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Therapeutic Agents Targeting at AGE-RAGE Axis for the Treatment of Diabetes and Cardiovascular Disease: A Review of Clinical Evidence

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Abstract

Advanced Glycation End Products (AGEs), together with its receptor (RAGE) are known to play a predominant role in the onset of diabetic micro- and macrovascular diseases. Therefore, therapeutic interventions which can target AGE-RAGE axis are of great interest in diabetic therapy. Animal studies demonstrated promising results for most of the AGE-RAGE inhibitors but their actual clinical values are not fully elaborated. Therefore, this review aimed to summarize clinical findings of well-known AGE-RAGE antagonists including AGE cross-link breaker (alagebrium), dicarbonyl scavengers (aminoguanidine), antidiabetic drugs (metformin, thiazolidinediones, meglitinides, sulfonylureas and dipeptidyl peptidase 4 inhibitor), lipid-lowering drugs (statins), antihypertensive agents (angiotensin receptor blockers, angiotensin converting enzyme inhibitors and calcium channel blockers), vitamin B1 (thiamine and benfotiamine) and B6 (pyridoxine and pyridoxamine) as well as other investigational pharmacotherapy. The inhibitory mechanism of the anti-AGE-RAGE agents are also discussed. To date, most of the therapeutic interventions targeting at AGE-RAGE axis produced conflicting clinical findings. Some of the most promising agents are metformin, thiazolidinediones and statins. It is postulated that the inhibition of AGE-RAGE axis may be more beneficial at the early stage of diabetes so as to delay the progression of the associated vascular complications. Future studies should aim to identify the subsets of diabetic patients whom will be truly benefited from AGE-RAGE inhibition.

Keywords

Glycation, Maillard reaction, Nephropathy, Neuropathy, Reactive carbonyl species, Statin, Thiazolidinedione

Abbreviations

ACE: Angiotensin Converting Enzyme; ADAM10: A Disintegrin and Metalloproteinase 10; AGE: Advanced Glycation End Product; ARB: Angiotensin Receptor Blocker; CCB: Calcium Channel Blocker; CML: Carboxymethyllysine; DPP4: Dipeptidyl Peptidase 4; ECM: Extracellular Matrix; esRAGE: Endogenous Secretory Receptor for Advanced Glycation End Product; HbA1c: Glycated Haemoglobin A1c; ICAM-1: Intercellular Adhesion Molecule-1; MAPK: Mitogen-Activated Protein Kinase; NF-κB: Nuclear Factor-Kappa B; PI3K-Akt: Phosphatidylinositol-Protein Kinase B; PPAR: Peroxisome Proliferator-Activated Receptor; RAAS: Renin-Angiotensin-Aldosterone System; RAGE: Receptor for Advanced Glycation End Product; RCT: Randomized Controlled Trial; sRAGE: Soluble Receptor for Advanced Glycation End Product; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; TZD: Thiazolidinedione; VCAM-1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor

Introduction

Diabetes mellitus which is one of the most widespread chronic metabolic diseases is swiftly transforming into global health threat due to the ever-increasing prevalence of modern risks, namely high blood glucose, physical inactivity, overweight and obesity [1]. In 2014, it was estimated that about 422 million adults were diabetic, approximately 90% of which were Type 2 Diabetes Mellitus (T2DM) [2]. Diabetic vascular complications, notably the macrovascular

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diseases like atherosclerosis and microvascular diseases like retinopathy, nephropathy and neuropathy are the major contributors of morbidity and mortality in diabetes. In this context, Advanced Glycation End Products (AGE) and the interaction with the Receptor for AGE (RAGE) has been long recognized to be one of the key pathological pathways driving the progression of diabetes and the associated vascular complications.

AGEs are irreversibly generated from the non-enzymatic glycation of reducing sugars to amino groups in proteins or lipids, followed by a series of rearrangements or oxidation reactions [3]. This process, which is known as the Maillard reaction, is concentration-dependent since the circulating AGE level is significantly higher in diabetic patients [4]. Along with the elevation of AGE, many reactive intermediates such as glyoxal, methylglyoxal and 3-deoxyglucosone which are collectively known as α-oxoaldehydes or dicarbonyls, are also increased [5]. These dicarbonyl compounds can be derived from polyol pathway [6], degradation of protein glycation intermediates [7] or lipid peroxidation and oxidative stress [8]. Under high carbonyl stress, these dicarbonyls act as the AGE precursors and promote the formation and accumulation of AGEs [9].

