Special Article

NUTRITION REVIEWS

Effect of advanced glycation end product intake on inflammation and aging: a systematic review

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Aging is associated with a chronic low-grade inflammatory status that contributes to chronic diseases such as age-related muscle wasting, kidney disease, and diabetes mellitus. Since advanced glycation end products (AGEs) are known to be proinflammatory, this systematic review examined the relation between the dietary intake of AGEs and inflammatory processes. The PubMed and Web of Science databases were screened systematically. Seventeen relevant studies in humans or animals were included. The intervention studies in humans showed mainly a decrease in inflammation in subjects on a low-AGE diet, while an increase in inflammation in subjects on a high-AGE diet was less apparent. About half of the observational studies found a relationship between inflammatory processes and AGEs in food. When the results are considered together, the dietary intake of AGEs appears to be related to inflammatory status and the level of circulating AGEs. Moreover, limiting AGE intake may lead to a decrease in inflammation and chronic diseases related to inflammatory status. Most of the trials were conducted in patients with chronic kidney disease or diabetes, and thus additional studies in healthy individuals are needed. Further investigation is needed to elucidate the effects of lifetime exposure of dietary AGEs on aging and health.

INTRODUCTION

Aging results in an increase of circulating inflammatory mediators such as cytokines and acute-phase proteins that appear to be associated with age-related functional decrease and frailty.[1] Advanced glycation end products (AGEs) are known to have proinflammatory features.[2] AGEs are molecules formed by the nonenzymatic glycation of proteins, lipids, and nucleic acid and are capable of forming covalent cross-links with proteins.[3] AGEs are not only produced endogenously; they can also be ingested via food, and there is some evidence that the concentration of circulating AGEs increases in individuals with a high-AGE diet.[2] AGEs are present mainly in food that has been processed at very high temperatures (such as frying, broiling, grilling, and roasting), resulting in a chemical modification known as the Maillard reaction.[3] More than 20 different AGEs have been identified. These can be divided into fluorescent cross-linking AGEs, nonfluorescent cross-linking AGEs, and non-cross-linking AGEs. The best-known AGEs are carboxymethyllysine, pyrraline (both non-cross-linking), and pentosidine (fluorescent cross-linking).[4–6] AGEs can cause dysfunction either by altering protein function[5,7] or by binding to the receptor for AGE (RAGE), which is present on cell surfaces of tissues, especially in heart, lung, and skeletal muscle.[3]

RAGE, a multiligand receptor that belongs to the immunoglobulin superfamily of cell surface molecules, recognizes three-dimensional structures and can bind to

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other ligands, beside AGEs, such as amyloid-β-peptide and S100/calgranulins.[8,9] As a result, RAGE can be considered a pattern recognition receptor.[10] The activation of RAGE leads to an inflammatory cascade that begins with activation of phosphatidylinositol-3 kinase (PI3-K), mitogen-activated protein kinase, and transcription factor nuclear factor-kappa B (NF-κB), a master regulator of proinflammatory genes. By activating the NF-κB pathway, a positive feedback loop is established, which results in an increase in RAGE expression, thus further increasing the level of inflammation. Additionally, the RAGE-AGE interaction increases oxidative stress by activating NADPH oxidase, which also leads to NF-κB stimulation.[11,12] On the other hand, the advanced glycation end product receptor 1 (AGER1), an AGE-specific type 1 transmembrane protein present on the cell surface, has anti-inflammatory characteristics and reduces oxidative stress through several pathways: AGER1 activation suppresses mitogen-activated protein kinase/NF-κB activity, increases the degradation of AGEs, and inhibits the AGE-induced production of cellular reactive oxygen species.[13–15] At the tissue level, the formation of AGE cross-links results in increased stiffness, as seen in skeletal muscle and other collagen-containing structures,[16,17] but it is unclear whether ingested AGEs can contribute to this process.

The exact pathways through which ingested AGEs enter the circulation and tissues are incompletely elucidated. About 10% of the AGEs ingested are absorbed.[18] The intestinal absorption of different AGEs has been described, mainly for carboxymethyllysine, pyrraline, and pentosidine, showing differences in the absorption rates.[5] A recent study showed that the peptide transporter 1 was responsible for the absorption of pyralline.[19] Serum levels of carboxymethyllysine and methylglyoxal seem to correlate with the dietary intake of AGEs.[2,20–23] Of the AGEs absorbed, two-thirds are deposited in tissues and one-third is excreted by the kidneys.[18]

The aim of this systematic review was to evaluate the literature on the influence of the dietary intake of AGEs on markers of inflammation. Given the close relationship between RAGE and the inflammatory processes, the influence of the dietary intake of AGEs on RAGE was also considered.

METHODS

Literature search

PubMed (using MeSH terms) and Web of Science were screened (last search performed October 18, 2013) using the key words (pentosidine OR crosslink OR [advanced glycosylation end product] OR [advanced glycation end product] OR carboxymethyllysine) AND (food OR eating OR nutrition OR feeding behaviour OR dietary), which resulted in, respectively, 489 and 787 hits. The following study designs were included: randomized controlled trials, nonrandomized controlled trials, noncontrolled trials, explorative/cross-sectional studies, and cohort studies, provided a relationship between dietary AGE intake and inflammation was described, either in humans or in animals; human subjects were adults without upper-limit age restriction.

In vitro studies and (anti-AGE) drug studies were excluded. This procedure resulted in the inclusion of 17 relevant articles (1 of which described both an intervention study and an observational study[23]).

Finally, the reference lists of the included articles were screened, which did not reveal additional relevant studies.

Quality assessment

All intervention studies were analyzed using the National Institute for Health and Clinical Excellence checklist,[24] and the observational studies were analyzed using the STROBE statement.[25] Assessments were performed independently by two reviewers, and if assessments were conflicting, a consensus-based final score was assigned.

Data extraction

First, the main characteristics of the participants were identified (human or animal subjects, type of population, age, gender). Next, the dietary aspects, the type of AGE, the inflammatory mediators that were analyzed, and/or the connective tissue alterations were recorded (see Tables 1 and 2).[26–37]

RESULTS AND DISCUSSION

Methodological quality of the included papers

Tables 3 and 4[2,20–23,26–38] give an overview of the methodological evaluation of the articles included.

For the 5 intervention studies in animals,[26–30] the overall quality was rather good, with a low risk of bias; most of these studies, however, lacked information on selection bias.

The 6 intervention studies in humans[20–23,32,37] were generally of lower quality; in most of them, the information necessary to properly judge the quality and to estimate the risk of the different types of bias was missing.

For the 7 observational studies,[2,23,31,33–36] the overall quality was reasonable, but none of the studies addressed potential sources of bias. Information also was lacking for

Table 1 **Overview of the characteristics and main findings of the animals studies included in the present review.**

