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Review article

Therapeutic interventions against accumulation of advanced glycation end products (AGEs)

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Abstract

Advanced Glycation End products (AGEs) are formed in a non-enzymatic reaction between reducing sugars and proteins, lipids or nucleic acids. AGEs build up in the body naturally during aging and are involved in the development of several pathologies such as diabetic complications, atherosclerosis and cardiovascular disease. Since AGE levels are a good predictor of diabetic complications and cardiovascular mortality, AGE measurements can provide new information to the current prognosis and treatment options of diabetic patients. Moreover, research regarding interventions to reduce AGE accumulation has been of major interest the latest years. This review examines interventions that have been studied in clinical trials or in *in vivo* studies when that compound is currently available for human use as well. Interventions can be aimed at different levels in the AGE formation pathway and depend on different mechanisms, among which antioxidant ability, scavenging of reactive carbonyl species (RCS) or breaking AGE-induced crosslinks. Pharmaceutical options show promising results, yet their clinical relevance is doubtful so far due to safety concerns. For individuals with high AGE levels but no clinical symptoms, lifestyle interventions such as a low AGE diet and physical exercise might be more effective. Nutraceuticals, derived from food sources and available as dietary supplements, have mostly been investigated in pre-clinical studies and showed positive effects on diabetic complications such as nephro- and retinopathy. Due to the deleterious effects of AGEs on diabetes and its complications, AGE-inhibitors are interesting agents to investigate more extensively.

KEY WORDS: advanced glycation end products (AGEs), diabetic complications, therapy, lifestyle interventions

Introduction on advanced glycation end products

Advanced glycation end products (AGEs) are a diverse set of compounds that accumulate in tissues during normal ageing and contribute to a range of diseases such as diabetes mellitus (DM) and its complications, neurodegeneration and inflammation (***Fig. 1***)[1]. AGEs are generated when reducing sugars react with proteins, lipids or nucleic acids in a non-enzymatic way. This glycation process is described as the Maillard reaction and is known for the browning of foods. This reaction is characterized by a few steps with intermediate products to eventually form AGEs. When the carbonyl group of reducing sugars react with the amino-terminal group of proteins, an unstable Schiff base is formed in a reversible process. During rearrangements, the more stable Amadori product is produced, *e.g.* the glycated hemoglobin HbA1c. When further reactions as rearrangements, oxidation and dehydration take place, AGEs will be produced [2]. During these rearrangements highly reactive intermediate α-dicarbonyls, also known as reactive carbonyl species (RCS), accumulate and cause carbonyl stress. Examples of these products are 3-deoxyglucosone (3-DG) and methylglyoxal (MGO) [3]. RCS and AGE formation can also occur by glycoxidation or lipid peroxidation [4].

Under physiological circumstances, the endogenous AGE production will take weeks or years and long-lived proteins such as collagen are the major target. Under stress conditions such as glycative stress (*e.g.* hyperglycemia) or oxidative stress this reaction accelerates and can also affect short-lived substrates (*e.g.* enzymes and hormones), inducing structural changes [5].

AGEs can also come from exogenous sources such as food. Animal-derived foods, high in fat and protein, consist of high AGE levels. In contrast, food that is enriched with carbohydrates, such as whole grains, vegetables and fruit, are generally low in AGEs. Since high temperatures can accelerate AGE formation, food processing by heating can contribute to the accumulation of AGEs in the body [6]. The total intestinal absorption of AGEs is estimated at ±10% of the total amount of ingested AGEs [7]. Additionally, smoking is an important exogenous source of AGEs [8].

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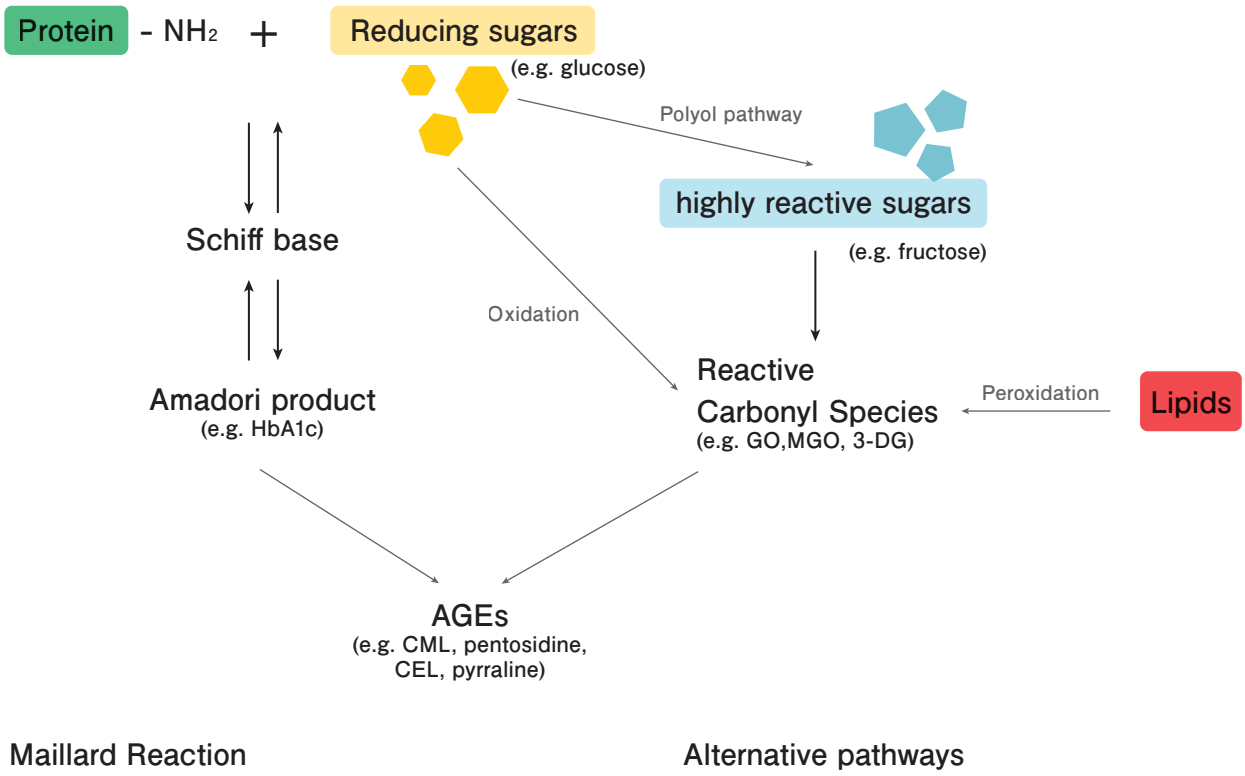

