery (n = 39): 49.2 ± 7.1 years old	Bariatric surgery: RYGB (n = 9) Sleeve gastrectomy (n = 24) Gastric banding (n = 5)	36 months	↑ sRAGE at baseline was correlated with postoperative ↑ %WL and ↓ HbA1c

(Continues)

TABLE 2 (Continued)

Reference	Sample	Intervention	Duration	Main results
	Sex: 32 female and 7 male BMI: 32.8 ± 1.4 kg/m^2 Medical weight management (n = 18): 55.2 ± 9.3 years old Sex: 13 female and 5 male BMI: 32.2 ± 2.0 kg/m^2	Medical weight management: Intensive lifestyle interventions, group and individual sessions of nutrition and physical activity counseling		
Miranda et al, 2018[36]	42 individuals with obesity ADF (n = 20): 44.0 years old (35.0-55.0) Sex: 17 female and 3 male BMI: 33 kg/m^2 (30.9-36.8) Control (n = 22): 43.0 years old (33.0-55.0) Sex: 18 female and 4 male BMI: 34.5 kg/m^2 (29.7-36.1)	ADF: 25% of baseline energy needs as a lunch on "fast days" and 125% of their energy needs across three meals on subsequent "feast days." Control group: No change in diet and not provided meals or dietary counseling.	6 months	ADF group: ↑ esRAGE, ↔ cRAGE, ↔ total sRAGE compared with control group

Abbreviations: ADF, alternate day fasting; ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; HbA1c, glycated hemoglobin A1c; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LAR, leptin-adiponectin ratio; LDL, low density lipoprotein; RYGB, laparoscopic Roux-en-Y gastric bypass; SBP, systolic blood pressure; sRAGEs, soluble receptor for advanced glycation end products; PP, pulse pressure; TC, total cholesterol; WL, weight loss.
Legend: ↔ Unchanged.

TABLE 3 Selected studies geographic distribution, type of study, and risk of bias

Reference	Country	Type of study	Overall risk of bias
Gugliucci et al, 2009[30]	Japan	Prospective cohort	Low risk (08/10)
Brix et al, 2012[33]	Austria	Longitudinal	Low risk (08/10)
Lorenzi et al, 2014[37]	France	Cohort	Moderate risk (06/10)
Parikh et al, 2014[34]	United States of America	Clinical trial	Low risk (11/12)
Rodríguez et al, 2014[31]	Chile	Clinical trial	Low risk (06/07)
Hagen et al, 2015[38]	Germany	Clinical trial	Moderate risk (05/07)
Horwitz et al, 2016[35]	United States of America	Retrospective cohort	Moderate risk (07/13)
Deo et al, 2017[32]	Australia	Clinical trial	High risk (01/07)
Miranda et al, 2018[36]	United States of America	Clinical trial	Moderate risk (6/11)

Legend: Classification of bias risk according to Agency for Healthcare Research and Quality criteria.[27] Low risk: >80% questions answered as low risk; moderate risk: >50% to 79% questions answered as low risk; high risk: <50% questions answered as low risk.

endogenous receptor for advanced glycation end products (esRAGE). They observed an increase in esRAGE after the ADF intervention, but cRAGE, total sRAGE concentrations, and cRAGE:esRAGE ratio remained unchanged.[36]

In one study, sRAGE and anti-sRAGE autoantibodies concentrations decreased in individuals with morbid obesity (BMI: 46.7 ± 9.9 kg/m^2) 12 months after being submitted to bariatric surgery. Moreover, the only changes in metabolic markers associated with the decrease in anti-sRAGE concentrations were an increase in high density lipoprotein (HDL-c).[37] In another clinical trial, patients with obesity and T2DM were either assigned to undergo bariatric surgery (BMI: 32.4 ± 1.8 kg/m^2) or a program of intensive lifestyle interventions, with nutrition and physical activity counseling (BMI: 32.8 ± 1.7 kg/m^2). Six months later, the concentrations of sRAGE remained unchanged in both groups. However, higher baseline sRAGE was associated with better weight loss outcomes in patients submitted to bariatric surgery.[34] Similarly, in another clinical trial, consisting of a 3-month very low-calorie diet (800 kcal/d) followed by a 3-month weight maintenance phase, there was no impact on sRAGE concentrations in individuals with morbid obesity (48.5 [38.1-45.4] kg/m^2), but changes in sRAGE concentrations from baseline to week 24 presented an inverse correlation with changes in BMI.[38] A positive correlation between baseline sRAGE concentrations versus postoperative weight loss, and a negative correlation between baseline sRAGE concentrations versus HbA1c after 36 months were also observed in a cohort study involving patients with T2DM that underwent bariatric surgery or an intensive lifestyle intervention program.[35]

