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Review

Therapeutic options to reduce advanced glycation end products in patients with diabetes mellitus: A review

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ABSTRACT

Diabetes mellitus (DM) defines metabolic disorders, characterised by elevated levels of blood glucose. Chronic hyperglycaemic state promotes consequently the formation of advanced glycation end products (AGEs) and the expression of their receptor (RAGE) which aggravate many diabetic complications. Due to the relevant role of AGEs and RAGE, several therapeutic approaches with an anti-AGE or RAGE-antagonizing effect are investigated. These therapeutic options include AGE cross-link breakers, AGE inhibitors, RAGE antagonists, drugs clinically approved for various indications like antidiabetic, antihypertensive drugs or statins, as well as dietary and phytotherapeutic approaches. The aim of this review is to give an overview of these therapeutic approaches, their outcomes in clinical studies and their role in the management of diabetes and its complications.

Contents

Abbreviations: ACE, angiotensin converting enzyme; AGE, advanced glycation end product; ALE, advanced lipoxidation end product; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; MG, methylglyoxal; NAC, N-acetylcarnosine; NO, nitric oxide; PKC, protein kinase C; PTB, N-phenacylthiazolium bromide; RAAS, renin-angiotensin-aldosterone-system; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; sRAGE, soluble receptor for advanced glycation end products; VEGF, vascular endothelial growth factor

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1. Introduction

Obesity and diabetes mellitus (DM) are among the most challenging threats to public health in the 21st century. Current IDF estimations tell us that currently approximately 415 million people worldwide suffer from DM and the incidence as well as prevalence of this metabolic disease increase constantly and it is predicted to reach 642 million by 2040 [1]. Approximately 90% suffer from type 2 DM while only 5–10% has type 1 DM. Diabetic nephropathy, neuropathy and retinopathy are known microvascular complications and diabetic nephropathy today is the leading cause for end stage renal disease and diabetic retinopathy represents the major cause for blindness in Europe and North America. Additionally, patients with DM have a higher risk for macroangiopathies like coronary heart disease, lower extremity arterial disease and cerebrovascular disease. The risk for cardiovascular death is approximately twice as high as compared to non-diabetic counterparts. Furthermore, people with DM have a higher prevalence to develop cataract, erectile dysfunction or cognitive impairment, like Alzheimer's disease [2]. While hyperglycaemia per se is a moderate risk factor for macrovascular complications, the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study [3,4] clearly highlighted hyperglycaemia as the major risk factor for microvascular complications.

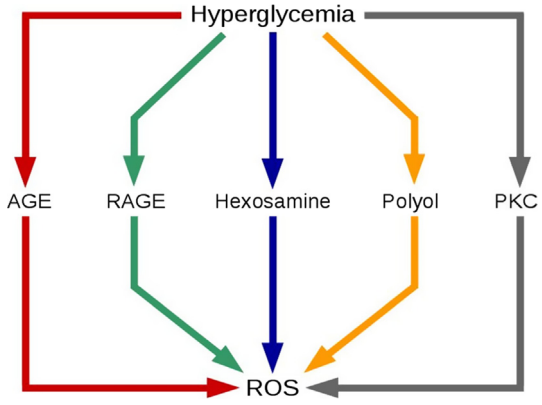


Fig. 1 – Five pathways of the ROS production caused by hyperglycaemia.

The mechanisms by which elevated glucose levels lead to tissue damage are multifaceted including direct glycation of lipids, proteins and DNA as well as via five pathways including an enhanced production of advanced glycation end products (AGEs), an amplified expression of the receptor for AGEs (RAGE), and an increased activation of the polyol, the protein kinase C (PKC) and the hexosamine pathway (Fig. 1). Via these five pathways, signal molecules, like NF-κB, tumor necrosis factor α, and transforming growth factor are increasingly produced and the nitric oxide (NO) production is decreased. The result is an increased generation of reactive oxygen species (ROS) [5].