The detrimental effects of AGEs have been summarized comprehensively in several reviews [10,11]. Two major mechanisms are implicated: (1) The formation of cross-linked products between AGEs in basement membrane of Extracellular Matrix (ECM); and (2) Ligand binding of AGEs to RAGE which triggers downstream cellular signaling. The former mechanism modifies the properties of structural proteins like collagen, vitronectin and laminin which subsequently, weakens the integrity of vascular structure and leads to vascular stiffening [12] and myocardial dysfunction [13]. The AGE-RAGE interaction, on the other hand, triggers the activation of various signaling cascades, resulting in functional changes in terms of proinflammatory response, programmed cell death, migration and proliferation [14]. AGE-mediated RAGE activation also triggers a positive feed forward loop, in which RAGE signaling activates NF-κB which further upregulates RAGE expression [15]. This self-perpetuating cycle intensifies the pathological progression of diabetic vascular diseases.

Considering the deleterious effects of AGEs, on-going investigations are being carried out to identify compounds that can inhibit the AGE-RAGE axis. Some of these AGE-RAGE inhibitors were tested in human clinical trials to examine their therapeutic effects on diabetes and diabetes-associated complications. Thus, the primary aim of this review was to outline the current clinical evidence of therapeutic drugs on AGE-RAGE

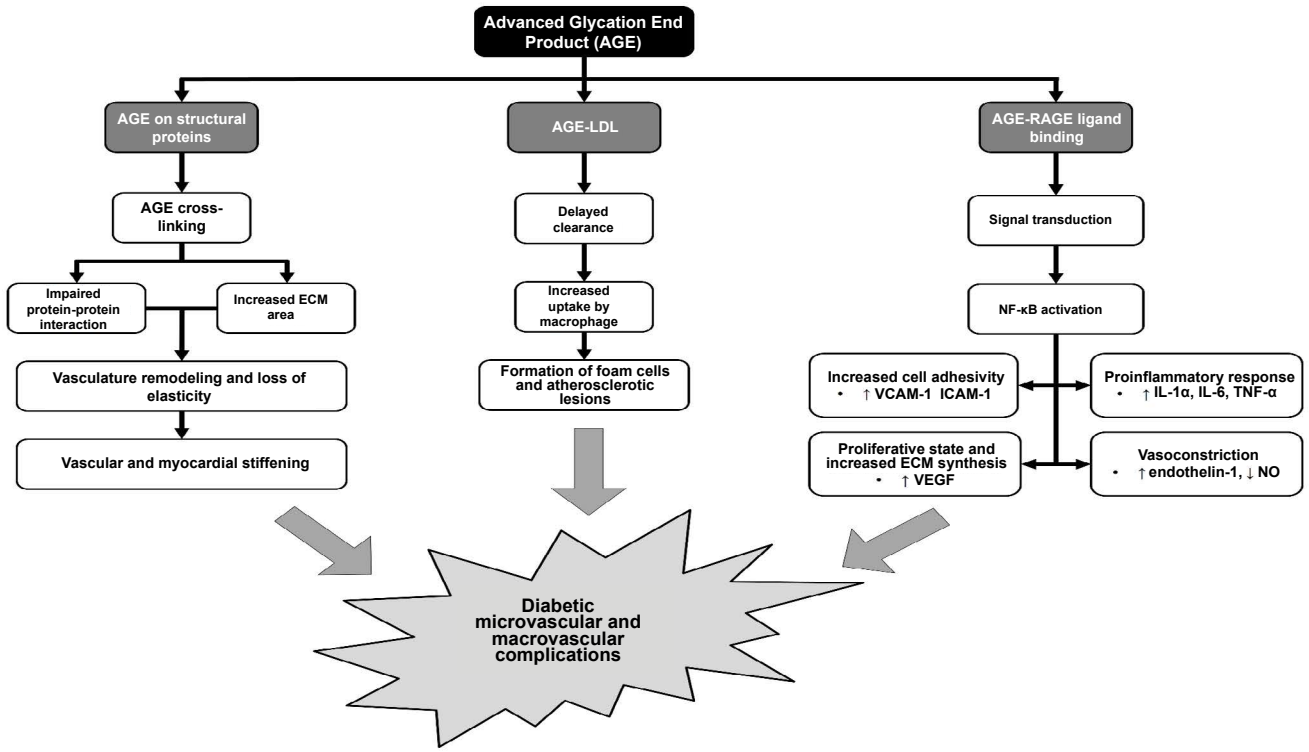

Figure 1: A summary of intra- and extracellular pathological effects associated to advanced glycation end products and its receptor which ultimately lead to the progression of micro- and macrovascular complications in diabetes mellitus.