Fig. 1. **Formation of AGEs.**

During the traditional Maillard reaction reducing sugars react with the amino group of proteins to form intermediate products Schiff bases and Amadori products and eventually AGEs. More recently it appeared AGEs can be formed through other pathways such as glycoxidation and lipid peroxidation where reactive carbonyl species (RCS) are generated that covalently bind to proteins. AGEs, advanced glycation end products; CML, carboxymethyl-lysine; CEL, carboxyethyl-lysine; GO, glyoxal; MGO, methylglyoxal; 3-DG, 3-deoxyglucosone.

Role of AGEs in health and disease

The formation of AGEs and accumulation in the body are natural processes during ageing (***Fig. 2***). Aging is explained as a multifactorial process leading to a gradual decline in physiological functions, affecting all tissues in the body [9]. High rates of AGE accumulation in the skin have been shown to correlate with aging [10] and excessive AGE accumulation can accelerate the aging process. The amount of AGEs is based on the rate of formation, determined by ROS and reducing sugars, and the rate of clearance, determined by the activity of the glyoxalase system, where glyoxalase I (Glo I) is able to detoxify reactive carbonyl compounds [11]. Aging can cause an imbalance in this system, since ROS is present in a larger extent while Glo I activity is decreased [12]. Furthermore, AGE accumulation is aggravated in some chronic diseases as well, such as cardiovascular disease, DM, renal failure and Alzheimer's disease [13]. AGEs can damage cells and tissues through several mechanisms and thereby contribute to aging or disease.

First, AGEs can bind to certain receptors (RAGE; receptor for Advanced Glycation End products) on different cells. This induces several signaling cascades, among which activation of MAP kinases and the JAK/STAT pathway [14, 15]. Many of these signaling pathways lead to the activation of transcription factors such as NF κB, which induces a diverse set of target genes. Pro-inflammatory genes (*e.g.* TNF-α, IL-1 and IL-6), adhesion molecules (*e.g.* VCAM-1) and vasoconstrictors are activated [1, 14]. In addition, reactive oxygen species (ROS) are generated by activation of NADPH oxidases and then stimulate the further formation of AGEs [15]. Oxidative stress and inflammation can in their turn elicit tissue damage and lead to accelerated aging [9].

Besides a receptor-mediated response, AGEs are responsible for alterations in protein function. Glycation of (intracellular) proteins can alter their structure and lead to impaired function of growth factors, enzymes and transcription factors, contributing to impaired cell function [5]. Furthermore, AGEs stimulate the formation of crosslinks between (intracellular) proteins, and can trap (lipo)proteins [12]. Accumulation of AGEs in the extracellular matrix (ECM) can result in crosslinking of collagen molecules leading to stiffness and decreased elasticity of tissues [16]. Particularly tissues rich in ECM and long-lived proteins such as skin, skeletal muscles, tendons, heart and lens are targeted by this stiffening and is associated with aging [17]. Under pathological conditions the consequences of crosslinking by AGEs include thickening of the capillary basement membrane, rigid vessels and development of atherosclerosis and glomerular sclerosis [18].

In patients suffering from diabetes or renal disease, AGEs accumulate more rapidly due to glycative stress, oxidative stress or impaired renal clearance. AGEs then contribute to the progression of these diseases and complications such as diabetic neuropathy, nephropathy and the formation of