2. Biochemistry of AGEs and RAGE

2.1. AGEs

AGEs are macromolecules generated by the Maillard reaction. Proteins, DNA and lipids react non-enzymatically with reducing carbohydrates, in vivo mostly glucose and carbonyl compounds [6]. Some carbonyls can also be produced via the fatty acid metabolism by lipid peroxidation which react with proteins, DNA and lipids, whereby advanced lipoxidation end products (ALEs) are formed. The origin of these carbonyls cannot be distinguished so that AGEs and ALEs are commonly summed-up, also in this review. Well-known AGEs and AGE precursors are N(6)-carboxymethyllysine, pentosidine, methylglyoxal-derived hydroimidazolone, malondialdehyde

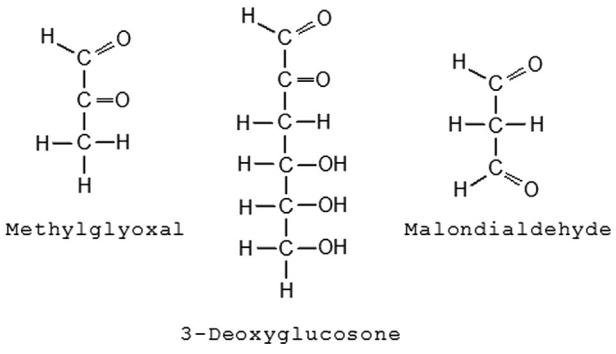


Fig. 2 – Chemical structural formulas of some AGE precursors.