AGE: Advanced Glycation End Products; AGE-LDL: AGE-Low-Density Lipoprotein; ECM: Extracellular Matrix; ICAM-1: Intercellular Adhesion Molecule-1; IL-1α: Interleukin-1α; IL-6: Interleukin-6; NF-κB: Nuclear Factor κB; NO: Nitric Oxide; TNF-α: Tumor Necrosis Factor-α; VCAM-1: Vascular Cell Adhesion Molecule-1; VEGF: Vascular Endothelial Growth Factor.

axis intervention with a major focus on diabetes-related health conditions. The putative mechanisms of action of the experimental drugs on the glycation pathway are also discussed.

Pathological Roles of AGE-RAGE Axis in Diabetic Vascular Complications

As mentioned previously, AGE and RAGE can induce both intra- and extracellular pathological changes which collectively, contribute to the development of endothelial damage, vasculature modification, proatherogenic and proinflammatory processes. Consequently, the cardiovascular function is tremendously jeopardized, resulting in vascular complications commonly seen in diabetic patients. The intra- and extracellular pathogenesis of AGE-RAGE axis is illustrated in Figure 1.

Generally, the extracellular effects of AGE accumulation are largely receptor-independent, but some of which can be aggravated by the activation of RAGE. Under physiological conditions, AGE accumulation is a normal aging process [16], but in diabetic patients, the process takes place at an accelerated pace. Non-enzymatic glycation can occur to virtually all proteins, lipids and nucleic acids, the last of which is less well-understood in diabetes mellitus. However, recent studies do suggest potential implication of glycated DNA in diabetic patients [17,18].

On the other hand, the impacts of protein glycation is extensively studied. AGE formation on the serum albumin can affect their drug binding capacity [19] and ability to induce platelet aggregation [20]. Furthermore, preliminary studies of glycated immunoglobulins revealed significant conformational alteration and loss of antibody-antigen interaction [21,22]. AGE aggregation is more prominent in structural proteins due to their slow turnover rate. These proteins, namely collagen, vitronectin and laminin, are responsible for the formation of basement membrane in the ECM. Increased AGE accumulation can modify the structural properties of the large matrix formed by these proteins via AGE-AGE interaction, or cross-linking [23]. These cross-links on the structural proteins increase the area of ECM [24] and hinder protein-protein interaction [25,26] which subsequently reduce their elasticity, leading to vascular and myocardial stiffening in diabetes and aging [27]. Moreover, AGE formation on Low-Density Lipoproteins (AGE-LDL) significantly impedes their clearance [28] and enhances their likelihood to be taken up by macrophages [29]. This promotes the formation of foam cells and atherosclerotic lesions, eliciting increased risk of atherosclerosis in diabetic patients.

Intracellularly, upon AGE-RAGE ligand binding, a series of signal transduction pathways are activated, among which are Mitogen-Activated Protein Kinase (MAPK), $p21^{ras}$, Src kinase, JAK-STAT, protein kinase C and phosphatidylinositol-protein kinase B (PI3K-Akt) pathways [14]. These signaling cascades modify the cellular response to apoptosis, autophagy, proliferation, motility and inflammation. One of the key proinflammatory transcription factors, Nuclear Factor-Kappa B (NF-κB) is also activated. The activated transcription factor will translocate into the nucleus to upregulate the expression of various downstream target genes. In the endothelial cells, RAGE-induced NF-κB activation promotes cell-cell and cell-ECM adhesion via the overexpression of Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) respectively [30,31]. When coupled with NF-κB-dependent overexpression of Vascular Endothelial Growth Factor (VEGF) which facilitates ECM thickening, the increased vascular adhesiveness greatly enhances leucocyte retention, infiltration and activation [32]. RAGE activation also mediates proinflammatory response via the release of cytokines like interleukins and tumor necrosis factor α [33]. Such a RAGE- and NF-κB-induced proliferative and inflammatory state leads to substantial vascular remodeling and chronic vascular insult, both of which act as the key pathology to the onset of atherosclerosis and endothelial failure in diabetic microvascular complications [34-36].