Reference	Study design	Population	Dietary aspects	Outcome measures	Main findings
Cai et al. (2007)[26]	Randomized controlled experiment	Male C57BL/6 mice (n = 84), 4 mo of age	Low-AGE (15.5×10^4 U/day) vs regular-AGE diet (30×10^4 U/day); CML & MG-like AGE in diet	CM-like AGE in serum, urine, tissue MG-like AGE in serum, urine, tissue RAGE in tissue AGER1 expression in tissue	RAGE expression in mice on Reg-AGE diet at 24 mo of age $3.5\times$ greater than at 4 mo of age ($P < 0.01$) RAGE expression in mice on low-AGE diet at 24 mo of age less than in mice on Reg-AGE diet at 24 mo ($P < 0.01$) RAGE expression in mice on low-AGE diet at 24 mo of age not different than at 4 mo AGER1 expression in tissue of mice on low-AGE diet at 24 mo $3\times$ greater than in tissue of mice on Reg-AGE diet at 24 mo & 4 mo ($P < 0.01$)
Cassese et al. (2008)[27]	Randomized controlled experiment	Female mice (n = 20), 4 wks of age	High-AGE standard rodent diet (718.5 U/mg) vs low-AGE standard rodent diet (209.7 U/mg) for 20 wks CML in diet	CML in albumin RAGE in tissue	↑ RAGE-mediated inflammatory cascade by ↑ RAGE-PKCα-Src complex in muscle of high-AGE diet mice
Cai et al. (2008)[28]	Randomized controlled experiment	6-mo study: Pups of dams fed on low-AGE diet before and during gestation (n = 15/group, 7M/8F) Long-term study: male C57BL/6 mice (n = 66), 4 mo of age	6-mo study: Reg diet (CML = 6×10^4 U/g; MG = 0.3×10^4 nmol/g) vs low-AGE diet (CML = 3.4×10^4 U/g; MG = 0.14×10^4 nmol/g)low-AGE + MG (CML = 6.4×10^4 U/g; MG = 0.38×10^4 nmol/g) Long-term study: CR diet (CML = 6.2×10^4 U/g; MG = 0.28×10^4 nmol/g) vs CR + high-AGE (CML = 17.4×10^4 U/g; MG = 0.45×10^4 nmol/g) diet vs Reg diet (CML = 6×10^4 U/g; MG = 0.3×10^4 nmol/g) CML & MG in diet	CML in serum, urine, tissue MG in serum, urine, tissue RAGE in tissue AGER1 in tissue	Long-term study: RAGE expression: ≈50–60% lower in CR-diet mice compared with Reg-diet & CR + high-AGE diet mice ($P < 0.05$) RAGE expression in Reg-diet & CR +high-AGE diet mice $3.5\times$ greater at 112 wks than at 16 wks ($P < 0.05$) AGER1 expression tissue of CR-diet mice at 112 wks $2\times$ greater than mice at 16 wks ($P < 0.05$); no changes in AGER1 expression in tissue of 112-wk-old mice on CR + high-AGE diet or Reg diet 6-mo study: levels of OS $2\times$ higher in pups on Reg diet or Low-AGE+MG diet ($P < 0.01$)
Tikellis et al. (2008)[29]	Randomized controlled experiment	Male C57BL6J mice (8 wks of age) and RAGE knockout mice (n = 10/group)	Standard diet (CML = 21 nmol) vs high-fat diet (CML = 65 nmol) CML in diet	Cardiac AGE (CML-modified protein) Myocardial expression of TNF-α Myocardial expression of IL-6 Myocardial expression of MCP-1 Myocardial expression of RAGE, AGE-R1, & AGE-R3 Myocardial NF-κB	In C57BL6J mice: myocardial inflammation (IL-6 & TNF-α) ↑ in HF diet ($P < 0.05$) Cardiac expression of ICAM-1 & MCP-1 ↑ in HF diet ($P < 0.05$) NF-κB and expression of RAGE ↑ in HF diet ($P < 0.05$) In RAGE-KO mice : ↓ inflammation in HF diet ($P < 0.05$) and no RAGE expression. No alteration of cardiac expression of AGER1 or AGE-R3 in HF diet in both groups and no difference between the groups (data not shown)
Sato et al. (2009)[30]	Randomized controlled experiment	Male rats (n = 12), 7 wks of age	Standard chow diet plus: Intervention: 8 wks *Lactobacillus* beverage-A (LB-A) (high AGE = 5.40 U/ml)) (n = 6) Control: 8 wks distilled water (n = 6) Glucose-derived AGE level in LB-A and other beverage measured by ELISA	AGE level in serum (not specified which) RAGE in tissue (liver & kidney)	In LB-A diet: RAGE expression increased in liver, but not statistically significant (*P* not reported)

Abbreviations: AGE: advanced glycation end product; AGER, advanced glycation end product receptor; CML, carboxymethyllysine; CR, calorie restriction; ELISA, enzyme-linked immunosorbent assay; HF, high-fat; ICAM-1, intercellular adhesion molecule; IL-6, interleukin 6; KO, knockout; MCP-1, macrophage chemoattractant protein 1; MG, methylglyoxal; mo, month; NF-κB, nuclear factor kappa B; OS, oxidative stress; PKCα, protein kinase Cα; RAGE, receptor for advanced glycation end products; TNF-α, tumor necrosis factor alpha; ↑, increased; ↓, decreased.

Table 2 **Overview of the characteristics and main findings of the human studies included in the present review.**

Reference	Study design	Population	Dietary aspects	Outcome measures	Main findings
Sebeková et al. (2001)[31]	Cross-sectional explorative study	9 vegans (mean age 39.6 ± 3 y) 19 lacto-ovo-vegetarians (mean age 36.1 ± 2.5y) 14 semi-vegetarians (mean age 35.4 ± 2.7 y) 19 omnivores (mean age 30.5 ± 1.6 y)	FFQ: intake of proteins, carbohydrates, milk products, and food groups containing mainly higher fructose vs glucose (Alimenta database) Dietary interview: 102 food items, food groups, & recipes No AGE level in diet quantified	Plasma CML Plasma CRP	No significant differences in CRP between the groups Plasma CML ↑ in vegans vs omnivores ($P < 0.05$); in lacto-ovo-vegetarians vs omnivores ($P < 0.01$); and in semi-vegetarians vs omnivores ($P < 0.05$)
Vlassara et al. (2002)[22]	Randomized crossover study (2-wk study) Randomized parallel-group study (6-wk study)	24 diabetes patients: 2-wk study: 11 patients (mean age 52 ± 5 y) 6-wk study: 13 patients (mean age 62 y)	Crossover: 2 wks of 1 study diet, then washout, 2 wks of alternate study diet Parallel group: randomized to low-AGE diet ($3.67 \pm 1.2 \times 10^6$ AGE U/day) or high-AGE diet ($16.3 \pm 3.7 \times 10^6$ AGE U/day) Standardized prepared meals AGE intake assessed using an AGE scoring system based on a database of 250 foods tested by ELISA (CML & MG)	CML in serum MG in serum CRP in serum PMNC-TNF-α	2-wk study: ↓ PMNC-TNF-α in low-AGE diet vs high-AGE diet ($P = 0.05$) 6-wk study: 35% ↑ CRP in high-AGE diet & 20% ↓ CRP in low-AGE diet ($P = 0.01$) 86.3% ↑ PMNC-TNF-α in high-AGE diet & 20% ↓ PMNC-TNF-α in low-AGE diet ($P = 0.006$)
Peppa et al. (2004)[21]	Randomized controlled trial	18 PD patients (12F/6M)	Low-AGE (5.5×10^6 U/day) high-AGE diet (17×10^6 U/day) over a 4-wk period Meals prepared by participants, who received instructions Different cooking methods were used to vary AGE content of food AGE intake assessed using an AGE scoring system based on a database of 250 foods tested by ELISA (CML & MG)	CML in serum, urine, dialysate MG in serum, urine, dialysate CRP TNF-α in PMNC	TNF-α lower in low-AGE diet vs high-AGE diet ($P < 0.05$) ↓ CRP in low-AGE diet ($P < 0.03$) No change in CRP in high-AGE diet
Schiekofer et al. (2006)[32]	Randomized controlled experiment	9 healthy volunteers (9M/0F) (mean age 31.8 ± 8.3 y)	Sorbitol (S)-casein meal (104.2 ± 23.3 ng CML/mg casein & no pentosidine) + glucose (G)-casein meal (301.7 ± 49.2 ng CML/mg casein & 4.28 pmol pentosidine/mg casein) Standardized prepared meals Dietary CML & pentosidine	CML in plasma Intracellular CML Mononuclear NF-κB	↑ NF-κB activation 2 h after ingestion of an S-casein ($P = 0.01$) and a G-casein ($P = 0.03$) No difference between S- and G-casein ($P = 0.80$)
Negrean et al. (2007)[20]	Randomized controlled trial, crossover design	20 diabetes patients (14M/6F) (mean age 55.4 ± 2.2 y)	High-AGE meal (15.10×10^3 U AGE) vs low-AGE meal (2750×10^3 U AGE) Standardized prepared meals with same ingredient but different cooking procedure	CML in serum MG in serum CRP in serum TNF-α IL-6 Fibrinogen	Low-AGE meal: ↓ IL-6 High-AGE meal:↑ IL-6 No significant differences between meals No changes in CRP, fibrinogen, or TNF-α after either meal
Uribarri et al. (2007)[2]	Cross-sectional explorative study	172 healthy individuals: 70M & 102 F, distributed in 2 groups: 116 younger (18–45 y) and 56 older (60–80 y)	3-d food record daily AGE intake estimated using food CML database of Goldberg et al.[45] (mean AGE intake: men < 45 y: $20 \pm 2 \times 10^6$ U/day; men > 60 y: $14 \pm 2 \times 10^6$ U/day; women < 45 y: $15 \pm 1 \times 10^6$ U/day; women > 60 y: $14 \pm 2 \times 10^6$ U/day)	CML in serum MG in serum hsCRP in serum TNF-α in PMNC	Intake of dietary AGEs ≈ levels of hsCRP ($r = 0.200$; $P = 0.042$)
de la Maza et al. (2007)[33]	Cross-sectional explorative study	41 nondiabetic men: 31 middle-aged (mean age 41 ± 5 y) and 10 elderly (mean age 74 ± 10 y)	Nutritional assessment + dietary recall (24-h and FFQ) AGE intake (CML & CEL) estimated using food database Goldberg et al.[45] (mean AGE intake/day: middle-aged men: $9.754 \pm 3.936 \times 10^3$ U/day; elderly men: $9.893 \pm 3.784 \times 10^3$U/day)	AGE in serum (not further specified) AGE in urine (not further specified) CRP	Serum and urinary AGEs ≈ CRP ($r = 0.58$ & $r = 0.44$) Concentrations of AGEs were not related to dietary intake
Sjögren et al. (2007)[34]	Cross-sectional	294 healthy men (mean age 63 ± 0.6 y)	7-d dietary record (quantitative & qualitative aspects of diet) No AGE level in diet quantified	CML in plasma sRAGE in plasma CRP IL-6 TNF-α	No relation between sRAGE, dietary habits, and CML (data not shown)