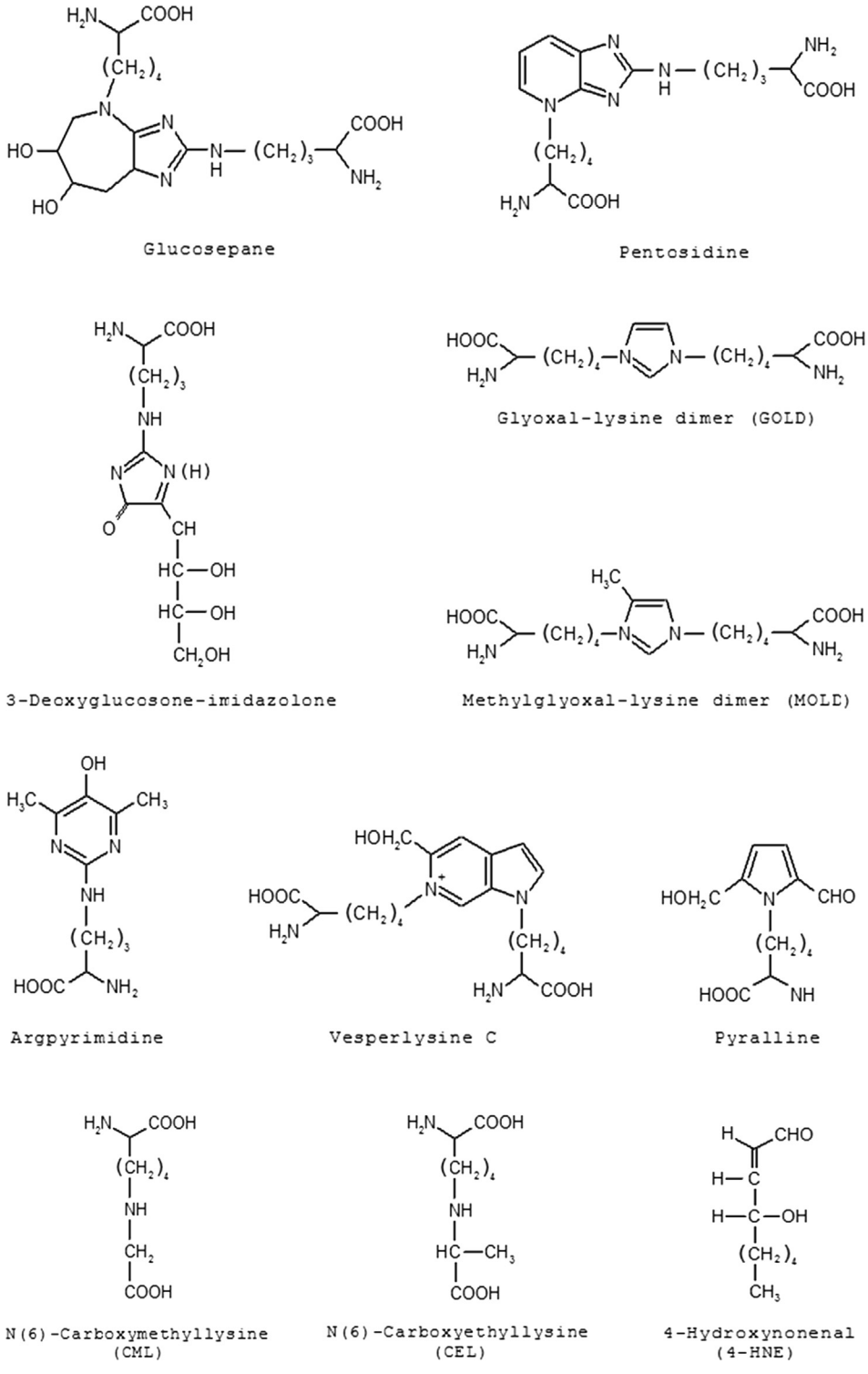


Fig. 3 – Chemical structural formulas of several AGEs.

and methylglyoxal (MG). Chemical structural formulas of some AGE precursors and AGEs are shown in Fig. 2 and Fig. 3.

In the first step of the Maillard reaction, the carbonyl group of the sugar molecule reacts with an amino group of an amino acid. The resulting product is an imine or Schiff base, which either dissociate into its educts or is converted into an Amadori product by the Amadori rearrangement. Amadori products are relative stable glycosamines. The more pronounced the hyperglycaemia and the longer it persists, this equilibrium reaction shifts more likely to the Amadori product. While the formation of Schiff base and Amadori product is reversible, the formation of a 'genuine' AGE is irreversible. Amadori products have reactive carbonyl groups by which AGE precursors can be generated [7]. In the last step of the

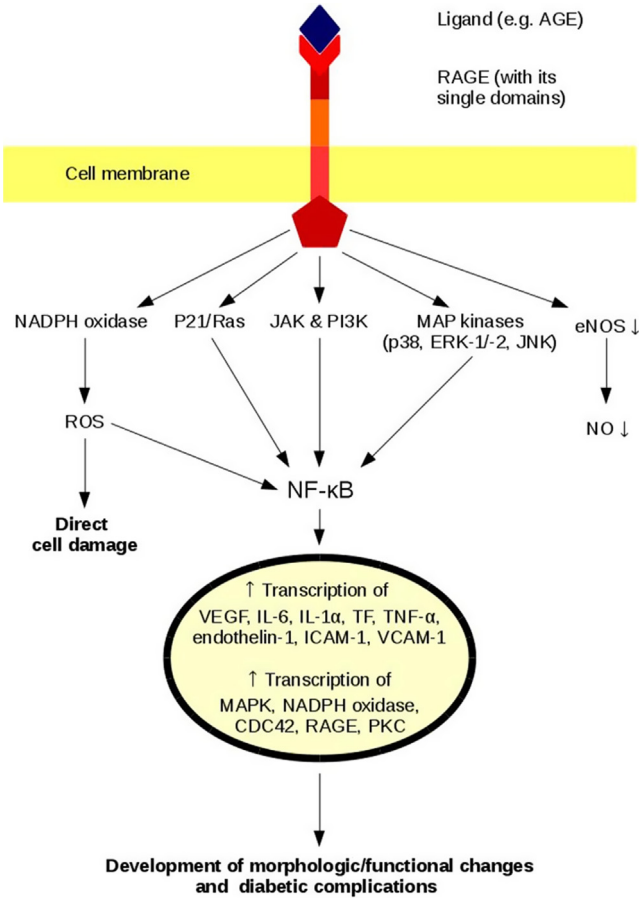


Fig. 4 – Intracellular signalling cascade of the RAGE activation modified after Barlovic et al. [14].

Maillard reaction, AGEs are finally formed from these dicarbonyls due to further chemical reactions, especially by oxidation and interactions of precursors with ROS. AGEs can be formed via oxidative and carbonyl stress too and an exogenous AGE intake via tobacco products or by food as free adducts is also possible [8–10].

