The potential role of dietary advanced glycation endproducts in the development of chronic non-infectious diseases: a narrative review

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Abstract

Increasing clinical and experimental evidence accumulated during the past few decades supports an important role for dietary advanced glycation endproducts (AGE) in the pathogenesis of many chronic non-infectious diseases, such as type 2 diabetes, CVD and others, that are reaching epidemic proportions in the Western world. Although AGE are compounds widely recognised as generated in excess in the body in diabetic patients, the potential importance of exogenous AGE, mostly of dietary origin, has been largely ignored in the general nutrition audience. In the present review we aim to describe dietary AGE, their mechanisms of formation and absorption into the body as well as their main mechanisms of action. We will present in detail current evidence of their potential role in the development of several chronic non-infectious clinical conditions, some general suggestions on how to restrict them in the diet and evidence regarding the potential benefits of lowering their consumption.

Introduction

During the last few decades, evidence derived from both clinical and experimental research has revealed that advanced glycation endproducts (AGE) have profound effects on human pathology. AGE are a large group of heterogeneous compounds formed either endogenously or ingested through the diet, which were initially reported to be involved in the pathogenesis of diabetes complications. However, the role of AGE has spread progressively to many non-transmissible diseases including CVD, obesity, the metabolic syndrome, autoimmune diseases, neurodegenerative diseases, cancer, as well as the normal ageing process, all of which have in common elevated levels of inflammation and oxidative stress (OS)[1]. In the present review we will describe dietary AGE, how they form and how they are absorbed into the body, their main mechanisms of actions, current evidence on their potential role in the development of chronic non-infectious clinical conditions, suggestions on how to restrict them and evidence supporting potential benefits of lowering their consumption.

What are advanced glycation endproducts?

AGE are a very large and heterogeneous group of compounds that originate from the spontaneous reaction of reducing sugars with free amino groups in amino acids in the so-called Maillard or browning reaction[2]. The Maillard reaction is well established, but AGE can also form through many other reactions, including oxidation of sugars, lipids and amino acids. Specific AGE such as pentosidine, N^ε-carboxymethyllysine (CML), N^ε-carboxyethyllysine (CEL) and methylglyoxal derivatives (MG-H1; N^δ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine) are some of the most commonly measured and well-described AGE in biological studies[3].

Endogenous AGE form physiologically in the body at a continuous slow rate, which is markedly increased in conditions of hyperglycaemia or elevated OS. AGE, however, can also form exogenously, outside of the body, in any system when the required reagents for the above reactions are available[4-6]. AGE form spontaneously in food, but their rate of formation is markedly increased when food is processed and cooked with

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heat. Higher temperature, longer time of application, lower moisture, presence of trace metals and higher pH of the cooking system enhance AGE formation[4-6]. Therefore, cooking methods that use dry heat, such as broiling, grilling, searing and frying have been shown to have the highest content of AGE, while cooking methods that use low heat application in the presence of high water content such as stewing, poaching or steaming produce significantly less AGE[4-6]. Only a fraction of the ingested dietary AGE are absorbed into the body AGE pool, where they become indistinguishable from their endogenous counterparts, both in structure and function[7].

Dietary AGE intake can be easily decreased by changing the method of cooking from a high dry heat application to a low heat and high humidity, independent of nutrient composition. Databases with the AGE content of common foods have been published and can be used to calculate dietary AGE intake as well as to provide guidance on how to consume meals with less AGE content[4-6]. The essential concept in the low-AGE diet is that the same type and amount of foods consumed can provide very different amounts of AGE depending on the cooking method. For example, using published data[5,6] in which the AGE content of food was measured with ELISA and expressed in arbitrary AGE kilounits (kU)/serving, a 90 g beefsteak contains 720 AGE kU when raw, 2199 kU when stewed and 6731 kU when broiled[5,6]. The temperature and method of cooking appear more critical to AGE formation than time of cooking; for instance, meat samples broiled or grilled at 230°C for shorter cooking times have higher AGE content when compared with samples boiled in liquid media at 100°C for longer periods[5]. Unfortunately, there is no specific threshold temperature above which AGE start to generate and one can only make the general recommendation that the lower the temperature the less the amount of AGE generated[4-6]. At present, there are no official recommendations about acceptable dietary AGE intake. It has been previously proposed that half of the current mean AGE intake, or about 7500 kU/d, would be a realistic goal[5,6] since some studies have shown that dietary AGE reduction of this magnitude is feasible and can significantly alter levels of circulating AGE, while at the same time reducing levels of markers of OS and inflammation and enhancing insulin sensitivity in diabetic patients[8]. Because the low-AGE diet depends on the culinary technique, and not on the food being cooked, it can be applied for any group of individuals; the same principles will apply whether the patient has diabetes, CVD or not.

AGE can be measured by several methods including fluorescence, ELISA and MS. Most of the early data on food AGE were based on ELISA measurements, which has raised significant criticism since these assays have more problems in assessing food matrices than methods using MS[9]. This controversy has prevented a faster development of this field and a general agreement in terms of actual quantification of the AGE content in different foods is still in discussion. At present, however, databases with the food AGE content measured by MS have been published and can be used by anyone[10].

A frequently ignored source of exogenous AGE is tobacco smoking[11]. Curing of tobacco generates large amounts of AGE that after smoke inhalation are absorbed into the circulation, increasing the body AGE pool similarly to food-derived AGE[11]. Once in the bloodstream, these AGE may react with serum proteins such as apoB as well as with vascular wall proteins and thereby accelerate the development of atherosclerosis, whose incidence is increased in smokers. These smoking-derived AGE have been shown to have the same actions as endogenous AGE and therefore may cross-link proteins and activate receptors throughout the body[11].