Table 2 **Continued**

Reference	Study design	Population	Dietary aspects	Outcome measures	Main findings
Vlassara et al. (2009)[23]	Cross-sectional + longitudinal analysis (2-y follow-up) + randomized controlled experiment	1. Cross-sectional: 66 CKD patients[a] (mean age 59 ± 2 y) and 325 healthy adults[a] (mean age young group : 30 ± 7 y and old group: 80 ± 7 y) 2. Longitudinal analysis with 49 healthy participants 3. Intervention: 30 healthy adults[a] (young and old) and 9 CKD-3 patients[a] (mean age 62 ± 3 y)	1. Cross-sectional + longitudinal analysis: 3-d food record; AGE intake estimated using food database (mean AGE intake/day: young: $15 \pm 1 \times 10^6$ U/day; old: $13 \pm 1 \times 10^6$ U/day) 2. Intervention in healthy adults (over period of 4 mo): Intervention: isocaloric low-AGE ($10 \pm 2 \times 10^6$ U AGE/day) Control: regular diet ($20 \pm 6 \times 10^6$ U AGE/day) Meals prepared by participants, who received instructions (cooking method) 3. Intervention in CKD patients (4 wks): Intervention: low-AGE diet ($8 \pm 2 \times 10^6$ U AGE/day)(standardized prepared meals) Control: usual diet ($12 \pm 3 \times 10^6$ U AGE/day)	CML in serum CML in urine MG in serum MG in urine PMNC-derived TNF-α hsCRP in serum PMNC RAGE & PMNC AGER1 mRNA expression Fibrinogen in plasma	1. Cross-sectional + longitudinal analysis: ↑ dietary AGE intake ≈ RAGE (β = 0.554; $P = 0.002$) & AGER1 (β = 0.422; $P = 0.022$) In the longitudinal analysis: Changes in serum CML levels ≈ changes in TNF-α ($r = 0.414$; $P = 0.002$) Changes in dietary AGE intake ≈ changes in serum CML ($r = 0.474$; $P = 0.014$) In younger subjects in upper tertile of dietary AGE intake, serum hsCRP, serum MG, and serum CML levels are comparable with those in older subjects 2. Intervention in healthy adults: low-AGE diet associated with ↓ TNF-α ($P = 0.001$) & RAGE ($P = 0.025$) & ↑ AGER1 ($P = 0.043$) 3. Intervention in CKD patients: low-AGE diet associated with ↓ TNF-α ($P = 0.037$) & RAGE ($P = 0.117$) & ↑ AGER1 ($P = 0.014$)
Piroddi et al. (2011)[35]	Cross-sectional	10 (6M/4F) ambulatory predialysis patients with CKD (mean age 72.6 ± 13.2 y) 10 (5M/5F) healthy subjects (mean age 57.8 ± 9.5 y) 10 (4M/6F) stable ESRD on HD patients (mean age 68.4 ± 18.9 y)	3-d food record 24-h dietary recall CML intake estimated using food CML database of Goldberg et al.[45] (mean dietary intake CML in CKD patients: $6 \pm 3 \times 10^6$ U/day; in healthy controls: $13 \pm 6 \times 10^6$ U/day; HD patients ≈ same diet control group)	CML in plasma Pentosidine in plasma IL-6 in plasma CRP in plasma	CML intake in food did not correlate with inflammatory parameters
Jara et al. (2012)[36]	Cross-sectional	40 healthy men (median age 46 y) 17 patients with type 2 diabetes (7F/10M; median age 69 y) 15 patients with type 1 diabetes (6F/9M; median age 23 y)	FFQ & 24-h recall CML intake based on food database of Uribarri et al.[51] (median CML intake according to FFQ: healthy men: 21.945×10^3 U/day; type 2 diabetes: 7.314×10^3 U/day; type 1 diabetes: 24.143×10^3 U/day median CML intake according to 24h-recall: healthy men: 8.556×10^3 U/day; type 2 diabetes :3.943×10^3 U/day; type 1 diabetes: 13.640×10^3 U/day)	CML in serum hsCRP in serum	No relationship between hsCRP and serum CML, or with CML intake in any group (P = NS)
Luévano-Contreras et al. (2013)[37]	Randomized controlled experiment	34 patients with type 2 diabetes (of whom 8 were excluded from analysis): 13 on low-AGE diet (1M/12F; mean age 46.0 ± 5 y) 13 on standard-AGE diet (2M/11F; mean age 48.5 ± 6.2 y)	Initial 2-day dietary history and after initial FU of 6 wks without diet change: Low-AGE (baseline CML = $8956 \pm 3587 \times 10^3$ U/day, changes after 6 wks: $-4990 \pm 3380 \times 10^3$ U/day [$P < 0.00005$]) vs standard-AGE diet (CML = $9910 \pm 4164 \times 10^3$ U/day, changes after 6 wks:+ $2304 \pm 4169 \times 10^3$ U/day [$P < 0.00005$]) for 6 wks standard diet: patients' usual meals Low-AGE diet: prepared by participants, who received instructions about cooking method AGE content estimated using food CML database of Goldberg et al.[45]	Pentosidine in serum CRP in plasma TNF-α	TNF-α significantly ↓ in low-AGE diet vs standard-AGE diet ($P < 0.00001$)

Abbreviations: AGER, advanced glycated end product receptor; CE, carboxyethyllysine; CKD, chronic kidney disease; CKD-3, stage 3 chronic kidney disease; CML, carboxymethyllysine; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; FFQ, food frequency questionnaire; FU, follow-up; HD, hemodialysis; hs, high-sensitivity; IL-6, interleukin-6; MG, methylglyoxal; mRNA, messenger ribonucleic acid; NF-κB, nuclear factor kappa B; NS, nonsignificant; PD, peritoneal dialysis; PMNC, peripheral blood mononuclear cells; RAGE, receptor for advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products; TNF-α, tumor necrosis factor alpha., U, units.