2.2. *RAGE*

RAGE is a surface receptor which belongs to the immunglobulin superfamily and was first described in 1992 [11]. RAGE consists of five protein domains including three extracellular domains, one transmembranous domain, which anchored the receptor into the cell membrane, and one cytoplasmic domain, which accomplishes the signal transduction. The three extracellular domains can be subdivided into one variable and two constant domains and only the variable domain is able to bind ligands. RAGE can be found in tissues and organs like endothelial or neural cells, kidney, and lung and AGEs are not the only binding partner of RAGE. Other ligands are high-mobility group protein B1, also known as amphoterin, several S100 proteins (S100A4, S100B, S100P), Mac-1 and amyloid-β [12]. There are various isoforms of RAGE which are formed by posttranscriptional splicing of the pre-mRNA. The most important isoform is soluble RAGE (sRAGE) from which two subtypes exist, endogenous secretory RAGE and cleaved-type soluble RAGE. Both subtypes consist only of the extracellular domain so that the signal transduction cannot be initiated because of the missing cytoplasmic domain. Otherwise, AGEs can bind to the subtypes and can be inactivated on this way [13].

If a ligand binds to RAGE, signalling cascades will be activated leading finally to an activation of the transcription factor NF-κB (Fig. 4) [14]. NF-κB binds on the DNA inducing a transcription of several proteins like vascular endothelial growth factor (VEGF), tissue factor, interleukins, tumor necrosis factor α and vascular cell adhesion molecule-1 [15]. Moreover, NF-κB ensures an activation of signal transduction molecules like mitogen-activated protein kinases and PKC and an upregulation of RAGE itself [16]. Thus, a vicious circle is generated triggering the inflammatory reaction and causing a general cell dysfunction.

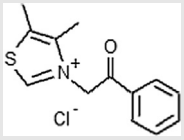
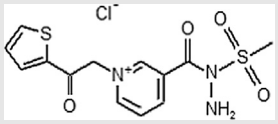
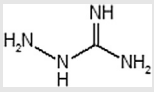
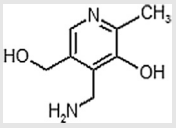
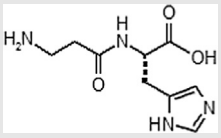
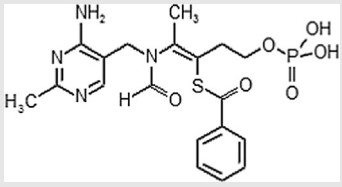
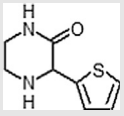
3. Effects of AGEs and RAGE

AGEs and RAGE seem to play a key role in diabetic complications [17,18]. AGEs deposit in vessels by cross-linking with extracellular proteins resulting in stiffer protein fibres and slower breakdown [19]. AGEs and RAGE amplify oxidative stress and reduce NO quantity. Additionally, AGEs cause a release of growth factors. As a result, endothelial dysfunction, fibrosis, and vessel wall proliferation occur and plaque progression is increased [5,20].

In diabetic nephropathy, cell proteins are directly glycated due to the hyperglycaemia and AGE depositions accumulate largely in the mesangium as well as in glomerular and tubular basement membrane [21]. An increased production of growth factors is mediated via the RAGE signalling cascade, which promotes glomerulosclerosis [22]. Additionally, there is an enhanced production of numerous pro-inflammatory molecules and the permeability is increased by VEGF causing hyperfiltration and albuminuria [23]. A relationship between the AGE/RAGE-axis and renin-angiotensin-aldosterone-system (RAAS) could also be established. Rats getting infusions with AGE-modified rat albumin had significantly higher values of renin, angiotensin converting enzyme (ACE) and angiotensin receptor subtype I and developed also a glomerular hypertrophy as well as a reduced glomerular filtration rate ($p < 0.05$). If those rodents received infusions of angiotensin II, the amount of the deposited renal AGEs and serum AGEs increased significantly [24]. However, the exact mechanism between AGE/RAGE-axis and RAAS has still not been elucidated. Alterations of the small vessels and tissue-specific cells can also be found in diabetic retinopathy and neuropathy. AGEs accumulate in the retinal vessel wall and upregulate VEGF promoting angiogenesis and proliferative retinopathy [25]. AGEs deposit also play a role in the pathogenesis of neuropathy. In humans, AGE accumulation was found in Schwann cells, perineurium, axoplasm and in endoneural vessels [26].