4 | DISCUSSION

To our knowledge, this was the first systematic review examining the impact of weight management interventions on serum AGE concentrations and of their receptors (sRAGE, esRAGE, and cRAGE). The incidence of obesity worldwide has increased parallelly with the adoption of unhealthy dietary patterns, with higher intake of AGEs. Interestingly, AGE intake may contribute to increase serum AGE concentrations.[8] The clinical relevance of AGEs lays on their capacity to induce inflammation and oxidative stress by binding to their specific membrane bound receptors.[30,33] Higher AGE serum concentrations have been correlated with body weight gain, and cardiometabolic diseases increased risk in both mice[44,45]and human.[46,47] Moreover, AGEs-RAGE interaction can cause adipocytes hypertrophy, overproduction of ROS, and attenuate insulin sensitivity through inhibition of the PI3K-AKT pathway.[22,23] On the hand, sRAGE have been inversely associated with obesity and metabolic syndrome.[48-51] Thus, AGEs and its receptors are likely to play a role in inducing obesity and related complications. Following, we discuss the mechanisms by which weight loss may lead to serum AGE concentration reduction, as well as the role of different sRAGE isoforms on weight management interventions response.

4.1 | Possible mechanisms involved in AGE reduction after weight loss

The reduction of AGE serum concentrations in response to body weight loss is likely to be associated with of the six mechanisms (Figure 2) discussed below.

The first mechanism is related to the use of an overall caloric restriction, as a nutritional strategy for weight loss. Previous animal studies demonstrated an association between reducing calorie intake and lower tissue AGE accumulation throughout the lifespan.[52-54] Although these compounds are formed endogenously as a normal consequence of metabolism, under hyperglycemia and elevated oxidative stress, their formation is accelerated; in turn, both conditions are also consequence of overeating.[55,56] During hyperglycemia, the "carbonyl stress" pathway can be activated, favoring dicarbonyl compounds formation through the oxidation of sugars. It is estimated that such compounds are 20 000 times more reactive than glucose, and they are the main intermediates during the formation of AGEs in vivo.[57] Therefore, a reduction in total energy intake will likely reduce the availability of substrates, for AGE formation and consequently