[a] Gender distribution not reported.

Table 3 **Compliance of the intervention studies included in the present review with the NICE guidelines.[24]**

Criteria	Reference										
	Vlassara et al. (2002)[22]	Peppa et al. (2004)[21]	Schiekofer et al. (2006)[32]	Cai et al. (2007)[26]	Negrean et al. (2007)[20]	Tikellis et al. (2008)[29]	Cai et al. (2008)[28]	Cassese et al. (2008)[27]	Sato et al. (2009)[30]	Vlassara et al. (2009)[23]	Luévano-Contreras et al. (2013)[37]
An appropriate method of randomization was used to allocate participants to treatment group (which would have balanced any confounding factors equally across groups)	+	+	?	?	+	+	?	+	?	+	+
There was adequate concealment of allocation (such that investigators, clinicians, and participants cannot influence enrollment or treatment allocation)	?	?	?	?	+	?	?	?	?	?	–
Groups were comparable at baseline, including all major confounding and prognostic factors	?	+	?	?	+	?	?	?	?	+	+
Risk of bias	Unclear	Low	Unclear (no randomization of treatment administration sequence)	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Comparison groups received the same care apart from the intervention(s) studied	?	?	?	+	+	?	+	+	+	?	+
Participants receiving care were blinded to treatment allocation	?	–	?	NA	?	NA	NA	NA	NA	–	–
Individuals administering care were blinded to treatment allocation	?	–	?	?	+	?	?	?	?	–	+
Risk of bias	Unclear	High	Unclear	Low	Low	Unclear	Low	Low	Low	High	Low
All groups were followed up for an equal length of time	+	+	+	+	+	+	+	+	+	+	+
How many participants did not complete treatment in each group?	?	4/4	?	0/0	?	?	0/0	0/0	?	2 (unclear which group)	4/4
Groups were comparable for treatment completion	?	?	?	NA	?	?	NA	NA	?	?	+
For how many participants in each group were no outcome data available?	?	4/4	?	0/0	?	?	0/0	0/0	?	2 (unclear which group)	0/0
Groups were comparable with respect to the availability of outcome data	?	?	?	NA	?	?	NA	NA	?	?	NA
Risk of bias	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Study had an appropriate length of follow–up	+	+	?	+	+	+	+	+	+	+	+
Study used a precise definition of outcome	+	+	+	+	+	+	+	+	+	+	+
A valid and reliable method was used to determine the outcome	+	+	+	+	+	+	+	+	+	+	+
Investigators were blinded to participants' exposure to the intervention	?	?	?	?	+	?	?	?	?	?	+
Investigators were blinded to other important confounding and prognostic factors	?	?	?	NA	?	?	NA	NA	?	?	?
Risk of bias	Low	Low	Unclear	Low	Low	Low	Low	Low	Low	Low	Low

Abbreviations and symbols: NA, not applicable; ?, unclear; +, yes; –, no.

Table 4 **Compliance of the observational studies included in the present review with the STROBE checklist.[25]**

Criteria	Reference						
	Sebeková et al. (2001)[31]	Sjögren et al. (2007)[34]	Uribarri et al. (2007)[2]	de la Maza et al. (2007)[33]	Vlassara et al. (2009)[23]	Piroddi et al. (2011)[35]	Jara et al. (2012)[36]
Indicates the study's design with a commonly used term in the title or abstract	+	+	+	+	+	+	+
Provides in the abstract an informative and balanced summary of what was done and what was found	+	+	+	+	+	+	+
Explains the scientific background and rationale for the investigation being reported	+	+	+	+	+	+	+
States specific objectives, including any prespecified hypotheses	+	−	+	+	+	+	+
Presents key elements of study design early in the paper	+	−	+	+	+	+	+
Describes the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	−	+	+	−	+	+	+
Provides the eligibility criteria as well as the sources and methods of selection of participants	−	−	+	−	+	+	+
Clearly defines all outcomes, exposures, predictors, potential confounders, and effect modifiers. Gives diagnostic criteria, if applicable	+	+	+	−	+	+	+
For each variable of interest, gives sources of data and details of methods of assessment (measurement). Describes comparability of assessment methods if there is more than one group	+	+	+	+	+	+	+
Describes any efforts to address potential sources of bias	−	−	−	−	−	−	−
Explains how the study size was determined	−	+	−	−	−	−	−
Explains how quantitative variables were handled in the analyses. If applicable, describes which groupings were chosen and why	+	+	+	+	+	+	+
Describes all statistical methods, including those used to control for confounding	+	+	+	+	+	+	+
Describes any methods used to examine subgroups and interactions	−	+	+	+	+	+	+
Explains how missing data were addressed	−	−	−	−	−	−	−
If applicable, describes analytical methods, taking into account the sampling strategy	?	?	+	?	+	?	?
Describes any sensitivity analyses	?	?	−	?	−	−	−
Reports numbers of individuals at each stage of study; number potentially eligible, number examined for eligibility, number confirmed eligible, number included in the study, number completing follow-up, and number analyzed	−	+	+	−	+	−	+
Gives reasons for nonparticipation at each stage	−	−	−	?	−	?	?
Considers use of a flow diagram	−	−	−	NA	−	−	−
Gives characteristics of study participants (demographic, clinical, social) and information on exposures and potential confounders	+	+	+	−	+	+	+
Indicates number of participants with missing data for each variable of interest	−	−	−	?	−	−	−
Reports numbers of outcome events or summary measures	+	+	+	−	+	+	+
Gives unadjusted estimates and, if applicable, confounder-adjusted estimates, along with their precision (e.g., 95% confidence interval). Makes clear which confounders were adjusted for and why they were included	NA	+	+	NA	+	NA	+
Reports category boundaries when continuous variables were categorized	NA	NA	+	+	+	NA	+
If relevant, considers translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA	+	NA	+	NA	+
Reports results of other analyses, e.g., analyses of subgroups, interactions, and sensitivity analyses	NA	NA	+	−	+	NA	+
Summarizes key results with reference to study objectives	+	+	+	+	+	+	+
Discusses limitations of the study, taking into account sources of potential bias or imprecision. Discusses both direction and magnitude of any potential bias	+	+	+	+	+	+	+
Gives a cautious overall interpretation of results, considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	+	+	+	+	+	+	+
Discusses the generalizability (external validity) of the study results	−	+	+	−	+	−	+
Gives the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	+	+	+	+	+	+	+

Abbreviations and symbols: NA, not applicable; , unclear; +, yes; −, no.

the statistical methods, especially on how missing data were addressed, on sampling strategy, and on sensitivity analyses. Most of the studies did not describe the reasons for nonparticipation at each stage, and the number of participants with missing data for each variable of interest was not indicated.