AGEs and RAGE are also important in the pathogenesis of diabetic macroangiopathies. AGE deposits could be found in atherosclerotic plaques of patients with DM [27]. Beside the general endothelial dysfunction and wall thickening, more low density lipoprotein (LDL) can be oxidized via the

Table 1 – Overview of various AGE cross-link breakers and inhibitors, their chemical structural formulas and their recent data on clinical parameters.

Active substance	Chemical structure	Clinical data
AGE cross-link breakers		
Alagebrium		Improvement of arterial compliance [35] Reduction of left ventricular mass [36]
TRC4186		Pharmacokinetic, safety & tolerability [38]
AGE inhibitors		
Aminoguanidine		Reduction of eGFR decrease and proteinuria Decrease of triglycerides Increase of HDL cholesterol Reduction of the diabetic retinopathy progression [40]
Pyridoxamine		Reduction of the change from baseline in serum creatinine [43] Improvement of eGFR [44]
Carnosine		Decrease of lens opacity Improvement of visual acuity and glare sensitivity [48]
Benfotiamine		Improvement of neuropathy scores [50,51]
Tenilsetam		Improvement of psychomotor activity, cognition and attention [53]

AGE/RAGE-axis by an increased ROS production [28]. In a follow-up study of subjects with type 1 DM, higher serum levels of AGEs were associated with a higher incidence of cardiovascular events and all-cause mortality, regardless of other risk factors [29]. In subjects with type 2 DM and coronary heart disease, Kilhovd et al. demonstrated significantly higher serum levels of AGEs compared to non-diabetic subjects [30].

AGEs and RAGE have an impact also in other diseases like cataract or Alzheimer's disease. Levels of several AGEs are higher in cataract and diabetic eye lenses than in normal human eye lenses [31]. In patients with Alzheimer's disease, RAGE is upregulated and AGEs are increasingly found together with tau proteins and amyloid-β peptides in senile plaques [32,33].

4. Therapeutic options against AGEs and RAGE

Currently, there are six therapeutic options to reduce AGEs and antagonizing RAGE available, including AGE cross-link

breakers, AGE inhibitors, RAGE antagonists, already clinically approved drugs, nutrition and phytotherapy, whereas only a few of them have been clinically evaluated. Table 1 shows an overview of various AGE cross-link breakers and AGE inhibitors.

4.1. AGE cross-link breakers

This drug class can break up cross-links between AGEs and extracellular molecules. Members of this class include thiazolium derivatives, like N-phenacylthiazolium bromide (PTB) and alagebrium or ALT-711, and pyridinium derivatives, like TRC4186 and TRC4149, acting as AGE cross-link breakers. Although the exact mechanism of the AGE cross-link breakers is not fully understood, it seems that AGE cross-link breakers break diketone compounds up [34]. So far, clinical data are only available for alagebrium and TRC4186.

Alagebrium is one of the best-known AGE cross-link breaker. In one clinical trial, it improved arterial compliance significantly ($p < 0.005$ on the 28th day, $p < 0.05$ on 56th day), but the amelioration of other parameters, like cardiac output, diastolic and systolic blood pressure, was insufficient and 90% of the subjects had a pre-existing antihypertensive therapy [35]. In another trial, alagebrium demonstrated beneficial effects on diastolic heart failure by a reduction of the left ventricular mass ($p = 0.036$) and an improvement of the diastolic filling. However, there was no significant amelioration of the aortic compliance [36]. In the study by Hartog et al. [37], however a beneficial cardiac effect was not shown. Alagebrium was well tolerated in all three studies.

Another clinically investigated AGE cross-link breaker is TRC4186. However, only a phase I trial with investigations of pharmacokinetic, safety and tolerability of TRC4186 was performed demonstrating good tolerance and safety independent of sex or age [38].

4.2. AGE inhibitors

AGE inhibitors prevent the formation of AGE cross-links or even the development of AGEs. The individual substances feature different mechanisms to act as an AGE inhibitor.