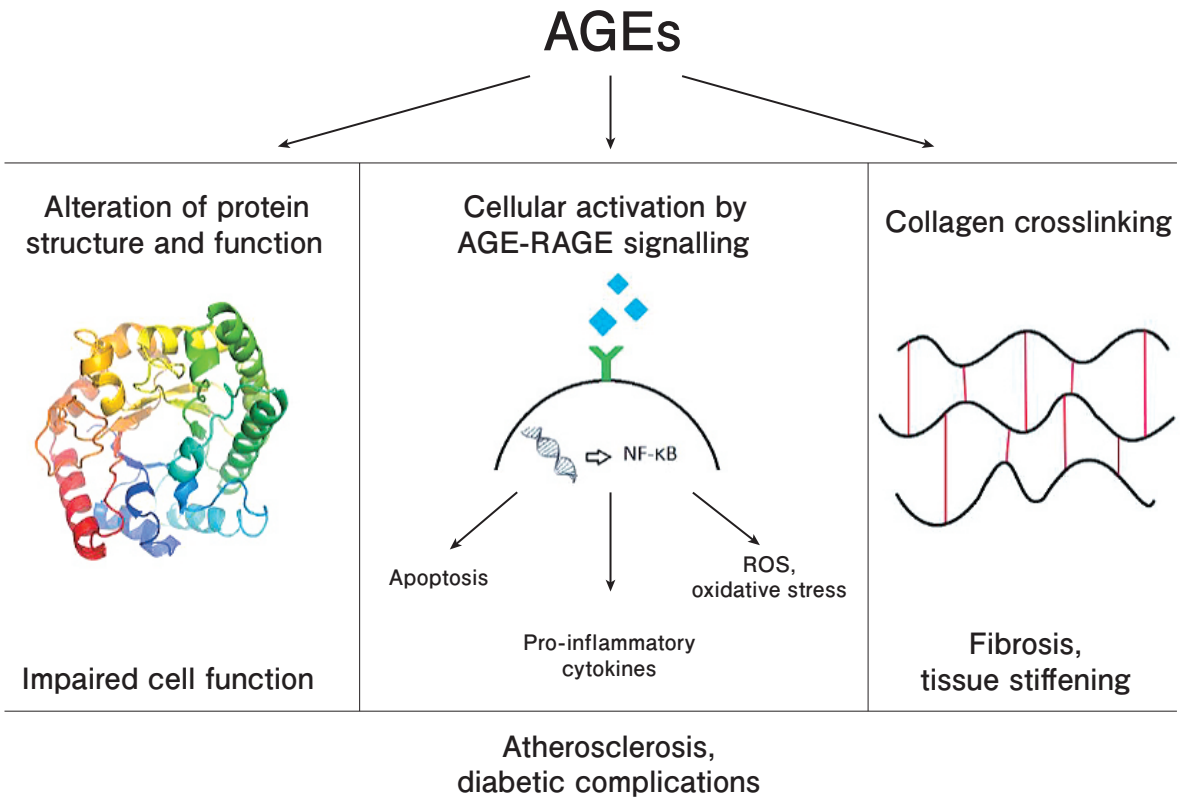

Fig. 2. **Effects of AGEs.**

AGEs contribute to aging and disease by different mechanisms. Glycation of proteins alters their structure and function, leading to impaired cell function. AGE-RAGE interaction activates NF-kB, inducing several cellular responses, such as apoptosis, production of pro-inflammatory cytokines and ROS. Finally, AGEs form crosslinks between collagen and other proteins, leading to tissue stiffening. These are key processes in many diabetic complications, such as atherosclerosis, diabetic nephropathy and diabetic neuropathy. AGEs, advanced glycation end products; RAGE, receptor for AGEs; ROS, reactive oxygen species.

cataract. Atherosclerosis is the major cause of death in diabetic patients [19] and is characterized by cross-linking of extracellular matrix proteins in the vessel wall by AGE accumulation, thereby trapping plasma proteins [20]. Moreover, AGEs in the vessel wall interfere with the nitric oxide (NO)-mediated relaxation ability of the endothelium [21].

NF-κB signaling and ROS induce apoptosis of pericytes and endothelial cells [22], contributing to diabetic retinopathy. This is enhanced by hyper permeability of capillaries, resulting in vascular leakage [23]. In addition, the thickening of the capillary basement membranes by increased synthesis of collagen and other matrix molecules is a mechanism by which retinopathy is strengthened [24]. The same mechanisms play a role in the pathophysiology of diabetic nephropathy. Apoptosis of mesangial cells [25] and the thickening of the glomerular basement membrane is partly responsible for altered filtration, albuminuria and eventually renal failure [2]. AGE accumulation represents 'glycemic memory': the phenomenon that explains the sustained beneficial effects long after a period of intensive glycemic control, as well as the prolonged harmful effects after hyperglycemia [26, 27]. Together with their role in diabetic complications, measuring AGEs is emerging as a tool to predict the odds of developing complications and detect patients at risk. The AGE Reader (Diagnoptics, Groningen, the Netherlands) provides a non-invasive, quick and reproducible way for the AGE-related skin autofluorescence (SAF). Skin AGE levels proved to be an independent predictor of microvascular complications in type 2 diabetes mellitus (T2DM) [28]. Furthermore, skin autofluorescence is, except for age, the best predictor for cardiovascular (CV) mortality and provides additional information to conventional CV risk assessment engines [29].

Interventions to lower AGEs

Since AGEs have shown to play an important role in aging and the development and progression of many chronic diseases, they are an excellent target for new therapies (***Fig. 3***). To diminish the harmful effect of AGEs on cellular and tissue functioning, interventions are proposed that either avoid the further formation or accumulation of AGEs or remove the AGEs that are already formed. This review gives an overview of existing and potential interventions that can inhibit AGEs now or in the near future, which are classified in pharmacologic, lifestyle and nutraceutical interventions.