Intervention studies

Animal studies. Five randomized controlled experiments with rats or mice were identified (see Table 1).[26–30] In 4 studies, the intervention consisted of a high- versus a low-AGE diet,[26–28,30] and in 1 study, a diet with an AGE-inhibitor was compared with a standard or a fast-food diet.[29] Besides examining the effect of a high- versus a low-AGE diet, Cassese et al.[27] also analyzed the effect of injection of glycated and nonglycated albumin into skeletal muscle as well as the effect of intravenous injections. All 5 studies reported data on tissue levels of RAGE and/or AGER1,[26–30] and 1 study also measured myocardial expression of tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), intercellular adhesion molecule 1 (ICAM-1), NF-κB, and macrophage chemoattractant protein 1 (MCP-1).[29] Some trials also measured markers from oxidative stress, such as 8-isoprostane, $p66^{shc}$,[26,28] and superoxide production.[29] Four of the 5 studies reported only carboxymethyllysine as circulating AGE.[26–29] One trial also measured methylglyoxal (an α-oxaldehyde and precursor of AGE),[28] and in 1 study, the type of AGE was not specified.[30] Concerning the AGE-content of the diets, 2 trials measured carboxymethyllysine,[27,29] 2 measured carboxymethyllysine and methylglyoxal,[26,28] and 1 trial did not specify which AGE was measured.[30] One study also examined the association of Src, protein kinase C (PKC) α, and RAGE in skeletal muscle of mice fed high-AGE diets.[27] Four studies[26–29] showed significantly increased expression of RAGE in tissues of animals fed a high-AGE diet, and 1 trial[30] showed a nonsignificant increase of RAGE expression in the liver of mice fed a *Lactobacillus* (high-AGE) beverage. In addition to increased RAGE expression, Tikellis et al.[29] also described increased myocardial inflammation (increase in TNF-α and IL-6), increased cardiac expression of ICAM-1 and MCP-1, and increased myocardial hypertrophy and fibrosis in mice fed a high-fat/high-AGE diet. Cai et al.[26] described an increase of AGER1 expression in mice fed a low-AGE diet. There was also an increase in markers of oxidative stress in the mice fed a high-AGE diet.[26,28,29]

Cassese et al.[27] demonstrated activation of Src phosphorylation and the formation of a multimolecular complex that included RAGE/insulin receptor substrate 1 (IRS-1)/Src and PKC in muscles from mice fed high-AGE diets, which could lead to an increase in the RAGE-mediated inflammatory cascade. This mechanism was first analyzed in vitro by injection of human glycated albumin either directly into the muscle or intravenously in mice.[27]

Four trials in animals (mice and rats)[26,28–30] all had as a primary objective the examination of the effect of AGE intake (by comparing high- versus low-AGE meals) on inflammation. From these studies, it can be concluded that dietary AGE intake is significantly correlated with inflammatory processes and oxidative stress. The study by Cassese et al.[27] explored the effect of dietary AGEs in inflammatory processes in skeletal muscle, but its main focus was on the role of AGEs in insulin resistance. In all of the trials, the AGE content was quantified, and in the high-AGE diets, the AGE content was minimally 2-fold to maximally 5-fold higher than in the low-AGE diets.

The quality of these 5 intervention studies was fairly good, although the selection of the animals in the studies was not described well, and 4 of the 5 studies[26–28,30] used only RAGE as an inflammatory parameter. In other experimental rodent studies not included in this review, there is evidence that a high consumption of AGEs has negative health effects and induces the development of diabetes and chronic kidney diseases, while restriction of AGEs in food could prevent these diseases.[39–43] The extrapolation of results from animals to humans must be done with care. The experimental conditions are far from the real-life situation, and the absorption of AGEs and their effect on the various organs might be different in animals and humans. Moreover, some argue that experiments with heat-processed food in these animals are not representative, since rodents in their natural environment have no access to such food.[44]

Human intervention studies. Six randomized intervention trials in humans were identified (see Table 2)[20–23,32,37]; the dietary intervention consisted of a high- versus a low-AGE diet. Half of the trials used standardized prepared meals,[20,22,32] while the other 3 trials provided participants with instructions on using different cooking procedures to vary the AGE content of the meals.[21,23,37] Circulating levels of TNF-α and C-reactive protein (CRP) were the most frequently investigated inflammation-related parameters. Vlassara et al.[23] also measured fibrinogen and peripheral mononuclear cell AGE receptors (RAGE and AGER1), Negrean et al.[20] measured IL-6 as well as fibrinogen, and Schiekofer et al.[32] reported only on mononuclear NF-κB. Besides those inflammatory parameters, parameters of oxidative stress, which are indirectly related to inflammation, and markers of endothelial dysfunction, such as E-selectin, vascular adhesion molecule-1 (VCAM-1), ICAM-1, vascular endothelial growth factor, 8-isoprostane, plasminogen activator inhibitor-1, thiobarbituric acid-reactive substance, $p66^{shc}$,

and malondialdehyde, were measured in 5 trials.[20–23,37] In 4 of the 6 studies, the circulating AGEs reported were carboxymethyllysine and methylglyoxyl,[20–23] Schiekofer et al.[32] examined only carboxymethyllysine in serum and in the cytoplasm of mononuclear cells; Luévano-Contreras et al.[37] measured only pentosidine in serum. Dietary AGEs were either measured (mainly carboxymethyllysine and methylglyoxal) or estimated; estimations were based on the food database from Goldberg et al.[45]

Five studies demonstrated a decrease in circulating concentrations of inflammatory parameters with a low-AGE diet.[20–23,37] Peppa et al.[21] showed a decrease in inflammation following a low-AGE diet but failed to demonstrate a significant increase after a high-AGE diet. Vlassara et al.,[22] in their 2-week study, also found a decrease in inflammation after a low-AGE versus a high-AGE diet and found a significant increase in inflammation in the high-AGE group in their 6-week study. Vlassara et al.[23] described a decrease in TNF-α and RAGE and an increase in AGER1 after a low-AGE diet. Schiekofer et al.[32] showed a significant increase in mononuclear NF-κB activation after a single meal, but this was not related to the AGE content of the meal. Negrean et al.[20] showed a decrease in IL-6 after a low-AGE meal and an increase after a high-AGE meal but no significant difference between meals, and there was no significant change in CRP, TNF-α, or fibrinogen after the meals. Finally, Luévano-Contreras et al.[37] reported a significant decrease in TNF-α after the low-AGE versus the standard diet. The trials also demonstrated a reduction in oxidative stress and markers of endothelial dysfunction with the low-AGE diet,[20–23] and Negrean et al.[20] showed an increase in those markers after high-AGE meals.

The relationship between dietary AGEs and inflammatory processes was the primary objective in most of the studies[21–23,32,37]; however, the main goal of Negrean et al.[20] was to analyze the effect of dietary AGEs on vascular dysfunction in diabetes patients. Depending on the goal of the study, 5 of the trials were conducted over a period of 1 to 16 weeks. Schiekofer et al.[32] evaluated the influence of carboxymethyllysine in a single meal on postprandial NF-κB activation. The inflammatory mediators that were measured differed between the studies; moreover, most of the studies also assessed markers of oxidative stress and endothelial dysfunction.[20–23]

In general, these intervention studies demonstrated a relationship between the exogenous AGEs and the inflammatory status of the participating subjects, especially a suppression of inflammatory parameters in diets with low AGE content. Thus, through intervention studies in both humans and animals, inflammation and tissue damage could be prevented by restricting the intake of dietary AGEs. Most of the intervention studies on the role of dietary AGEs were performed in patients with diabetes or renal failure, and there is a lack of studies in healthy individuals. Of the intervention trials included in this review, only the study by Schiekofer et al.[32] was conducted in healthy volunteers, albeit in a very small sample (9 participants). In addition to patients with chronic kidney disease, Vlassara et al.[23] tested a healthy group of 30 subjects (of whom 15 were >60 y of age) and showed an age-independent decrease in inflammation in those subjects on a low-AGE diet. Evidence of the impact of long-term exposure to dietary AGEs, specifically on the health of older individuals, is scarce and has hardly evolved since it was reviewed in 2010 by Luévano-Contreras.[5]

Two types of dietary interventions in the human intervention trials were analyzed. In the trials of Peppa et al.,[21] Vlassara et al.,[23] and Luévano-Contreras et al.,[37] participants had to prepare their meals themselves, using instructions for the cooking procedures. This method raises questions about compliance, standardization of the meals, and the presence of other ingredients in the food. The other studies[20,22,32] used standardized prepared meals, which may be a more reliable method. Both approaches resulted in a decrease in the level of inflammation with the low-AGE diet.