Gastrointestinal absorption of dietary advanced glycation endproducts

Gastrointestinal metabolism of dietary AGE depends on two phenomena: hydrolysis of proteins and absorption of the resulting free amino acids or small peptides containing the AGE. The nutritional value of proteins is reduced by the Maillard reaction, mainly due to a reduction of the digestibility of proteins and the bioavailability of some amino acids[12,13]. Accessibility of digestive enzymes for hydrolysis is restricted by chemical modifications of the target amino acids and structural changes of proteins that limit enzyme–substrate interactions[13-15], all of which reduce the rate of protein hydrolysis[16] and increase the molecular weight of the resulting peptides[14,17,18]. The extent of hydrolysis of a protein containing Maillard modifications depends on the type of AGE that are formed[15,17], the extent of modification of the protein[14] and the protein source[17]. For example, after hydrolysis of a CML-modified casein under simulated gastric and intestinal conditions, most of the CML-containing peptides resulted in molecular weights between 250 and 1000 Da, which are assumed to be digested, yet not necessarily absorbable[17].

Absorption of dietary AGE depends on the molecular weight of the products of protein hydrolysis[14,17], the type of transporters present in the gastrointestinal epithelium[19,20] and the type of AGE being transported[21]. Some free-form AGE can be absorbed by simple diffusion[22], while peptide-bound AGE require peptide transporters to cross the epithelium[20], for example the di- and tripeptide transporter PEPT1[19]. Glycated dipeptides can cross a barrier of epithelial cells probably using the peptide transporter PEPT1[20]. This was demonstrated for low molecular-weight peptides containing pyrraline that once inside the cell are hydrolysed allowing free pyrraline to enter the basolateral side by simple diffusion[23]. Furthermore, the transport of peptide-bound pyrraline across Caco-2 cells was shown to be 15-fold higher compared with free pyrraline[23].

In one clinical study, approximately 10 % of the dietary intake of AGE reached the systemic circulation[7], which is consistent with a recent study in pigs[24] showing that the apparent ileal digestibility of CML, N^ε-carboxyethyllysine (CEL) and fructose-lysine ranged between 0 and 30 %.

The intestinal *in situ* formation of fructose-derived AGE has been postulated, which once absorbed, become part of the body AGE pool, similar to dietary AGE[25]. Intraluminal formation of fructose-derived AGE may be facilitated by increased intake of beverages and food containing high-fructose maize syrup in which the ratio of fructose to glucose is higher than 1:1, therefore creating conditions of potential fructose malabsorption favouring intraluminal generation of fructose-derived
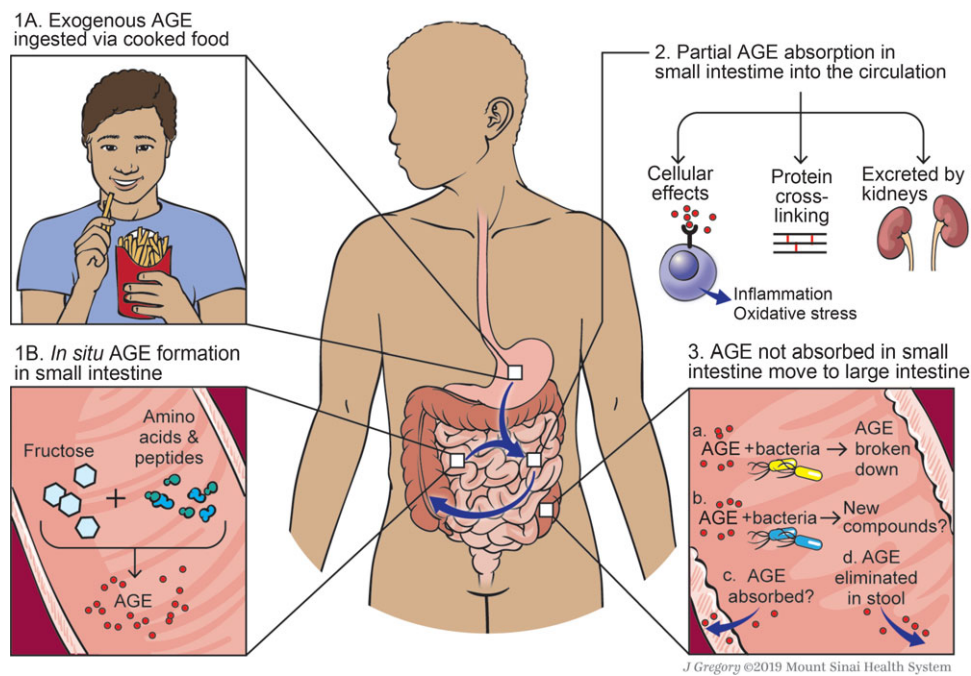
Fig. 1. Metabolism of dietary advanced glycation endproducts (AGE). Panel 1A: Food AGE are ingested. Panel 1B: Some AGE may form *in situ* within the lumen of the intestine in conditions of high local fructose. Panel 2: Both exogenous and *in situ*-formed AGE may be partially absorbed through the small intestine into the circulation from where they can be excreted in the urine by the kidneys or reach the tissues where they can produce direct protein cross-linking or react with cellular receptors to induce inflammatory cytokines or oxidative stress. Panel 3: AGE not absorbed in the small intestine move to the colon where several things can happen. 3a: AGE may be broken down by bacteria of the microbiota. 3b: AGE may react with bacteria, releasing compounds that may be absorbed across the colon. 3c: AGE may potentially be absorbed through the colon mucosa or locally activate RAGE. 3d: AGE can be eliminated in the stools. For a colour figure, see the online version of the paper.

AGE[25]. Preliminary *in vitro* studies have confirmed this postulation[26,27]. Increased fructose intake and absorption as such may also potentially increase the endogenous formation of AGE and therefore increase the body AGE pool with all its subsequent effects[28].