Aminoguanidine or pimagedine is a guanidine derivative acting primarily as a dicarbonyl scavenger. It reacts with carbonyls and prevents thus AGE cross-links or AGE formations [39]. The effects of aminoguanidine on diabetic nephropathy in patients with type 1 and type 2 DM were investigated by two trials (ACTION I and ACTION II) [40,41]. The ACTION II was stopped prematurely due to futility and severe side effects, like impaired liver function, influenza- and lupus-like symptoms as well as an ANCA-associated vasculitis. Similar side effects were described in the ACTION I, which was however finished. The primary end point of the ACTION I was the time to doubling in serum creatinine level, which was not significantly influenced by aminoguanidine ($p = 0.099$). Only the decrease of the estimated glomerular filtration rate (eGFR) was slower in the aminoguanidine-treated group than in the placebo-treated group ($p = 0.05$). Additionally, 150 mg aminoguanidine were more effective regarding the decline of the 24-hour total proteinuria than 300 mg aminoguanidine (mean reduction of the proteinuria in placebo group 35 mg/24 h vs. 732 mg/24 h, $p < 0.001$ in the 150 mg aminoguanidine group, vs. 329 mg/24 h, $p < 0.001$ in the 300 mg aminoguanidine group). More than 90% of the subjects in the trial had at any time during that trial an ACE inhibitor therapy. Another secondary end point of the ACTION I was the evaluation of retinopathy progression and aminoguanidine seemed to delay that progression ($p = 0.03$) which was determined by the Early Treatment of Diabetic Retinopathy Study score. Unfortunately, those retinal effects were not further investigated [40].

Pyridoxamine is an amine of vitamin B6 which acts mainly as an AGE inhibitor via chelation of metal ions catalysing processes of the Maillard reaction [42]. In a clinical trial [43], it did neither ameliorate creatinine clearance nor albuminuria, while high-dose pyridoxamine therapy (500 mg daily) reduced significantly the change in serum creatinine from baseline ($p = 0.032$). Lewis et al. [44] demonstrated a significant improvement of the eGFR in subjects with a serum creatinine concentration of <1.85 mg/dl by pyridoxamine. However, that benefit was not observed in subjects with a serum creatinine level >1.85 mg/dl. Pyridoxamine was classified as safe and tolerable in both trials.

Carnosine, a dipeptide consisting of β-alanine and histidine, inhibits AGEs via three mechanisms. It acts as an antioxidant by intercepting ROS [45], has metal chelator properties [46] and it reacts with the carbonyl group on already MG-modified proteins developing protein-carbonyl-carno sine-adducts. This process is called 'carnosinylation' and prevents further cross-linking with other glycated proteins. Moreover, these carnosine-modified AGEs cannot interact with RAGE any longer [47]. The acetylated form of carnosine, N-acetylcarnosine (NAC), was investigated in clinical trials as a potential therapeutic agent against cataract. The administration of 1%-NAC eye drops led to a significant reduction of the lens opacity, but only in 41.5% of the investigated eyes. Visual acuity and glare sensitivity were significantly improved ($p < 0.001$) compared to the control group and maintained a statistically significant level even after 24 months of treatment. Moreover, the improved visual acuity did not correlate with the objectively determined lens opacity level, and additionally, the number of participants was small [48].

Benfotiamine is a vitamin B1 derivative which activates the transketolase. Transketolase converts monosaccharides formed in the AGE, PKC and hexosamine pathway into ribulose-5-phosphate which is metabolized via the pentose phosphate pathway. Benfotiamine depletes by transketolase activation consequently more metabolites of the AGE, PKC and hexosamine pathway [49]. In clinical trials, Benfotiamine showed a significant improvement of the neuropathy which was determined by neuropathy scores and was well tolerated. On the other hand, secondary end points like tuning fork test had no significant changes and patients with an existing diabetic polyneuropathy of more than two years were excluded from the studies [50,51]. The effectiveness of benfotiamine is therefore not fully enlightened and clinical trial results for benfotiamine concerning other diabetic complications are not yet available.

Tenilsetam is an AGE inhibitor which is classified among the nootropics. Tenilsetam seems to act as a carbonyl scavenger by covalent binding to the reactive carbonyl groups

inhibiting AGE formation [52]. In the late Eighties, Saletu et al. [53] performed a clinical study with tenilsetam on Alzheimer's disease improving the psychomotor activity, cognition and attention without amelioration of psychological changes and reaction time. However, the effect of tenilsetam as an AGE inhibitor was unknown at that time. Therefore, no parameters concerning AGEs were measured and it remains unknown how strong tenilsetam affected the AGE/RAGE-axis.