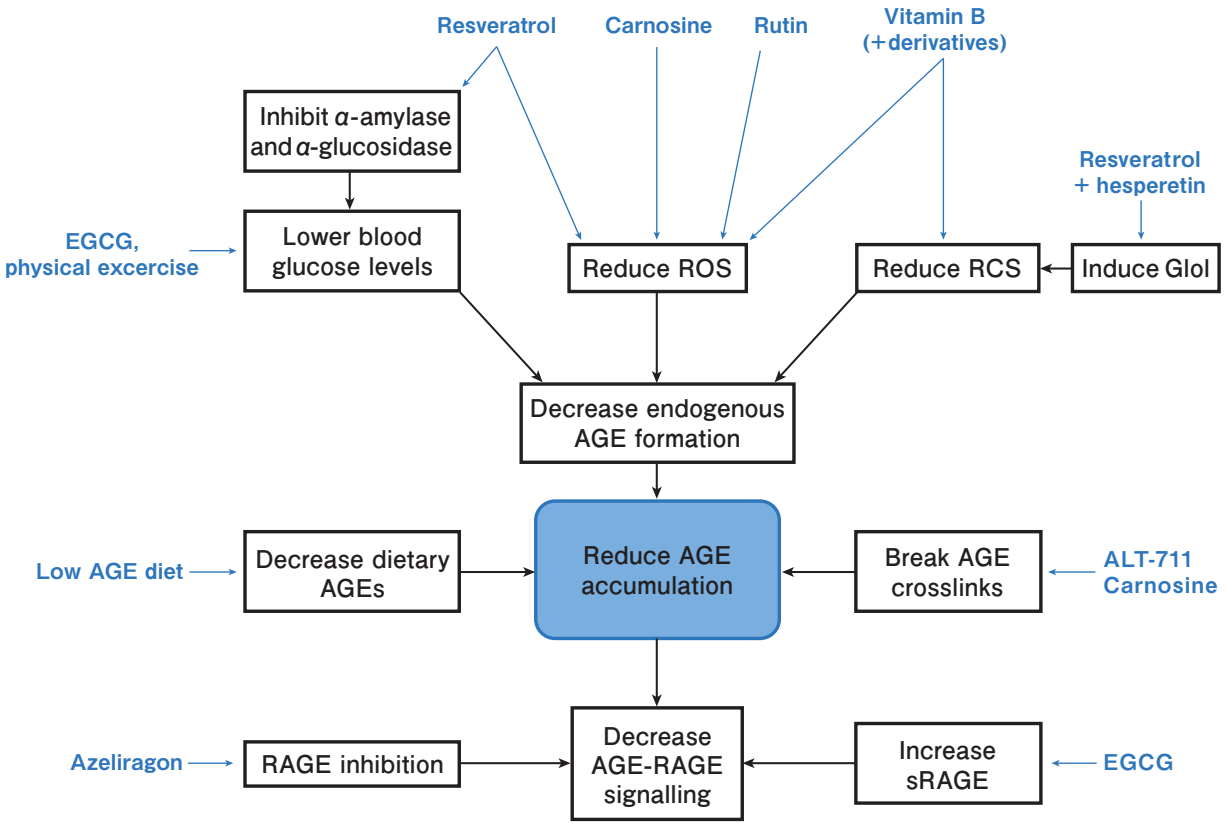

Fig. 3. **Interventions to reduce AGE accumulation.**

The deleterious effects of AGEs can be stopped by reducing AGE accumulation and decrease RAGE signaling. The AGE formation pathway can be targeted at different levels by pharmaceutic, lifestyle and nutraceutical interventions. AGEs, advanced glycation end products; RAGE, receptor for AGEs; sRAGE, soluble RAGE; ROS, reactive oxygen speciesS; RCS, reactive carbonyl species; GloI, glyoxalase I; EGCG, epigallocatechin 3-gallate.

Pharmacologic interventions

Researchers have been ambitious to find substances with AGE-reducing properties. Compounds that have been studied extensively are aminoguanidine (AG) and Alagebrium (ALT-711).

AG is a small molecule that reacts with dicarbonyl compounds (*e.g.* MGO and 3-DG) and Amadori intermediates to inhibit the formation of AGEs [30]. The first clinical trial (ACTION) was performed to evaluate the effect of AG on the further development of diabetic nephropathy. A large cohort of 690 patients with type 1 diabetes mellitus (T1DM) and known nephro- and retinopathy participated and were treated for 2-4 years with AG. Overall, a significant reduction of diabetes complications was observed. AG administration reduced the 24-hour proteinuria and could prevent the decrease in glomerular filtration rate. However, the inhibition of AGE formation by AG showed no effect on serum creatinine [31]. A second trial, involving AG therapy in T2DM patients, was early terminated due to undesirable side effects such as abnormalities in liver function, gastrointestinal problems and anemia [32].