Once exogenous AGE are absorbed into the circulation, they act in the circulation and at different cellular and tissue levels inducing either protein cross-linking or a variety of cellular effects that eventually lead to increased OS and inflammation, precursors of most non-infectious chronic diseases.

Fig. 1 illustrates the metabolism of dietary AGE within the gastrointestinal tract.

The role of unabsorbed dietary advanced glycation endproducts in the colon

The major part of the dietary AGE escapes gastrointestinal absorption with a potential effect of unabsorbed dietary AGE in the colon microbiota and even directly in the colon wall. Some of these AGE could bind to the receptor for AGE (RAGE) or Toll-like receptors in the colon cells inducing a local inflammatory response with subsequent release of inflammatory mediators into the circulation eventually producing chronic diseases, or they could alter the microbiome profile in the gut, which in turn leads to release of toxins or inflammatory mediators into the circulation[29]. We know from studies in mice that activation of RAGE-dependent signalling is key in creating mucosal barrier dysfunction after haemorrhagic shock[30]. One could postulate that this RAGE-dependent disruption of the

intestinal epithelial barrier may contribute to systemic inflammation by facilitating translocation of endotoxin, microbial fragments and other factors produced locally by the gut flora[31].

Degradation of CML and pyrraline by human gut microbiota has been well documented[32]. The products of this degradation of dietary AGE in the large intestine could in turn modulate the profile of the bacterial population and the metabolites produced by them, which in turn could facilitate systemic illnesses[30].

A 2-week randomised two-period cross-over study, in which two different diets were consumed by male adolescents, showed negative correlation between faecal lactobacilli and enterobacteria numbers and dietary CML content[33]. A different study analysed the effects of a low- *v.* high-AGE diet for 1 month in a small group of peritoneal dialysis patients[34]. Dietary AGE restriction altered the bacterial gut microbiota with a significant reduction in *Prevotella copri* and *Bifidobacterium animalis* relative abundance and increased *Alistipes indistinctus*, *Clostridium citroniae*, *C. hathewayi* and *Ruminococcus gauvreauii* relative abundance[34]. The exact significance and systemic effects of these changes in the faecal microbiota, however, remain to be determined.

The role of the advanced glycation endproduct–receptor for advanced glycation endproduct–reactive oxygen species loop

During the last three decades, compelling evidence derived from both clinical and experimental research has revealed that AGE have profound effects on human pathology, far beyond diabetes

complications[1,2,35]. High dietary AGE intake produces a sustained oxidant overload that may overwhelm host defences and lead to unopposed OS and chronic subclinical inflammation, which over time raises susceptibility to a variety of chronic clinical conditions[36].

AGE exert their action through different mechanisms; one is based on the capacity of these compounds to alter the function of many biomolecules, either by reducing its biological activity or by inducing cross-linking with proteins[37]. Additionally, several AGE-binding proteins have been identified. Some of these proteins play an important role in the removal of AGE, including the AGE receptor complex, AGE-R1/OST-48, AGE-R2/80K-H, AGE-R3/galectin-3, as well as some members of the scavenger receptor family[35,37]. Very interestingly, the activity of AGE-R1 is not only restricted to clearance of AGE, but also it has further activities linked to counteract the pro-oxidant activities of AGE[38,39]. Furthermore, AGE also bind to RAGE on different cell types, thus activating key cell signalling pathways with subsequent modulation of inflammation-related gene expression. The RAGE–ligand interaction triggers activation of NF-κB and other signalling pathways through stimulation of p21ras, extracellular signal-regulated kinase (ERK) 1/2, p38 mitogen-activated protein kinase (p38 MAPK), stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK), Rho GTPases, phosphoinositide 3-kinase (PI3K) and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways[40-44]. Subsequently, expression of many inflammatory gene products is increased, leading to the establishment of an inflammatory niche[45].

RAGE binds ligands other than AGE, particularly high-mobility group protein box-1 (HMGB1), calgranulins, amyloid-β-protein, triggering cellular responses extensively involved in different pathophysiological scenarios including inflammation, proliferation, angiogenesis, migration and fibrosis[46-49]. Binding of RAGE not only causes an inflammatory gene expression profile, but also a feed-forward loop, in which inflammatory stimuli activate NF-κB, which induces RAGE expression, subsequently followed by sustained NF-κB activation. Thus, RAGE can function as a master switch, converting short-lasting pro-inflammatory responses into long-lasting cellular dysfunction[50,51].

The complexity of signalling is further demonstrated by the presence of alternative adaptor molecules such as DAP10, and even by the recruitment of TIRAP (Toll/IL-1 receptor domain-containing adapter protein) and MyD88, well-known adaptor proteins for downstream signal transduction of Toll-like receptor (TLR)-2 and TLR-4, which are critical for enhancing RAGE-mediated signalling[52,53].

RAGE and TLR also share common ligands and signalling pathways, and accumulating evidence points towards their cooperative interaction. This fact is supported by several experimental findings, such as the capacity of AGE to induce PPARγ down-regulation-mediated inflammatory signalling via TLR4 and RAGE[54], as well as that AGE-modified molecules activate TLR signalling through binding to either TLR receptors on the cell surface or the intracellular adaptor proteins of TLR[55].

The *RAGE* gene undergoes extensive alternative splicing to produce a variety of transcripts with diverse functions. In this context, soluble variants include a secreted form RAGE v1 (previously named as sRAGE, secretory C-truncated RAGE, esRAGE, hRAGE sec or sRAGE1/2/3) and an N-terminally truncated isoform RAGE v2 (previously named Nt-RAGE, N-RAGE or N-truncated RAGE)[56]. However, endogenous soluble RAGE isoforms may be generated by mechanisms other than alternative splicing, such as membrane-associated proteases, including the sheddase A disintegrin, metalloprotease 10 (ADAM-10) and matrix metalloproteinase-9 (MMP-9)[57,58].