All of the trials evaluated in this review quantified the AGE levels in the diets, and the content of AGEs in a high-AGE diet versus a low-AGE diet ranged from a minimal 2-fold difference to a maximal 5-fold difference. It can be assumed that these differences in AGE content are sufficiently high to produce substantial dietary effects, although the absorption of dietary AGEs is estimated to be only 10%.

The presence of AGEs in food was assessed in various ways. In 4 of the trials, a food database based on the carboxymethyllysine content in food, as measured by enzyme-linked immunosorbent assay (ELISA), was used to estimate carboxymethyllysine.[21–23,37] One trial measured the content of pentosidine in food, using high-performance liquid chromatography.[32] One trial did not specify which AGE in the food was measured.[20] Carboxymethyllysine is the best-studied AGE in food and is, therefore, used in many trials as a marker of dietary AGE. However, there are several other dietary AGEs, including pyrraline and pentosidine, which have not been studied as thoroughly.[5,46] The methods for quantifying carboxymethyllysine in food are not always fully validated; chromatographic methods are considered to be better than the frequently used ELISA technique.[47,48]

Observational studies

Seven cross-sectional observational studies in humans were identified (see Table 2).[2,23,31,33–36] Dietary features

were recorded using a nutritional assessment (a food frequency questionnaire or a 3- or 7-day food record) of the subjects, although Sebekova et al.[31] also compared vegetarian diets with semivegetarian and omnivorous ones. Most studies used circulating carboxymethyllysine as the AGE parameter.[2,23,31,34–36] Piroddi et al.[35] also measured circulating pentosidine, Vlassara et al.[23] and Uribarri et al.[2] also measured circulating methylglyoxal, and de la Maza et al.[33] did not specify which type of AGE was measured. Besides measuring circulating AGE, Vlassara et al.[23] also measured urinary carboxymethyllysine and methylglyoxal. The AGE most commonly assessed in food was carboxymethyllysine, and AGE content was calculated according to the database of Goldberg et al.[45] CRP and TNF-α were the most frequently measured inflammatory mediators. Sjögren et al.[34] also measured soluble RAGE and IL-6, Vlassara et al.[23] measured fibrinogen and peripheral mononuclear cell AGE receptors (RAGE and AGER1), and Piroddi et al.[35] measured, besides CRP, only IL-6. Some of the studies measured markers of oxidative stress and endothelial dysfunction, such as 8-isoprostane, VCAM-1, ICAM-1, and E-selectin, in addition to inflammatory markers. Three of the 7 studies found a positive correlation between AGE intake and AGE levels in serum and/or inflammatory parameters,[2,23,33] while the other 4 trials did not find this correlation.[31,34–36] Vlassara et al.[23] showed that, in younger subjects with a high dietary AGE intake, the levels of carboxymethyllysine, methylglyoxal, VCAM-1, and high-sensitivity CRP were as high as those in persons older than 60 years with a low dietary intake of AGE and that, after 2 years of follow-up, the changes in serum carboxymethyllysine levels correlated positively with changes in 8-isoprostane, TNF-α, and VCAM-1 levels. Uribarri et al.[2] found a positive correlation between the intake of dietary AGEs and serum levels of high-sensitivity CRP but not with levels of 8-isoprostane. The researchers de la Maza et al.[33] found that serum AGE concentration and urinary excretion of AGE were significantly associated with CRP but not with dietary intake of carboxymethyllysine.

Three of the 7 cross-sectional studies were conducted in large populations. Vlassara et al.[23] studied 325 healthy subjects and 66 patients with chronic kidney disease. They described the relationship between dietary intake of AGEs and levels of AGEs in serum, markers of oxidative stress, and proinflammatory markers such as CRP, TNF-α, and fibrinogen. Uribarri et al.[2] analyzed the effect of dietary AGEs on oxidative stress and inflammation in 172 healthy adults (older vs younger). Sjögren et al.[34] investigated the relationship between dietary habits, serum levels of AGEs, and endothelial activation in 294 healthy men. Although this last trial measured inflammatory markers, no relationship with AGEs is described, and no relationship between plasma carboxymethyllysine, plasma-soluble RAGE (sRAGE), and dietary aspects was found. The 2 other trials[2,23] did find a correlation between dietary AGE intake and inflammation in healthy individuals, and in both studies the levels of serum carboxymethyllysine and inflammatory cytokines were higher in the elderly population. Moreover, Vlassara et al.[23] showed that younger people with an excess of AGEs in their diet had the same levels of CRP and carboxymethyllysine as the healthy elderly. As mentioned before, aging is related to an increase of proinflammatory cytokines[1] and an increase of circulating AGEs, which is probably related to increased production, lifetime dietary intake, and lower renal excretion of AGEs.[49] Vlassara et al.[23] also described a relationship between these dietary AGEs and markers of oxidative stress. These results suggest that, in healthy individuals, an excess of dietary AGEs leads to inflammatory processes and oxidative stress, which increases the risk of diseases, while a reduction in dietary AGEs could contribute to healthy aging.

The 4 other cross-sectional studies were conducted in smaller populations. One of these studies did find a correlation between dietary AGE intake and inflammation.[33] The 3 other studies[31,35,36] did not find any relationship between dietary AGE intake and inflammation. The population sample in these studies was small, and the main outcome measured was not inflammation but the relation between dietary and plasma AGEs.

Dietary assessment was performed in the 7 cross-sectional studies. This assessment consisted of either a 3-day food record,[2,23] a 24-hour diet recall combined with a food frequency questionnaire,[33,36] a 3-day record combined with a 24-hour diet recall,[35] a 7-day food record,[34] or a dietary interview combined with a food frequency questionnaire.[31] Each of these methods has advantages and disadvantages. With a food record and 24-hour dietary recall, a quantified intake of food is obtained, but many days are needed to average the intake. A food frequency questionnaire provides information about the whole diet, but this method is more qualitative and less quantitative. A combination of the two methods, such as a 24-hour diet recall combined with a food frequency questionnaire, should be more accurate to estimate the usual intake of some nutrients.[50] Most studies used the food database published by Goldberg et al.,[45] which is based on carboxymethyllysine content in food as measured by ELISA. As mentioned earlier, other techniques are considered more accurate for measuring carboxymethyllysine in food, and the database does not account for other AGEs in food. Moreover, this database is based on American food products and may not be applicable to foods in other countries; nevertheless, it remains the only published database known. While it was recently updated by Uribarri et al.,[51] that version is not yet validated and requires further testing.