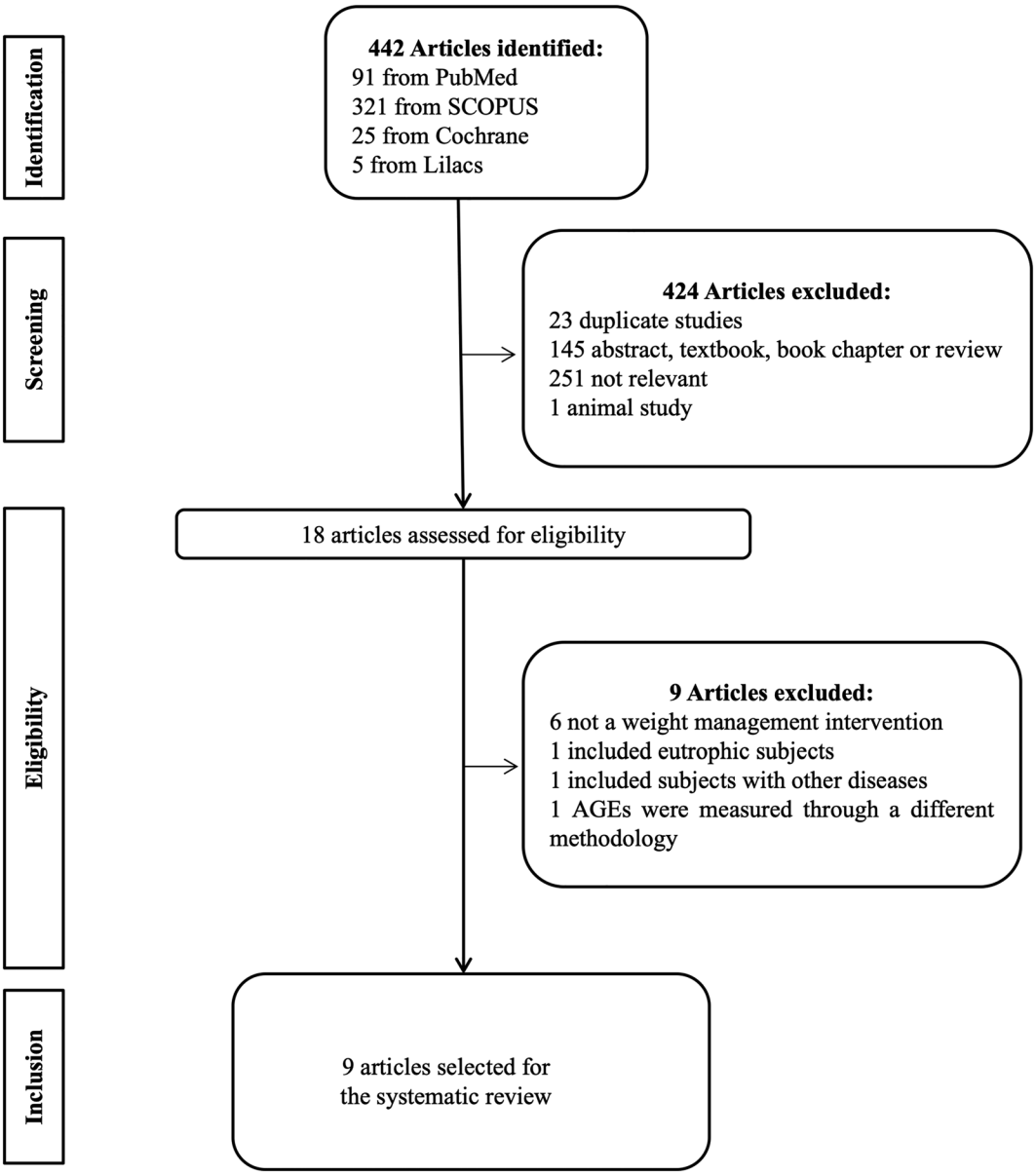

FIGURE 1 Flowchart of the study selection process

accumulation within the body.[30,58] Hence, energy restriction could also contribute to decrease the total pool of AGEs through both lowering glucose levels and limiting substract availability.

Diet itself is a major source of AGEs, contributing largely to its endogenous pool. It is estimated that 10% to 30% of the AGEs consumed are readily absorbed into the bloodstream.[59] Although nutrient composition of the diet is a key factor in AGE formation, the reaction that leads to AGE formation depends directly in the temperature and the time applied in food preparation and processing. AGE formation is mainly increased during frying, roasting, grilling, and baking.[8] Therefore, the second mechanism through which an energy restrict diet may decrease AGE serum concentrations is directly related to the adoption of dietary strategies that can decrease AGE intake by avoiding ultra-processed products and preference for cooking methods which generates less AGEs, eg, boiling and steaming.[8]

The third mechanism is mainly related to the overall diet quality. Through the modification of dietary habits as part of a weight management program, people tend to increase the intake of whole-grain cereals, vegetables, and fruits[60] and reduce the consumption of extensively processed thermically treated foodstuff.[8] These foods are sources of compounds with antiglycation and/or antioxidant properties, such as phenolic compounds, besides B, C, and E vitamins complex.[8,61-63]

The fourth proposed mechanism is linked to a possible AGE accumulation in different compartments of adipose tissue. Contrary to what would be expected, some studies have reported an inverse correlation between obesity and serum AGE concentrations.[64-67] These results have raised the hypothesis that AGEs may preferentially accumulate in adipose tissue.[67] In fact, individuals with higher body fat have higher AGE accumulation and RAGE expression in