Soluble RAGE is thought by many authors to function as a decoy receptor, and thus preventing the interaction with the membrane-anchored full-length RAGE[24]. In this context, there is evidence supporting a role for soluble RAGE contributing to the removal/detoxification of AGE[59].

In the 1990s, it was initially reported that RAGE activation by AGE was associated with increased OS, as demonstrated either by the use of blocking antibodies to RAGE or antioxidants, both *in vivo* and *in vitro*[60]. As a consequence of RAGE engagement, multiple signalling pathways are induced, including the generation of reactive oxygen species (ROS), mainly due to the activation of the NADPH oxidase (NOX) pathway[61,62]. Interestingly, AGE–RAGE-induced cytosolic ROS production also facilitates mitochondrial superoxide production in hyperglycaemic environments, which play a central role in inducing diabetic-associated organ damage[63]. Of note, the cytoplasmic domain of RAGE binds to the formin molecule mDia1, through its conserved poly-proline rich formin homology-1 (FH1) domain, and this interaction is strictly required for RAGE ligands to activate cell signalling responses. Formins such as mDia1 are actin-binding molecules that contribute to signal transduction mechanisms, in part via Rho GTPase signals[64], and particularly Rac1, which is a key component in NADPH oxidase activation[65-67]. There is increasing evidence that ROS induced by NADPH oxidases not only causes cell damage, but also acts as a second messenger implicated in proliferation, differentiation and apoptosis, which finally may lead to disease onset and progression[68-72].

OS and inflammation are inseparable actors in the pathogenesis of many human diseases. For instance, by activating NF-κB, a redox-sensitive transcription factor of major importance in inflammation, OS promotes the expression of pro-inflammatory cytokines and chemokines, increasing the recruitment and activation of leucocytes and resident cells, thereby fuelling inflammatory processes[73-77]. Additionally, plasma proteins are prone to be oxidised by ROS. These oxidised protein products, termed advanced oxidation protein products (AOPP), have been linked to vascular lesions in diabetes, chronic renal disease, obesity, immune-mediated inflammatory diseases, neurodegenerative diseases, cancer, the metabolic syndrome and atherosclerosis[78-81].

Of note, RAGE has also been described as a receptor of AOPP-modified albumin[82,83]. Furthermore, RAGE expression on kidney podocytes is highly increased in response to chronic loading of AOPP. The AOPP–RAGE interaction activates NADPH oxidase, leading to ROS production and to a perpetuation of renal OS[84-86].

Finally, oxidants, derived from either the phagocyte NADPH oxidase or the myeloperoxidase–H_2O_2–chloride system, may
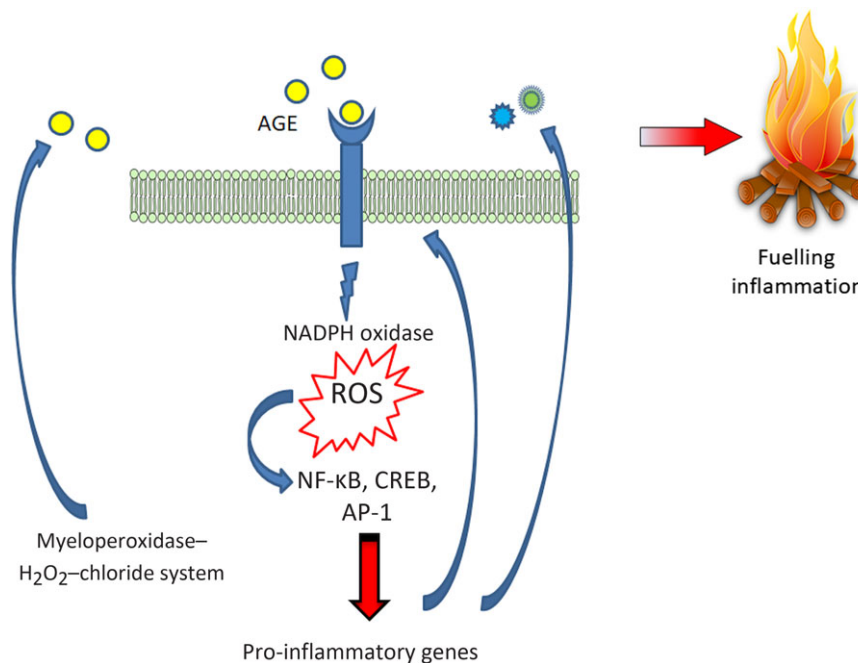
Fig. 2. Advanced glycation endproduct–receptor for advanced glycation endproduct–reactive oxygen species (AGE–RAGE–ROS) loops. RAGE engagement by AGE produces an early increase in NADPH oxidase-derived ROS which in turn, activate the redox-sensitive transcription factor NF-κB, and thus favouring a transcriptional pro-inflammatory profile fuelling inflammation and a positive feed-forward loop for RAGE itself. Additionally, ROS are also involved in another relevant amplifying loop, by promoting the formation of AGE, particularly N^ε-carboxymethyllysine. CREB, cAMP response element-binding protein; AP-1, activator protein 1. For a colour figure, see the online version of the paper.

lead to AGE production, particularly CML. These CML adducts of proteins act as ligands for RAGE and could potentially generate an important amplifying loop in tissue damage at inflammation sites[87,88] (Fig. 2).

Potential role of dietary advanced glycation endproducts in chronic diseases

The effect of dietary AGE on a variety of clinical conditions in human subjects has been studied by many, using either acute oral loads of AGE[7,89-93] or dietary interventions[94-106], ranging from a few weeks up to 1 year consisting essentially of changing the way of cooking food without interfering with the actual energy and macronutrient intake. A summary of these studies with their main findings is listed in Table 1. One of the critiques of these clinical studies is that changing the way of cooking may change not only AGE but also many other factors such as vitamins and phytochemicals contained in food that may confound the interpretation of the effects resulting only as the results of the changes in food AGE content[107]. In order to address this critique, studies were performed in mice by providing a chronic load of a pure synthetic AGE precursor that produced the same effect as those of a high-AGE diet created by cooking with high heat[108]. However, no similar studies in human subjects are available.