Role of AGE intake in inflammation and age-related skeletal muscle wasting

The age-related loss of skeletal muscle mass and strength[52] is increasingly recognized as a major contributor to the problem of frailty and dependency in old age. Recent research has highlighted the relationship between chronic low-grade inflammation and age-related muscle wasting.[53] AGEs may play a role in the pathophysiology of age-related muscle wasting, given their proinflammatory character,[3] the resulting endothelial dysfunction of the microcirculation of the skeletal muscle,[54] and the formation of cross-links in skeletal muscle collagen and elastin.[17] The accumulation of AGEs in serum has been independently associated with a low walking speed[55] and a poor grip strength in elderly persons.[56] Since the modern diet is the major source of exogeneous AGEs,[45] it is not surprising that nutritional habits involving ingestion of high levels of AGEs have a negative impact on muscle tissue and accelerate muscular aging. A systematic review linking AGEs in food to inflammatory processes and the skeletal muscle yielded only 2 papers, both conducted in animals. The first study,[27] which is included in the present review, dealt with the skeletal muscle of mice fed a high- or low-AGE diet and used RAGE as the only inflammatory parameter. The authors observed an increase of RAGE, PKCα, and Src in the muscle of mice fed the high-AGE diet, which can lead to an inflammatory cascade.[27] The second study on the skeletal muscle system, from Grasa et al.,[57] compared 4 different diets that contained different levels of AGEs and showed an increased stiffness in the tendons of mice fed the diet with the highest level of AGEs, which led to higher stress and strain in the muscle belly; this observation can be explained by the cross-linking of collagen due to AGEs. Limitations of this study were the absence of measurements of circulating AGEs and of specific AGEs in the diet. Since only the total dietary AGE content was calculated, no information on the presence of cross-linking and non-cross-linking AGEs in the diet was provided. Such information could have been important because cross-linking and non-cross-linking AGEs are thought to have different effects on the muscular connective tissue. Moreover, the study of Grasa et al.[57] did not analyze any inflammatory parameter. Two studies in humans were not included in the present review because the scope of their investigations was limited to the effect of calorie restriction or weight gain. These studies did, however, analyze the effect of AGEs on the skeletal muscle.[38,58] de la Maza et al.[58] investigated the effect of weight change over 10 years on the accumulation of AGE (carboxymethyllysine), RAGE, and TNF-α in skeletal muscle biopsies from healthy middle-aged weight gainers versus weight maintainers and a control group of healthy elderly (age > 65 years). They observed an increase of AGE/RAGE and TNF-α in the skeletal muscle of weight gainers and healthy elderly. Other limitations of this study, besides the lack of dietary analysis, were the small sample, especially in the elderly subjects ($n = 4$), and the self-reporting of weight changes. Furthermore, they measured only the concentration of carboxymethyllysine, which is a non-cross-linking AGE and whose role on the skeletal muscle can only be indirect, via activation of RAGE and the inflammatory pathway. Iwashige et al.[38] conducted a noncontrolled intervention study on the effect of calorie restriction and fasting in patients with rheumatoid arthritis. They found a significant decrease in inflammation and in urinary levels of pentosidine in patients who adhered to a low-energy diet. Urinary excretion of pentosidine was significantly higher in rheumatoid arthritis patients than in the control group. Limitations of this study were the small sample size, the absence of a placebo intervention, the lack of follow-up for the control group, the use of a spot instead of a 24-hour urine collection to measure pentosidine, and the absence of information on the AGE content of foods.

These findings form the basis of a hypothesis: dietary AGEs increase stiffness in muscle tissue, possibly through cross-linking of collagen and elastin and through their role in inflammation, which leads to alterations in muscle function. This hypothesis must be viewed with caution, however, as the impact of dietary AGEs on skeletal muscle has not been adequately studied and requires further investigation.

CONCLUSION

Recent literature indicates an increasing interest in dietary AGEs, including their harmful effects on different tissues, their relation to the aging process, and their role in the development of age-related diseases such as chronic kidney disease, diabetes, cardiovascular disease, Alzheimer's disease, and age-related muscle wasting.[3,5] This review focused on the influence of AGEs on the inflammatory processes, since aging and age-related chronic diseases are characterized by increased levels of oxidative stress and circulating inflammatory mediators.[1,59] This is believed to be the first systematic review of studies on AGEs in food and the effect of dietary AGEs on inflammatory processes. Only 17 studies fulfilled the inclusion and exclusion criteria.

The results of this review are mainly descriptive and do not allow a synthesis about dose responses, the threshold for toxicity, or the importance of the duration of exposure. There is evidence in the literature of a positive relationship between inflammatory markers and the dietary intake of AGEs; in addition, the concentration of circulating AGEs appears to be correlated with dietary

intake of AGEs. The few intervention studies in humans found mainly a suppression of inflammatory parameters in subjects on low-AGE diets, suggesting that a restriction of AGE intake might prevent inflammation and age-related chronic diseases. However, there is a lack of studies in healthy individuals, and the harmful effects of long-term exposure to dietary AGEs on the aging process is not yet fully elucidated. Most of the studies measured carboxymethyllysine, but there are many other AGEs in the diet that need to be investigated for their effects on health and the aging process.