Alagebrium (ALT-711) has the ability to break crosslinks of Maillard reaction products and demonstrated positive effects on atherosclerosis and diabetic nephropathy *in vivo*. Clinical studies that have been performed mostly investigated the use of Alagebrium in patients with hypertension or heart failure. Two studies that examined hypertensive patients treated with Alagebrium for a relative short period (8-10 weeks) [33, 34], showed some beneficial effects on several cardiovascular variables, such as an increase in arterial compliance and a decrease of arterial pulse pressure [33]. Furthermore endothelial function was improved and the therapy might reduce arterial remodeling. Nevertheless, the same study reported no changes in cardiac output, blood pressure and systolic or diastolic function and other cardiovascular variables [34]. In a study where 23 patients with diastolic heart failure were treated for four months ambiguous results were found. Although diastolic function and left ventricular mass were improved, no change in maximal oxygen consumption (VO2 max), blood pressure or aortic distensibility were found [35]. Another study observing 102 heart failure patients after 9 months of treatment did not show positive results and could not find an improvement of diastolic and systolic function, AGE

accumulation or New York Heart Association (NYHA) classification [36]. Similarly, no convincing results on hemodynamics or exercise capacity could be detected after 1 year of treatment in healthy individuals [37, 38]. Due to the mentioned safety and efficacy problems, it is implausible that AG and Alagebrium will be used for the treatment or prevention of diabetic complications.

Azeliragon is a RAGE inhibitor and has been tested in clinical trials to diminish Alzheimer's disease. RAGE is not only a receptor for AGEs, but can bind amyloid β as well. In Alzheimer's disease, RAGE expression is upregulated in the brain and contributes to inflammation, oxidative stress and neurodegeneration [39]. RAGE antagonist Azeliragon (also known as TTP488 or PF-04494700) was administered to 399 patients for 18 months to inhibit the interaction between RAGE and amyloid β and block signal transduction [40]. This also might be interesting to counteract the detrimental effects of AGEs through its receptor. A low dose was suggested to have a decreased decline on the Alzheimer's Disease Assessment Scale – cognitive (ADAS-cog), a test that determines parameters as memory, reasoning, language and orientation [41]. Nevertheless, there was no significant difference in other clinical markers and the study was terminated early [42]. The drug was developed earlier for diabetic neuropathy but this study was discontinued as well.

Besides pharmaceuticals that specifically target AGEs, there is another subset of generic drugs, initially developed to decrease blood pressure or cholesterol, but happen to have an effect on AGEs as well. Several small studies on metformin, glucose-lowering medication, showed some beneficial effects on glycation measures, such as a decrease of MGO [42] and lower AGEs and oxidative stress in patients with T2DM [43]. Not all studies were able to find additional effects, therefore the AGE-inhibition capacity of metformin might be attributed merely to improved glycemic control instead of dicarbonyl quenching. Lipid-lowering medication might inhibit AGE formation as well due to anti-oxidative properties, which partly reduces lipid peroxidation. Atorvastatin showed a decrease in serum AGEs in non-alcoholic steatohepatitis (NASH) patients with dyslipidemia after 12 months of treatment [44]. Serum AGEs were also reduced in patients with non-diabetic chronic kidney disease and dyslipidemia after one year of atorvastatin treatment [45]. This effect was also observed in diabetic patients that received cerivastatin for three months [46]. In addition to the decrease in serum AGEs, simvastatin showed a decrease of RAGE expression in carotid artery plaques, by inhibition of AGE formation [47].

Finally, blood pressure-regulating medication also has a potential effect on AGEs. Until now, only one small study on ACE-inhibitors has evaluated the effect on AGE formation. Ramipril treatment for two months decreased fluorescent AGEs, but not non-fluorescent carboxymethyl lysine (CML), alongside reduced blood pressure and proteinuria [48]. Furthermore, Angiotensin Receptor blockers have shown in several small studies that they possess AGE-reducing effects. One year of valsartan treatment decreased serum AGEs, but did not affect other metabolic and oxidative markers in diabetic hypertensive patients [49]. Candesartan administration to diabetic patients for three months decreased urinary AGEs [50] and in addition slightly improved creatinine clearance in diabetic kidney disease patients [51]. In contrast, a larger randomized controlled trial with a longer follow-up period could not detect a treatment effect of irbestartan on AGEs in T2DM subjects with microalbuminuria [52].

Lifestyle interventions

Pharmaceutic interventions against AGEs are not approved yet to be clinically used. For individuals that have high AGE levels but no clinical signs of disease yet, non-medical interventions such as adopting a healthy lifestyle might be a more effective approach to prevent further AGE accumulation and increase healthspan (*i.e.* the disease-free time of life).

Low AGE diet

Since the composition and especially the preparation of food largely determine the amount of exogenous AGE intake, a diet low in AGEs can reduce the absorbed AGEs from the gut. Several studies on a low AGE diet have been completed, using different study populations (healthy and obese subjects as well as patients with diabetes and renal failure). The duration of the low AGE differed between studies, but were all between 1 and 4 months. The decrease of AGEs in the diet was between 30 and 60 %, which was generally due to differences in cooking methods. In all studies an isocaloric, low AGE diet showed a decrease in serum AGEs and in most studies, except for one [53], this decrease is accompanied by a reduction in markers of inflammation and oxidative stress [54-59]. In diabetic and obese subjects with insulin resistance, the HOMA-determined insulin sensitivity improved [60, 61]. A calorie-restricted diet reduced plasma AGEs as well, which can be due to a reduced intake of food AGEs or because of other mechanisms such as upregulation of sRAGE or decreased ROS formation [62]. It must be noted that AGE intake can largely differ in different populations and countries due to differences in the preparation of food. The effects of a low AGE diet should not be undermined since the contribution of dietary AGEs is larger than the endogenously amount of formed AGEs in plasma [63].