The variability of method used in estimating dietary AGE content, mentioned above, also extends to measurements of AGE is serum, plasma or urine. Different methodologies including ELISA with commercially prepared kits or in-house developed

antibodies as well as more precise MS/HPLC-based assays have been used by different groups. In order to give the readers a more balanced view of the different outcomes we are also including the AGE measurement methodology for each study listed in Table 1.

Four of the six acute oral AGE load studies showed that this load significantly increased circulating AGE levels in parallel with increases in markers of inflammation and endothelial dysfunction[7,90-92], while two studies did not find this association[89,93].

In Table 1 we also briefly mention two studies with energy restriction that demonstrated that this intervention is associated with reduced dietary AGE intake, probably related to the low AGE content of the replacement meals used for the studies[109,110]. Another study looked at the effect of energy restriction with a Mediterranean-type diet and showed a significant fall of serum CML levels; subjects were not given the actual meals but only instructions on how to eat[111]. The effect of the Mediterranean diet was tested in healthy elderly subjects in Spain and also showed that this intervention decreased serum AGE levels, although the magnitude of the change was small[112].

In the next few sections we will review the above information, first in healthy subjects and in individuals with the metabolic syndrome, diabetes and kidney disease where evidence for a potential effect from dietary AGE comes from intervention studies (Table 1), and then in conditions such as CVD, dementia, sarcopenia and cancer in which intervention studies have not been performed, but there is a rationale for the potential involvement of dietary AGE.

Table 1. Dietary advanced glycation endproduct (AGE) interventions in human subjects

Study	Population	Study design	Outcome
Acute oral AGE loads			
Koschinsky et al. (1997)[7]	Diabetics and healthy (USA)	Single AGE meal	Increased serum AGE over the next few hours. AGE measured by ELISA using in-house prepared antibodies
Schiekofer et al. (2006)[89]	Healthy volunteers (Germany)	Single AGE meal	Increased in mononuclear NF-κB activation unrelated to meal AGE content/serum CML measured by ELISA (Roche Diagnostics)
Stirban et al. (2006)[90]	Diabetics (Germany)	Single high-AGE meal before and after benfotiamine therapy	Micro- and macrovascular (FMD) endothelial dysfunction following high-AGE meal, which was prevented by benfotiamine. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Uribarri et al. (2007)[91]	Diabetics and healthy (Germany)	Single AGE oral load (beverage)	Increased serum AGE, PAI-1 and VCAM-1 and decreased FMD. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Negrean et al. (2007)[92]	Diabetics (Germany)	Single low- or high-AGE meal	High-AGE meal induced a more pronounced acute impairment of vascular function (FMD and microvascular) than the low-AGE meal. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Davis et al. (2015)[93]	Overweight and obese adults (USA)	Cross-over of high-fat, high-AGE v. low-fat, low-AGE single test meals	The rise in serum CML was associated with the fat, not the AGE content, of meals. Inflammation markers were not affected by either diet. CML measured by ELISA (Microcoat)
Low-dietary AGE interventions			
(1) Healthy subjects			
Vlassara et al. (2009)[94]	Healthy (USA)	Two parallel groups (high and low AGE)	Decreased serum AGE and markers of OS and inflammation. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Birlouez-Aragon et al. (2010)[95]	Healthy (France)	Two parallel groups (high and low AGE)	Decreased serum AGE and HOMA-IR. CML measured by GC/MS/MS
Semba et al. (2014)[96]	Healthy (USA)	Two parallel groups (high and low AGE	Decreased serum AGE but no change in endothelial function and inflammation. CML measured by ELISA (Microcoat)
(2) Overweight/metabolic syndrome			
Mark et al. (2014)[97]	Overweight women (Denmark)	Two parallel groups (high and low AGE)	Decreased urinary AGE and HOMA-IR. AGE measured by liquid chromatography–tandem MS
Macias-Cervantes et al. (2015)[98]	Overweight or obese men (Mexico)	Three parallel groups (diet + exercise)	Decreased sAGE and body weight. CML and MG-H1 measured by ELISA using in-house prepared antibodies
De Courten et al. (2016)[99]	Overweight healthy men and women (Denmark)	Two parallel groups (high and low AGE)	Decreased sAGE and insulin resistance. CML, CEL and MG-H1 measured by MS
Vlassara et al. (2016)[100]	Men and women with metabolic syndrome (USA)	Two parallel groups (high and low AGE) for 1 year	Decreased sAGE, markers of OS and inflammation and HOMA-IR. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Di Pino et al. (2016)[101]	Pre-diabetic subjects (Italy)	Two parallel groups (low and standard AGE) for 24 weeks	Decreased lipids and inflammatory markers and reduced atherosclerotic burden. No AGE measured
Baye et al. (2017)[102]	Overweight and obese healthy adults (Australia)	Cross-over low- v. high-AGE diet for 2 weeks each	Low-AGE diet did not improve inflammatory markers or lipid profile. AGE were not measured
(3) Diabetes			
Vlassara et al. (2002)[103]	Diabetics (USA)	Cross-over	Decreased serum AGE and markers of OS and inflammation. CML and MG-H1 measured by ELISA using in-house prepared antibodies

Table 1. (*Continued*)