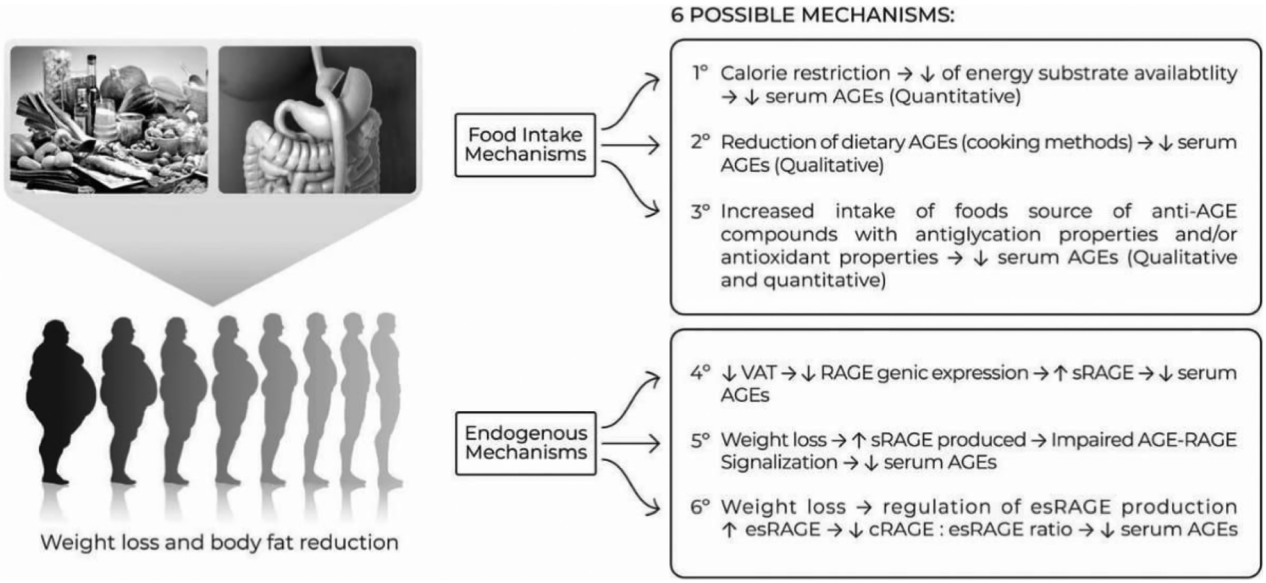

FIGURE 2 Six mechanisms that explain the effect of calorie restriction and bariatric surgery on AGEs and sRAGE
Legend: Abbreviations: AGEs: advanced glycation end products; sRAGE: soluble receptor for advanced glycation end product; RAGE: receptor for advanced glycation end product; VAT: visceral adipose tissue; esRAGE: endogenous secretory receptor for advanced glycation end products; cRAGE: cleaved receptor for advanced glycation end product

subcutaneous (SAT) and specially in visceral adipose tissue (VAT) when compared with normal weight individuals.[21] VAT is an inflammatory fat deposit associated with increased metabolic disease risk, and therefore the increased accumulation of AGEs and simultaneous RAGE overexpression in adipose tissue, specially VAT, is likely to be involved in metabolic dysfunction.[21] Moreover, these interactions contribute to adiponectin (which has anti-inflammatory properties) reduction and insulin resistance development in adipocytes.[21,46,68] In summary, weight loss could also play a role in reducing tissue inflammation through preventing AGEs-RAGE interaction in adipose cells.[36]

The fifth mechanism used to explain serum AGE reduction is associated with an increase in sRAGE production as a consequence of BMI reduction, which may in turn reduce the circulating load of AGEs.[30] The interaction between AGE-RAGE activates inflammatory and oxidative stress pathways.[16,17] However, sRAGE acts as a protective agent, preventing signaling induced by AGE-RAGE interaction and its consequent damage.[25,26] Individuals with obesity usually present lower sRAGE concentrations.[36,38,51,69-72]

sRAGE is negatively correlated with BMI and waist-hip ratio.[51,69,73,74] Koyama et al (2005) also verified an inverse correlation between esRAGE and metabolic syndrome determinants in healthy subjects with diabetes. Hence, body weight reduction reduces inflammation and increases the concentration of anti-inflammatory factors, such as sRAGE, which in turn reduces serum AGE concentration.[71] The endogenous secretory RAGE (esRAGE) is a sRAGE isoform generated by alternative splicing of RAGE pre-RNA. Therefore, esRAGE and sRAGE have so far been considered equivalent.