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REFERENCES

1. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. Exp Gerontol. 2004;39:687–699.
2. Uribarri J, Cai W, Peppa M, et al. Circulating glycotoxins and dietary advanced glycation endproducts: two links to inflammatory response, oxidative stress, and aging. J Gerontol A Biol Sci Med Sci. 2007;62:427–433.
3. Semba RD, Nicklett EJ, Ferrucci L. Does accumulation of advanced glycation end products contribute to the aging phenotype? J Gerontol A Biol Sci Med Sci. 2010;65:963–975.
4. Ulrich P, Cerami A. Protein glycation, diabetes, and aging. Recent Prog Horm Res. 2001;56:1–21.
5. Luevano-Contreras C, Chapman-Novakofski K. Dietary advanced glycation end products and aging. Nutrients. 2010;2:1247–1265.
6. Ahmed N. Advanced glycation endproducts – role in pathology of diabetic complications. Diabetes Res Clin Pract. 2005;67:3–21.
7. Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. JAMA. 2002;288:2579–2588.
8. Bierhaus A, Humpert PM, Morcos M, et al. Understanding RAGE, the receptor for advanced glycation end products. J Mol Med. 2005;83:876–886.
9. Chuah YK, Basir R, Talib H, et al. Receptor for advanced glycation end products and its involvement in inflammatory diseases. Int J Inflam. 2013;2013:403–460.
10. Schmidt AM, Yan SD, Yan SF, et al. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J Clin Invest. 2001;108:949–955.
11. Lukic IK, Humpert PM, Nawroth PP, et al. The RAGE pathway: activation and perpetuation in the pathogenesis of diabetic neuropathy. Ann N Y Acad Sci. 2008;1126:76–80.
12. Lin L, Park S, Lakatta EG. RAGE signaling in inflammation and arterial aging. Front Biosci. 2009;14:1403–1413.
13. Cai W, He JC, Zhu L, et al. AGE-receptor-1 counteracts cellular oxidant stress induced by AGEs via negative regulation of $p66^{shc}$-dependent FKHRL1 phosphorylation. Am J Physiol Cell Physiol. 2008;294:C145–C152.
14. Cai W, He JC, Zhu L, et al. Advanced glycation end product (AGE) receptor 1 suppresses cell oxidant stress and activation signaling via EGF receptor. Proc Natl Acad Sci USA. 2006;103:13801–13806.
15. Lu C, He JC, Cai W, et al. Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. Proc Natl Acad Sci USA. 2004;101:11767–11772.
16. Verzijl N, DeGroot J, Oldehinkel E, et al. Age-related accumulation of Maillard reaction products in human articular cartilage collagen. Biochem J. 2000;350(Pt 2):381–387.
17. Haus JM, Carrithers JA, Trappe SW, et al. Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. J Appl Physiol. 2007;103:2068–2076.
18. Koschinsky T, He CJ, Mitsuhashi T, et al. Orally absorbed reactive glycation products (glycotoxins): an environmental risk factor in diabetic nephropathy. Proc Natl Acad Sci USA. 1997;94:6474–6479.
19. Geissler S, Hellwig M, Zwarg M, et al. Transport of the advanced glycation end products alanylpyrraline and pyrralylalanine by the human proton-coupled peptide transporter hPEPT1. J Agric Food Chem. 2010;58:2543–2547.
20. Negrean M, Stirban A, Stratmann B, et al. Effects of low- and high-advanced glycation endproduct meals on macro- and microvascular endothelial function and oxidative stress in patients with type 2 diabetes mellitus. Am J Clin Nutr. 2007;85:1236–1243.
21. Peppa M, Uribarri J, Cai W, et al. Glycoxidation and inflammation in renal failure patients. Am J Kidney Dis. 2004;43:690–695.
22. Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci USA. 2002;99:15596–15601.
23. Vlassara H, Cai W, Goodman S, et al. Protection against loss of innate defenses in adulthood by low advanced glycation end products (AGE) intake: role of the antiinflammatory AGE receptor-1. J Clin Endocrinol Metab. 2009;94:4483–4491.
24. National Institute for Health and Care Excellence. Methodology checklist: randomised controlled trials. Available at: http://publications.nice.org.uk/the-guidelines-manual-appendices-bi-pmg6b/appendix-c-methodology-checklist-randomised-controlled-trials. Published November 30, 2012. Accessed August 18, 2014.
25. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61:344–349.
26. Cai W, He JC, Zhu L, et al. Reduced oxidant stress and extended lifespan in mice exposed to a low glycotoxin diet: association with increased AGER1 expression. Am J Pathol. 2007;170:1893–1902.
27. Cassese A, Esposito I, Fiory F, et al. In skeletal muscle advanced glycation end products (AGEs) inhibit insulin action and induce the formation of multimolecular complexes including the receptor for AGEs. J Biol Chem. 2008;283:36088–36099.
28. Cai W, He JC, Zhu L, et al. Oral glycotoxins determine the effects of calorie restriction on oxidant stress, age-related diseases, and lifespan. Am J Pathol. 2008;173:327–336.
29. Tikellis C, Thomas MC, Harcourt BE, et al. Cardiac inflammation associated with a Western diet is mediated via activation of RAGE by AGEs. Am J Physiol Endocrinol Metab. 2008;295:E323–E330.
30. Sato T, Wu X, Shimogaito N, et al. Effects of high-AGE beverage on RAGE and VEGF expressions in the liver and kidneys. Eur J Nutr. 2009;48:6–11.
31. Sebeková K, Krajcoviová-Kudlácková M, Schinzel R, et al. Plasma levels of advanced glycation end products in healthy, long-term vegetarians and subjects on a Western mixed diet. Eur J Nutr. 2001;40:275–281.
32. Schiekofer S, Franke S, Andrassy M, et al. Postprandial mononuclear NF-κB activation is independent of the AGE-content of a single meal. Exp Clin Endocrinol Diabetes. 2006;114:160–167.
33. de la Maza MP, Bravo A, Leiva L, et al. Fluorescent serum and urinary advanced glycoxidation end-products in non-diabetic subjects. Biol Res. 2007;40:203–212.
34. Sjögren P, Basta G, de Caterina R, et al. Markers of endothelial activity are related to components of the metabolic syndrome, but not to circulating concentrations of the advanced glycation end-product Nε-carboxymethyl-lysine in healthy Swedish men. Atherosclerosis. 2007;195:e168–e175.
35. Piroddi M, Palazzetti I, Quintaliani G, et al. Circulating levels and dietary intake of the advanced glycation end-product marker carboxymethyl lysine in chronic kidney disease patients on conservative predialysis therapy: a pilot study. J Ren Nutr. 2011;21:329–339.
36. Jara N, Leal MJ, Bunout D, et al. Dietary intake increases serum levels of carboxymethil-lysine (CML) in diabetic patients. Nutr Hosp. 2012;27:1272–1278.
37. Luévano-Contreras C, Garay-Sevilla ME, Wrobel K, et al. Dietary advanced glycation end products restriction diminishes inflammation markers and oxidative stress in patients with type 2 diabetes mellitus. J Clin Biochem Nutr. 2013;52:22–26.
38. Iwashige K, Kouda K, Kouda M, et al. Calorie restricted diet and urinary pentosidine in patients with rheumatoid arthritis. J Physiol Anthropol Appl Human Sci. 2004;23:19–24.
39. Teillet L, Verbeke P, Gouraud S, et al. Food restriction prevents advanced glycation end product accumulation and retards kidney aging in lean rats. J Am Soc Nephrol. 2000;11:1488–1497.
40. Hofmann SM, Dong HJ, Li Z, et al. Improved insulin sensitivity is associated with restricted intake of dietary glycoxidation products in the *db/db* mouse. Diabetes. 2002;51:2082–2089.
41. Zheng F, He C, Cai W, et al. Prevention of diabetic nephropathy in mice by a diet low in glycoxidation products. Diabetes Metab Res Rev. 2002;18:224–237.
42. Sandu O, Song K, Cai W, et al. Insulin resistance and type 2 diabetes in high-fat-fed mice are linked to high glycotoxin intake. Diabetes. 2005;54:2314–2319.
43. Sebekova K, Hofmann T, Boor P, et al. Renal effects of oral Maillard reaction product load in the form of bread crusts in healthy and subtotally nephrectomized rats. Ann N Y Acad Sci. 2005;1043:482–491.
44. Sebekova K, Somoza V. Dietary advanced glycation endproducts (AGEs) and their health effects – PRO. Mol Nutr Food Res. 2007;51:1079–1084.
45. Goldberg T, Cai W, Peppa M, et al. Advanced glycoxidation end products in commonly consumed foods. J Am Diet Assoc. 2004;104:1287–1291.
46. Ames JM. Determination of Nε-(carboxymethyl) lysine in foods and related systems. Ann N Y Acad Sci. 2008;1126:20–24.

47. Delatour T, Hegele J, Parisod V, et al. Analysis of advanced glycation endproducts in dairy products by isotope dilution liquid chromatography-electrospray tandem mass spectrometry. The particular case of carboxymethyllysine. J Chromatogr A. 2009;1216:2371–2381.
48. Assar SH, Moloney C, Lima M, et al. Determination of Nε-(carboxymethyl) lysine in food systems by ultra performance liquid chromatography-mass spectrometry. Amino Acids. 2009;36:317–326.
49. Peppa M, Uribarri J, Vlassara H. Aging and glycoxidant stress. Hormones (Athens). 2008;7:123–132.
50. Thompson FE, Subar AF. Dietary assessment methodology. In: Coulston AM, Boushey CJ, Ferruzzi MG, eds. *Nutrition in the Prevention and Treatment of Disease*. San Diego: Elsevier Academic Press; 2013:5–46.
51. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc. 2010;110:911–916.e12.
52. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr. 1997;127(5 Suppl):990S–991S.
53. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care. 2012;15:12–22.
54. Payne GW. Effect of inflammation on the aging microcirculation: impact on skeletal muscle blood flow control. Microcirculation. 2006;13:343–352.
55. Semba RD, Bandinelli S, Sun K, et al. Relationship of an advanced glycation end product, plasma carboxymethyl-lysine, with slow walking speed in older adults: the InCHIANTI study. Eur J Appl Physiol. 2010;108:191–195.
56. Dalal M, Ferrucci L, Sun K, et al. Elevated serum advanced glycation end products and poor grip strength in older community-dwelling women. J Gerontol A Biol Sci Med Sci. 2009;64:132–137.
57. Grasa J, Calvo B, Delgado-Andrade C, et al. Variations in tendon stiffness due to diets with different glycotoxins affect mechanical properties in the muscle-tendon unit. Ann Biomed Eng. 2013;41:488–496.
58. de la Maza MP, Uribarri J, Olivares D, et al. Weight increase is associated with skeletal muscle immunostaining for advanced glycation end products, receptor for advanced glycation end products, and oxidation injury. Rejuvenation Res. 2008;11:1041–1048.
59. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature. 2000;408:239–247.