Physical exercise

Physical exercise has shown to be protective against cardiovascular disease, increases longevity and is an important tool to prevent the development of diabetes in subjects with impaired glucose tolerance [64]. The influence of exercise on AGE levels has been described in several studies.

The first study investigated the effect of short and long runs on changes in methylglyoxal (MGO) content in red blood cells of trained and untrained students. Long runs showed to have the largest reduction in MGO concentration; 41% and 60% in untrained and trained students respectively [65]. Another study explored the influence of life-long endurance running on the accumulation of AGEs in connective tissue and found that life-long runners had a 21% lower AGE crosslink density of pentosidine in patellar tendons, accompanied by an 11% decrease in skin AGE levels [66]. Doing Tai Chi, an exercise of moderate intensity and an aerobic nature, for twelve months, showed a decrease in serum AGEs, most likely by stimulating antioxidant enzymes that reduce oxidative stress [67]. In addition, a study involving middle-aged females in a 12-week lifestyle modification demonstrated a decrease in serum AGEs, as well as reductions in body fat and serum HDL-cholesterol compared to the control group [68].

Furthermore, in a 6 months interventional program that was focused on stimulating mild to moderate physical activity in Japanese elderly, a reduction in serum sRAGE was demonstrated. The decrease in sRAGE levels could be explained by a reduction of plasma AGEs, which in its turn can inactivate RAGE expression as well as sRAGE circulation as a scavenger of AGEs [69]. In contrast, moderate exercise for six months in T2DM women resulted in increased sRAGE levels and improved cardio-metabolic risk factors. This possibly improves scavenging of AGEs by sRAGE and decreases activation of the AGE-RAGE pathway, preventing cellular dysfunction [70]. Since these studies show opposing effects, which might be due to the study population, the clinical relevance of the relationship between exercise and sRAGE should be studied further.

Finally, in a 12-week study obese men participated in either a low AGE diet, physical (aerobic) exercise (45 minutes with an intensity of 65-75% of maximum heart rate, three times a week) or a combination of both. In contrast to the other studies, an AGE-reducing effect of performing exercise alone was not perceived. Only in combination with the low AGE diet, this intervention provided a decrease in serum CML and MGO [71].

Nutraceuticals

Instead of synthetic pharmaceuticals, compounds from natural sources have attracted attention to inhibit AGEs. Natural AGE inhibitors can be found in vegetables, fruit, tea and medicinal plants and many of them are available as dietary supplements.

Vitamin B and derivatives

It has been reported that diabetic patients have a substantial deficiency of vitamin B1 [72]. Vitamin B6 (pyridoxamine and pyridoxine) and vitamin B1 (thiamine and the synthetic prodrug benfotiamine) supplementation have been described as a potent AGE inhibitory strategy.

Pyridoxamine can inhibit the conversion of Amadori products to AGEs and is able to scavenge reactive oxygen species and the reactive carbonyl intermediates that are products of sugar and lipid degradation [73]. Although *in vivo* experiments demonstrated the efficient inhibition of AGEs by pyridoxamine along with positive effects on diabetic nephropathy [74], clinical evidence is more ambiguous. In 2007, a phase 2 trial including patients with kidney disease due to T1DM or T2DM, showed the inhibiting effect of pyridoxamine treatment (Pyridorin; NephroGenex, Inc., Jamison, PA, USA) on plasma AGEs. Additionally, 6 month pyridoxamine treatment suggested the potential to slow down renal disease by a reduced change in serum creatinine from baseline and urinary TGFβ excretion [75]. In contrast, a second trial in patients with type 2 diabetic nephropathy could not repeat this effect on creatinine, although patients with less renal impairment might profit. It is suggested that the effect of AGE inhibition is more effective in an earlier stage, which may be before the onset of pathologic changes [76].

The effect of high-dose thiamine (vitamin B1) therapy was examined in a pilot study with T2DM patients with microalbuminuria, and reported decreased urinary albumin excretion after 3 months but no effect on dyslipidemia, glycemic control or blood pressure [77]. Benfotiamine is a prodrug of thiamine with a higher bioavailability, and *in vitro* data indicates that it inhibits three major pathways that elicit hyperglycemic vascular damage, among which the AGE formation pathway. Benfotiamine is able to inhibit these pathways simultaneously by increasing the activity of the transketolase enzyme. In addition, NF-κB activation could be prevented by benfotiamine. These effects were able to reduce diabetic retinopathy in a diabetic animal model [78]. Human studies on benfotiamine are still inconclusive. Studies showing positive results include a beneficial effect on endothelial function, oxidative stress and AGE levels after consumption of a high AGE meal [79]. Another study reported normalisation of several indicators of hyperglycemia including AGE formation, although this last study only showed positive effects in combination with alpha-lipoic acid [80]. Alternatively, Alkhalaf *et al.* concluded in two studies that benfotiamine treatment for 12 weeks did neither reduce urinary albumin excretion (UAE) and excretion of a tubular damage marker, nor did it affect plasma or urinary AGEs and plasma markers of endothelial dysfunction [81, 82].