Study	Population	Study design	Outcome
Uribarri *et al.* (2011)[8]	Diabetics (USA)	Two parallel groups (high and low AGE)	Decreased serum AGE, OS, inflammation and HOMA-IR. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Luévano-Contreras *et al.* (2013)[104]	Diabetics (Mexico)	Two parallel groups (high and low AGE)	Decreased markers of OS and inflammation, but no changes in HOMA-IR or serum AGE. AGE measured by fluorescence
(4) CKD/ESRD			
Uribarri *et al.* (2003)[105]	ESRD, no diabetes (USA)	Two parallel groups (high and low AGE)	Decreased serum AGE and markers of inflammation. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Vlassara *et al.* (2009)[94]	CKD, no diabetes (USA)	Two parallel groups (high and low AGE)	Decreased serum AGE and markers of OS and inflammation. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Yacoub *et al.* (2017)[106]	ESRD, no diabetes (USA)	Two parallel groups (high and low AGE)	Decreased serum AGE. CML and MG-H1 measured by ELISA using in-house prepared antibodies
Other interventions leading to low dietary AGE intake			
Iwashige *et al.* (2004)[109]	Rheumatoid arthritis patients (Japan)	Ten patients exposed to 54 d energy restriction programme	Energy restriction decreased body weight and urinary pentosidine levels. Pentosidine measured by liquid chromatography
Gugliucci *et al.* (2009)[110]	Overweight and non-morbid obese subjects (Japan)	Thirty-seven subjects exposed to energy restriction for 2 months	Energy restriction decreased body weight and serum AGE levels. AGE measured by fluorescence
Rodriguez *et al.* (2015)[111]	Overweight and obese women (Chile)	3-month energy restriction with a Mediterranean-type diet	Energy restriction was associated with decreased serum CML and markers of insulin resistance levels. CML measured by ELISA (Abcam)
Lopez-Moreno *et al.* (2016)[112]	Healthy elderly aged ≥65 years (Spain)	Twenty subjects randomly assigned to three isoenergetic diets (one of them Mediterranean diet) for 4-week periods each in a cross-over design	The Mediterranean diet group consumed lower levels of dietary AGE and showed lower serum AGE levels than the other two groups during the intervention. CML and MG measured by ELISA

CML, N^ε-carboxymethyllysine; FMD, flow-mediated vasodilatation; MG-H1, N^δ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine; PAI-1, plasminogen activator-1; VCAM-1, vascular cell adhesion protein-1; OS, oxidative stress; HOMA-IR, homeostatic model assessment of insulin resistance; sAGE, serum AGE; CEL, N^ε-carboxyethyllysine; CKD, chronic kidney disease; ESRD, end-stage renal disease.

Healthy subjects

Three studies have studied the effect of the low-AGE diet in healthy subjects[94-96]. In all three studies the restricted dietary AGE intervention led to decreased circulating levels of AGE. In one of the studies[94], this occurred in parallel with decreasing levels of markers of OS and inflammation, while no effects on these parameters were observed in another study[96]. Levels of AGE decreased in parallel with levels of homeostatic model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, in another study[95].

Overweight and/or metabolic syndrome

At least six studies have looked at the effect of a low-AGE diet on overweight and/or metabolic syndrome subjects[97-102]. In four of these studies the low-AGE diet was associated with lower serum or urinary levels of AGE as well as a parallel decrease in HOMA-IR[96-99]. In the fifth study[101] decreased levels of lipids and inflammatory markers were reported, but serum AGE were not measured. In the last study the low-AGE diet did not improve inflammatory markers or lipid profile, but the trial was rather short (2 weeks) and AGE were not measured[102].

Diabetes

In 2016, an estimated 1·6 million deaths in the world were directly caused by diabetes[113]. Therefore, the search for strategies to reduce incidence and complications of this disease is of great public health importance. Endogenous production of AGE is elevated in individuals with diabetes because of elevated blood glucose levels, but several studies in animals and in human subjects suggest a significant contribution of dietary AGE to the body pool of AGE in individuals with diabetes[1,36].

A strong argument for the role of dietary AGE in diabetes has been demonstrated in clinical trials testing the effect of AGE restriction[8,103,105]. Two diets with the same energy and nutrient intake but differing only in their AGE content, one high AGE, and the other with 5-fold lower AGE content, were tested in twenty-four ambulatory individuals with diabetes[103]. During the high-AGE diet, serum AGE increased in parallel with levels of circulating markers of inflammation and endothelial dysfunction, while the opposite occurred in patients exposed to the low-AGE diet[103]. Before this study, high serum AGE levels in individuals with diabetes were thought to result exclusively from hyperglycaemia-induced endogenous overproduction. Therefore, the significant fall of serum AGE levels induced by the low-AGE diet, while maintaining the same overall glycaemic control, was a novel finding.

A randomised 6-week prospective study in type 2 diabetes subjects with standard diet (n 13) v. low-AGE diet (n 13) showed a significant decrease of TNF-α and malondialdehyde in the low-AGE diet group without a significant change in HOMA-IR or serum AGE[104]. A 4-month randomised study of an AGE-restricted diet on thirty-six subjects with diabetes showed that these patients had lower levels of serum CML, MGH1, 8-isoprostanes and HOMA-IR than subjects on regular AGE intake[8]. Reduction of HOMA-IR with the low-AGE diet in patients with type 2 diabetes raises the hypothesis that AGE have an important role in modifying insulin resistance itself in individuals with diabetes. Consistent with this hypothesis, an AGE-restricted diet, as shown above, has also been demonstrated to decrease HOMA-IR in subjects with the metabolic syndrome[97-100], broadening the potential beneficial effects of a low-AGE diet into pre-diabetes. If this effect of the low-AGE diet is further confirmed in larger clinical trials, it opens an opportunity for a safe, inexpensive and effective dietary modulation to prevent or improve diabetes and its secondary co-morbidities.