The sixth mechanism is also related to weight loss. BMI reduction increases esRAGE serum concentration, reducing cRAGE:esRAGE ratio and serum AGEs. cRAGE:esRAGE ratio was recently considered as an approach to assess the effect of alternate fasting day on sRAGE isoforms, including cRAGE,[36] which is a cleaved RAGE produced via proteolytic shedding of the RAGE ectodomain.[75,76]

4.2 | The role of different sRAGE isoforms on weight loss response

RAGE exists as a full-length isoform (FL-RAGE) consisting of three extracellular immunoglobulin-like domains. FL-RAGE is bound to cell membrane, and it can be found as soluble isoforms, which derive from alternative splicing.[75] sRAGE isoforms include cleaved RAGE (cRAGE) and endogenous secretory RAGE (esRAGE), as we mentioned above. Other soluble RAGE isoforms have been inferred from cloned transcripts, but at present, only esRAGE has been identified at the protein level.[75]

Previous studies have shown that esRAGE has the strongest correlation with BMI and body fat percentage, where changes in esRAGE negatively correlate with fat mass changes.[36,77] Conversely, a significant increase in total sRAGE as a result of weight-loss 24 and 36 months after bariatric surgery was verified.[33,35] Other studies have shown that when the follow-up period was shorter (12 months), sRAGE reduced after the surgery[37] and sRAGE concentration remains constant 6 months after bariatric surgery.[34,36,38] These differences according to the follow-up time after surgery suggests that weight regain can occur in the long term and therefore affect sRAGE concentration. Accordingly, a shorter follow-up may be insufficient to detect a significant weight loss capable to affect sRAGE concentration. However, as

mentioned, baseline sRAGE seems to predict weight loss during obesity treatments.

Weight loss increases adiponectin, which is a hormone secreted exclusively by adipose tissue. Such increase in adiponectin secretion was positively related with cRAGE:esRAGE changes, suggesting the existence of potentially independent regulation of the two isoforms as a consequence of weight loss. Given that they are produced by different mechanisms, it is assumed that they may be regulated by different stimuli.[36] Since adiponectin is an adipokine, its relationship with cRAGE:esRAGE suggests that changes in cRAGE and esRAGE are differentially regulated by fat loss. Thus, future mechanistic work is necessary to determine if changes in adiponectin secretion and the proportion of circulating sRAGE isoforms are in fact causally linked.[36] Although not many studies have investigated the sRAGE isoforms changes after weight loss, it was shown that improvements in body composition are related to increased sRAGE isoforms.[36,77]

5 | STRENGTHS AND LIMITATIONS

The duration of the studies varied considerably (2 to 36 months), which allowed a complete overview about the time response of the effects of weight loss on AGEs and sRAGE concentrations. However, the studies also had some limitations: (a) some studies evaluated only the serum AGEs or sRAGE, instead of evaluating the concentration of both glycation biomarkers at the same time; (b) there is no cut off point for these biomarkers so it is not possible to measure the weight loss intervention efficiency; (c) only one study evaluated the esRAGE isoform, an important marker to clarify the mechanisms discussed; and (d) most of the studies did not consider the AGEs from food as a potential source for the total pool of serum AGEs.

6 | CONCLUSIONS

The results of the chronic studies indicated that the consumption of energy-restricted diets (800-1700 kcal/day or 20 kcal/kg initial body weight or 25% of baseline energy) for 2 to 6 months reduced AGE serum concentrations. In addition, the results of postoperative bariatric surgery follow-up programs, conducted for 6 to 36 months, indicated increased sRAGE in three studies, remained unchanged in two studies and decreased in one study. Moreover, higher baseline sRAGE concentrations were associated with greater weight loss. These results corroborate with the hypothesis that these receptors could be a novel biomarker to identify patients with obesity that would most likely benefit from weight management interventions. However, further research is warranted.

These results are postulated to be associated with six mechanisms related to food intake and endogenous system, namely: reduced availability of substrates for AGE production, changes in cooking methods, increased intake of foods source of anti-AGE compounds (antioxidant and antiglycation properties), increased sRAGE concentration, altered lipid metabolism, and regulation of esRAGE production. Therefore, weight loss due to energy-restriction and bariatric surgery seem to reduce AGEs, increase sRAGE, and improve metabolic marker concentrations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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