Benfotiamine might be profitable for patients with diabetic polyneuropathy. In a double blind, placebo-controlled phase 3 trial, benfotiamine treatment for six weeks improved the Neuropathy Symptom Score (NSS) in the per protocol analysis, with the greatest improvement in the parameter pain [83]. Other studies examined the effect of benfotiamine in combination with other B vitamins. A combination of benfotiamine with vitamin B6 and B12 for 12 weeks improved the nerve conduction velocity in the peroneal nerve, and this result was repeated in a 9 month intervention study in 9 patients [84]. A different study on Milgamma-N (benfotiamine-vitamin B combination) reported therapeutic effects after six weeks on parameters pain and vibration sensation [85]. However, these results were contradicted in a 24-month study examining the effect of benfotiamine (Benfogamma, Wörwag Pharma, Uzbekistan, Tashkent) in T1DM patients without clinical neuropathy. No beneficial effects on peripheral nerve function or inflammatory biomarkers were reported, which might be explained by differences in study population, where an improvement in patients with almost normal nerve function might be unfeasible [86].

Carnosine

L-carnosine is a naturally occurring dipeptide that is primarily present in the central nervous system and skeletal muscles. *In vitro* studies demonstrated an effective anti-glycosylating effect by reacting with RCS and inhibiting protein crosslinking [87]. Other protective functions of carnosine are its antioxidant activity by scavenging of reactive oxygen species [88].

The results obtained from *in vitro* studies make carnosine an interesting potential therapeutic agent. In contrast to rodents, humans possess the carnosinase enzyme, which can degrade carnosine through hydrolysis. Therefore, carnosinase-resistant derivatives such as D-carnosine and its more bioavailable prodrug D-carnosine-octylester (DCO) have been developed. D-carnosine has been proved to have the same efficiency as L-carnosine in quenching RCS and diminishes the development of renal disease and dyslipidemia in obese Zucker rats [89]. Moreover, treatment with DCO was able to protect diabetic mice from atherosclerosis and renal disease [90, 91]. Various other *in vivo* studies supported the nephro- and retino-protective effect of carnosine treatment in diabetic animals [92]. However, in two of these studies, the

protective effects of carnosine could not be explained by the anti-oxidative and anti-glycation characteristics of carnosine, but were exerted through other mechanisms [93, 94].

In clinical studies, carnosine derivative N-acetylcarnosine has been investigated as a treatment for (glycation-induced) cataract. Eyedrops with 1% N-acetylcarnosine (Can-C™ Eye Drops; Wise Choice Products LLC., London, United Kingdom), which is more resistant to carnosinase than L-carnosine, improved vision in both subjects with cataract and without [95]. The effect of carnosine on the skin has been examined as well, since SAF increases during aging and correlates with AGE deposition in the skin [10]. AGEs induce apoptosis of dermal fibroblasts and crosslinking of collagen, leading to stiffness of the tissue [96]. The subjects in this study were given supplements that combine L-carnosine with competitive carnosinase inhibitors to increase tissue L-carnosine levels without increasing its concentration in blood plasma (Can-C Plus, Innovative Vision Products, Inc., New Castle, DE, USA). Oral supplementation for three months had a positive influence on signs of skin aging, such as reduction of fine lines and improved skin appearance [97].

Polyphenols

Many nutraceuticals are rich in polyphenols that possess anti-glycation activity through various mechanisms, such as regulation of glucose metabolism, antioxidant effects and inhibition of the Aldose Reductase (AR) pathway [98]. AR is an enzyme in the polyol pathway and active/enhanced under hyperglycemic conditions. The polyol pathway is an important source of diabetes-induced oxidative stress and the formation of reactive fructose and 3-DG that contribute to AGE accumulation [99].

Epigallocatechin 3-gallate

Epigallocatechin 3-gallate (EGCG) is the major polyphenol in tea that possesses anti-inflammatory and anti-cancer properties [100]. In a diabetic mouse model, induced by a high fat diet, EGCG proved to decrease AGE accumulation with 80% in kidney and 96% in heart. Furthermore blood glucose levels and weight gain induced by a high-fat diet were reduced and the formation of cataracts could be prevented or delayed [101]. In another study mice were treated with low and high doses of EGCG three times a week. After seventeen weeks, mice receiving a high dose of EGCG showed a near reversal of weight gain, improved glucose control and inhibited AGE accumulation in plasma, liver, kidney and adipose tissue [102]. In rats suffering from diabetic nephropathy, EGCG showed comparable results, ameliorating the decline of kidney function [103].

Additionally, green tea extract that is enriched with EGCG increased sRAGE levels in plasma of T2DM patients. sRAGE acts as a decoy for AGEs, preventing their interaction with RAGE [104]. Simultaneously, EGCG-rich green tea extract decreased RAGE ligand S100A12, which indicates EGCG is able to block RAGE-ligand signaling, and could possibly prevent the progression of inflammatory responses that lead to the complications in diabetes [105].

Although these results suggest the AGE inhibitory potential of the green tea derived EGCG, clinical studies are needed to show whether this could be a useful intervention for the treatment of diabetic complications. Examining the pharmacokinetics and safety issues is of great importance, since the dose used in *in vivo* studies far exceeds the amount of active substance in dietary supplements. Moreover, EGCG has been shown to have a low bioavailability, which led to the design of lipophilized derivatives that demonstrated slightly improved AGE-inhibitory activity *in vitro* [106].