Chronic kidney disease

Circulating AGE levels increase with progressive chronic kidney disease[112,114]. At least three clinical trials have tested the effects of an AGE-restricted diet in patients with renal disease in the absence of diabetes[94,105,106]. A group of stage 3 chronic kidney disease patients was randomly assigned to either a regular diet or an isoenergetic diet containing 50 % lower AGE for a period of 4 weeks. The low-AGE diet patients had markedly decreased markers of inflammation and OS, including AGE, TNFα, vascular cell adhesion protein-1 (VCAM-1) and RAGE compared with the regular-diet group[102]. The number of patients was too small and duration of study too short to allow demonstration of an effect on the diet on proteinuria and/or actual kidney function. In another study, a group of non-diabetic end-stage renal disease patients on maintenance peritoneal dialysis was randomised to follow either a regular- or a low-AGE diet for 4 weeks; the low-AGE diet group had significant falls of levels of circulating AGE and C-reactive protein[105]. Another similar intervention on peritoneal dialysis patients again demonstrated an effect of the low-AGE diet in decreasing circulating AGE levels, but other markers were not measured in this study[106].

CVD

CVD, such as CHD, cerebrovascular disease and chronic heart failure are major causes of death globally[115]. The CVD rate in adults with diabetes is two to three times greater than in adults without diabetes[116]. Several clinical studies have linked AGE to CVD, particularly in patients with diabetes mellitus. Observational studies have found associations of dietary AGE with markers of endothelial dysfunction, inflammation and OS such as TNF-α, VCAM-1, 8-isoprostane and mRNA RAGE, all consistently associated with CVD[117,118]. Additionally, a high-AGE meal was shown to induce a more pronounced acute impairment of vascular function than an otherwise identical low-AGE meal in patients with diabetes[91]. Moreover, diets with 5-fold lower AGE content significantly decreased serum levels of AGE, VCAM-1 and C-reactive protein, compared with equivalent regular-AGE diets in diabetic patients[90-92].

The postprandial response to a high-AGE meal has been measured and shown acute decreases in flow-mediated vasodilatation and increased levels of intercellular adhesion molecule-1 (ICAM-1) and VCAM-1[91]. In a similar study, levels of ICAM-1 and VCAM-1 increased 4 h after the high-AGE meal, while flow-mediated dilatation and microvascular function decreased by 20·9 and 67·2 %, respectively[92]. Furthermore, serum CML levels were associated with increased arterial

stiffness in relatively healthy, community-dwelling adults[117]. These findings suggest a pathological role of dietary AGE in vascular and cardiac stiffness in humans.

A recent meta-analysis of randomised controlled trials examining the effects of consumption of diets low in AGE on cardiometabolic parameters showed that low-AGE diets decreased insulin resistance, total cholesterol and LDL; in a subgroup of patients with type 2 diabetes, they also decreased fasting insulin, TNFα, VCAM-1, 8-isoprostane, leptin, circulating AGE and RAGE, while increasing protective factors adiponectin and sirtuin-1[118]. Whether these alterations ultimately affect cardiometabolic health, i.e. decreasing heart disease and death from heart disease, is yet to be determined.

Alzheimer's disease

Very little investigation has been done on the potential role of serum, diet or brain AGE levels on cognitive decline and incident Alzheimer's disease (AD). In a small sample of older human subjects, elevated dietary AGE, measured by a validated FFQ, were associated with faster cognitive decline[119]. There is cross-sectional evidence for higher levels of methylglyoxal and CML in cerebrospinal fluid of AD patients[120,121]. Elevated serum AGE levels have been associated with a lower level of cognitive functioning in older adults[122,123] but serum pentosidine levels did not differ between AD patients and normal controls[124]. Longitudinal studies have shown that elevated serum levels of MG-H1 (N^δ-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine) and of pentosidine are associated with more rapid cognitive decline in older adults with and without diabetes[125].

Several mechanisms may link elevated levels of AGE with impaired cognition and AD. Experimental studies in mice suggest that impaired clearance of β-amyloid may play a role. Mice fed a high-AGE diet had significantly higher hippocampal levels of β-amyloid and AGE compared with controls[123]. Human studies report that brain AGE are found in neurons, astrocytes and glial cells in AD brain[126-128]. AGE are suggested to take part in the transformation of soluble into insoluble β-amyloid and the aggregation of microtubule-associated protein τ[129,130]. Histochemical and immunoquantitative studies show that brain levels of AGE are increased in AD and that they constitute components of senile plaques and neurofibrillary tangles[131,132]. AGE-modified β-amyloid peptide seems to serve as a 'seed' to accelerate and stabilise the formation of amyloid plaques in the AD brain[130]. Some, but not all, studies suggest that brain AGE colocalise with amyloid or τ in AD brains[127].

There are animal data pointing to a link between AGE with proteins related to other dementias including α-synuclein[133]. AGE may affect cognition via accelerated cerebrovascular disease, as elevated AGE are associated with vascular risk factors, incident stroke and small vessel disease[123]. Human studies show brain AGE in small vessels of AD brain[123,126,128]. Moreover, human brain imaging studies suggest that AGE may accelerate regional cortical atrophy in both diabetics and non-diabetics[134]. AGE may also impair blood–brain barrier and white matter integrity[135].

While these data link AGE and cognition in older adults and while there is strong biological plausibility for the contribution of AGE to neuropathological substrates underlying cognitive impairment and AD, there are critical gaps in our knowledge. No study has shown that serum AGE are related to incident AD in older adults. Moreover, while AGE have been documented in human AD brains[126], no study has documented an association between brain AGE levels and cognitive decline. Finally, the inter-relationship of dietary, serum and brain levels of AGE in older adults with cognition is unknown. Since AD is a major epidemic, disentangling the role of these three pools of AGE on cognition may open new venues for treatment against this disease.