4.3. *RAGE antagonists*

Because RAGE activation triggers the inflammatory reaction and causes a general cell dysfunction, there are also therapeutic concepts concerning a RAGE blockage with RAGE antagonists. Agents of this rather unknown drug class are sRAGE, RAGE antibodies and RAGE inhibitors. RAGE blockage is done by different effect mechanisms.

sRAGE consists only of the three extracellular RAGE domains and is able to bind RAGE's ligands, including AGEs, without activating the signal transduction [13]. So far, there are preclinical results for sRAGE in which sRAGE acts antiatherosclerotic. The mean atherosclerotic lesion area could be reduced by sRAGE more than fourfold compared to murine serum albumin-treated mice ($p < 0.00001$) and also the severity of the formed atherosclerotic plaques was significantly decreased. sRAGE led also to a significant reduction of the lesion area in non-diabetic mice ($p = 0.03$) [54]. However, clinical data regarding sRAGE as a therapeutic agent in diabetic patients are still missing, which applies similarly to RAGE antibodies. RAGE antibodies are monoclonal and polyclonal antibodies, mostly from immunglobin G of rabbits. These are often used as reference substances in animal models, but have not yet been used in clinical trials.

Azeliragon, also known as TTP488 or PF-04494700, and TTP4000, an immunglobulin G with a RAGE binding domain, rank among the RAGE inhibitors. Azeliragon blocks the ligand binding to RAGE while TTP4000 leads to a RAGE inactivation due to a preferred ligand binding with itself instead of RAGE [55]. Both substances are classified as antidementives investigated in Alzheimer's disease. There are no clinical data regarding TTP4000 while on-treatment analyses suggested an improvement in cognitive function with Azeliragon [56].

4.4. *Drugs with clinical approval for various indications*

There are several drugs which are already clinically approved and which affect the AGE/RAGE-axis although their primary indication is a different one. These include antidiabetic and antihypertensive drugs as well as statins. However, clinical results regarding an anti-AGE or RAGE-antagonizing effect of these drugs are recently available only for specific drug classes.

One of this drug classes are insulin sensitizers, also known as glitazones. Koyama et al. [57] discovered in pioglitazone-treated subjects a significant increase of sRAGE and endogenous secretory RAGE. However, the authors meant that the effects of pioglitazone on RAGE are not mandatory to act as an insulin-sensitizer and to restore normoglycaemia. Another antidiabetic drug class are alpha-glucosidase inhibitors like acarbose, which acts AGE-inhibiting in patients with DM and decreases AGE serum levels ($p < 0.05$) [58].

Regarding antihypertensive drugs, angiotensin receptor I antagonists and ACE inhibitors were shown to reduce the AGE content in subjects significantly [59,60]. Furthermore, an inverse correlation between plasma AGEs and plasma sRAGE ($r^2 = 0.52$, $p = 0.047$) was demonstrated in the perindopril-treated patient group. Amlodipine, a calcium channel blocker, seemed to be an inadequate inhibitor of the AGE/RAGE-axis while azelnidipine achieved better results in human subjects [61].

Statins seem to act plaque stabilizing by RAGE downregulation, reduction in AGE [18], and an increase of sRAGE. Patients with a hypercholesterolemia have lower sRAGE levels than patients with normocholesterolemia while plasma sRAGE levels in statin-treated patients with hypercholesterolemia were significantly higher in untreated subjects with hypercholesterolemia. Additionally, sRAGE levels correlate inversely with LDL levels ($r = -0.36$, $p = 0.005$) and with total cholesterol ($r = -0.326$, $p = 0.011$) [62].

Sevelamer, a phosphate binding drug, seems to have a new effect mechanism on the AGE reduction compared to the other described drugs. The AGE reduction may be achieved by blocking of the intestinal absorption of dietary AGEs [63]. In that study, sevelamer significantly decreased the levels of N(6)-carboxymethyllysine, MG, HbA_{1c} and pro-inflammatory markers. Limitations of that trial are, however, a short study period, a small number of participants and most subjects had a concomitant antidiabetic or antihypertensive therapy including drugs affecting the AGE/RAGE axis.