Rutin

Rutin is a dietary flavonoid that is present in fruits, vegetables, tea and wine. Rutin is metabolized to a range of compounds such as quercetin, 3,4-dihydroxytoluene (3,4-DHT) and 3,4-dihydroxyphenylacetic acid (3,4-DHPAA). Rutin, along with its metabolites, can inhibit glucose autoxidation, the formation of AGEs and glycation of collagen [107]. Its anti-glycation capacity was again demonstrated on goat eye lens proteins, indicating rutins potential to scavenge free radicals and chelating metal ions. The inhibition of aldose reductase (AR) is another mechanism that explains the benefits of rutin [108].

The lowering effect of rutin on collagen fluorescence in diabetic rats was first described by Odetti *et al.* [109]. Further *in vivo* studies demonstrated that G-rutin, a rutin glucose derivative, could reduce glycation of serum and kidney proteins and lipid peroxidation in diabetic rats [110]. In addition, rutin had preventive effects on the development of diabetic nephropathy in rats. After 10 weeks not only the expression of AGEs and accumulation of collagen were significantly reduced, fasting glucose levels and oxidative stress were decreased as well. Furthermore, rutin treatment attenuated microalbuminuria and the thickness of the glomerular basement membrane [111]. Other studies examining the effect of rutin on rats with streptozotocin (STZ)-induced diabetes showed a protective function against kidney damage by positively regulating matrix remodeling [112] and improvement of hyperglycemia and dyslipidemia, while liver and heart toxicity induced by diabetes were ameliorated [113]. Hence, rutin supplementation might be a potential treatment for diabetic pathological conditions.

Resveratrol

Resveratrol has been described as a polyphenol that possesses anti-oxidant, anti-cancer, anti-inflammation and life extending effects [114]. Besides these positive health effects, resveratrol showed the ability to inhibit AGE formation *in vitro*. Resveratrol acted as an inhibitor of α-amylase and α-glucosidase, which are enzymes that catalyse the degradation of carbohydrates [115]. Inhibition of these enzymes modulates sugar release and postprandial hyperglycemia and could be used as a therapy to decrease the risk of diabetes complications [116].

Two *in vivo* studies report that resveratrol treatment did not affect AGE levels in liver and kidney, which might be due to relative short exposure time. Nevertheless, resveratrol improved antioxidant status and decreased plasma glucose and RAGE expression in liver and kidney of diabetic rats [117, 118]. Moreover, resveratrol treatment reduces the NF-κB-RAGE signaling pathway, thereby ameliorating vasculopathy in diabetic rats [119]. Furthermore, resveratrol can exert its beneficial effects on diabetic complications by inhibition of Aldose Reductase (AR), resulting in a decrease of AGE formation in the kidney and improvement of the glomerular filtration rate and renal function in diabetic rats. Since AR mediates the polyol levels that contribute to cataract formation, resveratrol is able to inhibit opacification of the lens [120]. Palsamy *et al.* support that resveratrol is able to

normalize AR activity, and additionally other polyol pathway enzymes such as sorbitol dehydrogenase and glyoxalase-I (Glo-I), which limits AGE formation and glycation damage to the kidneys [121]. In a clinical study the effect of resveratrol and hesperetin on vascular function was observed. These dietary bioactive compounds demonstrated to be strong inducers of glyoxalase-I, that is responsible for the detoxification of RCS compound MGO. Co-therapy of resveratrol and hesperetin, instead of individual administration, was able to improve fasting plasma glucose, oral glucose insulin sensitivity and arterial and renal function in obese subjects [122].

Conclusions

AGEs build up in the body naturally during aging. Yet, excessive AGE accumulation can accelerate the aging process and induce tissue damage, which is most evident in tissues consisting of long-lived proteins such as skin, heart, muscles and joints. Furthermore, AGEs are key players in the development and progression of many chronic diseases such as DM, cardiovascular disease and renal disease, and their complications. Since AGE levels could represent biological age and have shown to be a good predictor of cardiovascular and diabetes complications, AGE measurements can provide new information about a subject's health or to the current prognosis of diabetic patients. Consequently, the investigation of anti-AGE interventions has been of major interest the latest years. The complexity of AGE formation and interactions allow for interventions at different levels. The strategies that prevent AGE formation depend on different mechanisms such as antioxidant ability, scavenging of reactive carbonyl species and inhibition of aldose reductase. Pharmaceutical options show promising results, yet their clinical relevance is doubtful so far due to safety concerns. For individuals with high AGE levels but no clinical symptoms other interventions might be more effective. Lifestyle interventions such as a low AGE diet and physical exercise are easily to implement and show beneficial effects on plasma AGEs and reduce inflammation and oxidative stress. Nutraceuticals, derived from food sources and available as dietary supplements, have mostly been investigated in pre-clinical studies. Many studies evaluated these compounds as potential anti-AGE therapeutics and showed positive effects on diabetic complications such as nephro- and retinopathy. Until now, clinical evidence is mostly lacking and should be evaluated in the future. The duration of the interventions that is required to show a beneficial effect on AGEs is uncertain and might depend on the part of the AGE formation pathway the intervention is aimed at. Due to the fact that AGE accumulation represents glycemic memory, interventions against AGEs could have prolonged effects on health and prevention of diabetic complications.

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