Cancer

Over time the potential contribution of AGE to the onset and progression of other chronic and non-infectious diseases, such as cancer, has been widely documented[1]. Since the pioneering report showing that AGE taken up through RAGE played a role in promoting the growth of renal carcinoma cells[136], a large body of both clinical and experimental evidence supports the role of the activation of the AGE–RAGE axis on cancer onset and progression, by promoting protein damage, aberrant cell signalling, increased inflammatory responses, increased oxidative damage, changes in extracellular matrix composition and decreased genetic fidelity[137-141]. In addition, there is evidence indicating that dietary AGE are associated with a higher cancer incidence and mortality in modern society[142].

A recent study has shed light into how circulating AGE may promote resistance to tamoxifen in breast cancer patients[143]. Because dietary AGE restriction has been shown to be a successful approach to reduce the levels of circulating AGE[1], any intervention focused on lowering AGE levels may become an attractive option to improve the prognosis of breast cancer patients.

It is important to highlight the potential contribution of dietary AGE in explaining the disproportionately high levels of cancer incidence and mortality in modern society[142]. While both the socio-economic and environmental factors are now well-recognised contributors to this cancer disparity, the role of dietary AGE deserves special attention as a novel component of this disparity since populations of lower socio-economic status seem to have higher dietary AGE intake as well as higher cancer incidence[142].

Sarcopenia

In 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) revised its consensus on the definition and diagnosis of sarcopenia, which in the past was viewed as a geriatric syndrome of loss of muscle mass and function, and has now been more specifically redefined as a generalised skeletal muscle disease[144]. Sarcopenia has been associated with multiple adverse health outcomes including falls and fractures, impaired mobility and activities of daily living, cardiac disease, respiratory disease, longer hospitalisation, cognitive impairment and higher mortality[145].

Evidence for the contribution of AGE to sarcopenia includes the associations of higher plasma CML with lower handgrip strength among elderly, higher skin autofluorescence
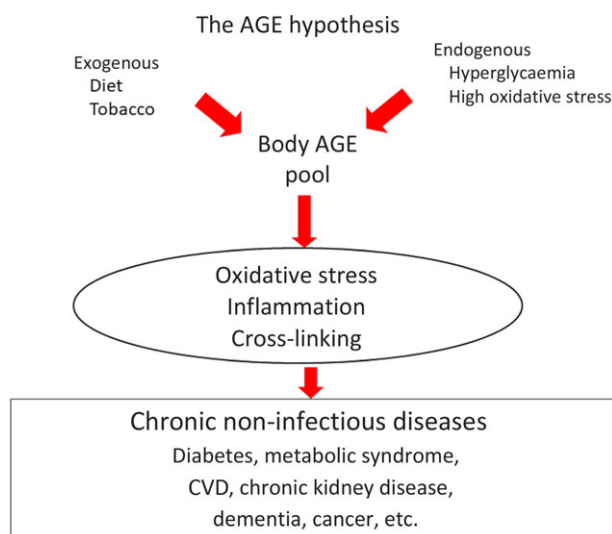
The AGE hypothesis

Fig. 3. The advanced glycation endproduct (AGE) hypothesis. Endogenous and exogenous AGE contribute to the body AGE pool that will affect body homeostasis through direct protein cross-linking as well as through several cellular receptors, which will in turn generate inflammatory cytokines and oxidative stress. All these factors eventually contribute to the genesis of chronic non-infectious diseases. For a colour figure, see the online version of the paper.

(a measure of skin AGE) with lower skeletal muscle mass measured by dual-energy X-ray absorptiometry in middle-aged adults, and with reduced muscle strength in type 1 diabetic patients[146-148]. Higher levels of muscle pentosidine were linked to lower muscle strength but not to loss of muscle mass among elderly, suggesting that collagen cross-links can produce rigidity of the muscle fibre, primarily affecting function and, less so, muscle mass[149]. Serum pentosidine was also associated with osteoporotic and sarcopenic degenerative lumbar scoliosis[150]. A systematic review on the subject indicated that higher levels of AGE are moderately but independently related to decline in walking abilities, activities of daily living, decreased muscle properties (strength, power and mass) and increased physical frailty among elderly subjects. In fact, AGE can alter the biomechanical properties of muscle tissue, increasing stiffness and reducing elasticity through cross-linking and up-regulated inflammation by RAGE binding and endothelial dysfunction in the intra-muscular microcirculation[151].

A direct role for AGE of dietary origin in sarcopenia remains to be established.

Conclusions

In recent years, numerous small clinical trials have measured the effects of a low-AGE dietary intervention on a variety of clinical conditions. These trials have demonstrated that a simple low-AGE dietary intervention decreases circulating levels of AGE, markers of inflammation and OS in healthy, chronic kidney disease and diabetic patients, and improves insulin resistance in diabetic and pre-diabetes patients. These data have generated a new paradigm of disease widely unrecognised, suggesting that excessive consumption of dietary AGE secondary to a 'Western lifestyle' represents an independent risk factor for

inappropriate chronic mild OS and inflammation during life, which over time facilitates the emergence of the chronic diseases of the modern world, especially diabetes and CVD (Fig. 3). An emerging role for dietary AGE is being postulated even in seemingly disconnected areas such as cancer. Simultaneously, we are seeing a rise in the processed food sector revealing that an increasing number of individuals are consuming modern processed foods, laden with AGE. This potential increase in health hazard should also be a concern for processed food industries and not only for the health industry[12]. Reducing the AGE content of common foods by simple changes in culinary techniques is a feasible, safe and easily applicable intervention in both health and disease. Large-scale clinical trials must be performed to replicate the small clinical trials that have been performed so far and provide broader evidence for the deleterious role of dietary AGE on chronic disease. If this evidence continues being reiterated, then reduction of AGE content in common foods may convey an enormous public health impact.

Acknowledgements

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