4.5. *Nutrition and phytotherapeutic options*

Dietary and phytotherapeutic options are an alternative way of reducing AGEs. Food products which are highly heated for a long time and rich in proteins and fats have a higher AGE content than those which are rich in carbohydrates [10]. Koschinsky et al. [64] demonstrated a proportional correlation between high-AGE diet and an increase of serum AGE levels ($r = 0.8$, $p < 0.05$). Additionally, approximately 10% of the ingested AGEs are absorbed by the intestine from which approximately two-thirds are deposited in tissues. High-AGE-diet achieved in comparison to a low-AGE-diet a 1.5-fold deterioration of the macrovascular function measured by flow-mediated dilatation and a threefold aggravation of the microvascular function measured by Laser-Doppler flowmetry. Markers of the endothelial dysfunction increased significantly at the same time due to a high-AGE diet [65]. Moreover, four-month low-AGE diet reduced the homeostasis model assessment index (5.3 ± 0.4 vs. 3.4 ± 0.6, $p = 0.023$) and improved the plasma insulin levels ($p = 0.001$) in patients with DM. However, a low-AGE diet had no significant differences on insulin resistance in healthy subjects [66].

Plants and phytopharmaceuticals with an AGE-reducing effect originated primarily from the Asiatic herbal medicine. Some are also known in Western world, for example *Panax ginseng* or *Cassia tora*. AGE-reducing substances of such plants are anthraquinones [67], saponins [68] or polyphenols [69] which have mostly been investigated in vitro or in animal studies yet.

5. Discussion

AGEs and RAGE play an important role in the pathogenesis of DM and its complications. Therapeutic options demonstrating anti-AGE and RAGE-antagonizing effects in clinical trials include AGE cross-link breakers, AGE inhibitors, RAGE antagonists, antidiabetic drugs, antihypertensive drugs, statins, sevelamer and dietary options. Almost all of those options and pharmacological substances demonstrated in preclinical studies promising results in diabetic complications. However, those results could not be reproduced or just partially in human clinical trials.

Drugs, which are already clinically approved and used in the treatment for DM like antidiabetic or antihypertensive drugs, seem to have the most promising anti-AGE and RAGE-antagonizing effect, amongst all recent therapeutic options with acceptable side effects. However, specific mechanisms are not fully elucidated yet and clinical results concerning the AGE/RAGE-axis are rare. It is most likely that the primary effects of antidiabetic drugs, statins and antihypertensive drugs are more important than the secondary effect as an AGE inhibitor or RAGE antagonist.

Nearly all recent AGE cross-link breakers, AGE inhibitors and RAGE antagonists have their weaknesses in pharmacokinetics and clinical effectiveness. Carnosine seems to be not kinetically competent to prevent a sufficient AGE formation and AGE cross-link breakers have a distinct chemical instability. Furthermore, AGE cross-link breakers can only break-up previously formed AGE cross-links, while the formation of new AGE cross-links are not prevented. Carnosine, aminoguanidine, pyridoxamine, azeliragon and alagebrium failed due to insufficient effectiveness and inconsistent results, as stated above. Results for benfotiamine in diabetic polyneuropathy are still controversial.

Clinical nutritional trials investigating anti-AGE effects are rare and preclinical phytotherapeutic results cannot necessarily be applied to the human metabolism because phytopharmaceuticals represents a multicomponent mixture of many substances with complex interactions.

Additionally, mainly AGE-modified lipids or proteins were measured in clinical trials to determine the effect of the respective therapeutic option against AGEs, whereas the effect of the respective therapeutic approach on unbound AGEs are still unclear.

Future clinical trials with these therapeutic approaches against AGEs and RAGE are necessary to evaluate the benefits of an anti-AGE and RAGE-antagonizing treatment in patients with DM. Until further convincing data are available, the most effective protection against the AGE/RAGE-axis seems to be a normoglycaemic metabolism.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Compliance with ethical standards

No animal or human studies were carried out by the authors for this article (review).

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