RAGE activation also plays a role in vasoconstriction by stimulating the overexpression of a potent vasoconstrictor, endothelin-1 [37]. Furthermore, AGE aggregation has been shown to impair the biosynthesis of nitric oxide which is a crucial vasodilator. The inhibitory effect on nitric oxide bioavailability is caused by transcriptional suppression and direct inhibition of endothelial nitric oxide synthase [38,39]. The cumulative effect of reduced nitric oxide and elevated endothelin-1 impairs the blood perfusion considerably, resulting in a hypoxic state and progressive ischaemic injury to the peripheral tissues [40-42] (Figure 1).

Therapeutic Agents Targeting at AGE-RAGE Axis

AGE cross-link breaker and dicarbonyl scavenger

Some of the most extensively studied pharmacological interventions acting on AGE-RAGE axis are dicarbonyl scavengers (aminoguanidine) and AGE cross-link breaker (alagebrium). The clinical efficacy of these compounds are summarized in Table 1.

Aminoguanidine (or pimagedine) is an investigational drug that inhibits AGE formation by scavenging AGE precursors. It has two crucial functional groups, namely a nucleophilic hydrazine and a guanidino groups, both of which facilitate irreversible interaction with dicarbonyls, especially glyoxal, methyglyoxal and 3-deoxyglucosone [43]. Such a scavenging effect of aminoguanidine

Table 1: Clinical findings of the effectiveness of aminoguanidine and alagebrium on AGE-RAGE axis.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Aminoguanidine	Double-blind RCT	T2DM, proteinuria (n = 599) • Placebo (n = 194) • 50-300 mg aminoguanidine (n = 207) • 100-600 mg aminoguanidine (n = 198)	Planned to be 2 years	• Terminated early due to low benefit-to-risk ratio of the drug.	[47]
Aminoguanidine	Double-blind RCT	T1DM, nephropathy, retinopathy (n = 690) • Placebo (n = 236) • 150 mg aminoguanidine (n = 229) • 300 mg aminoguanidine (n = 225)	2 to 4 years	• No significant difference between groups in the progress of serum creatinine doubling. • Aminoguanidine slowed down decrease in estimated glomerular filtration rate and reduced total urinary proteinuria compared to placebo.	[46]
Alagebrium	Single-arm study	Elderly, diastolic heart failure (n = 23) • 420 mg alagebrium	16 weeks	• Alagebrium reduced left ventricle mass and improved diastolic filling without changing blood pressure, peak exercise oxygen consumption and aortic distensibility.	[55]
Alagebrium	Single-arm study	Systolic hypertension (n = 13) • 420 mg alagebrium	8 weeks	• Alagebrium improved arterial stiffness and endothelial function.	[56]
Alagebrium	Double-blind RCT	Hypertension, vascular stiffening (n = 93) • Placebo (n = 31) • 210 mg alagebrium (n = 62)	56 days	• Alagebrium reduced pulse pressure and improved arterial compliance compared to placebo.	[50]
Alagebrium	Double-blind RCT	Heart failure (n = 102) • Placebo (n = 52) • 400 mg alagebrium (n = 50)	36 weeks	• Alagebrium did not result in beneficial effect in exercise tolerance, diastolic function, systolic function and AGE accumulation.	[52]
Alagebrium	Factorial design, RCT	Physically inactive, elderly (n = 48) • Placebo and exercise (n = 12) • Placebo without exercise (n = 12) • 200 mg alagebrium and exercise (n = 12) • 200 mg alagebrium without exercise (n = 12)	1 year	• Alagebrium did not improve vascular function and arterial stiffness.	[53]
Alagebrium	Factorial design, RCT	Physically inactive, elderly (n = 62) • Placebo and exercise • Placebo without exercise • 200 mg alagebrium and exercise • 200 mg alagebrium without exercise	1 year	• Alagebrium alone improved left ventricle stiffness but did not affect left ventricle mass and end-diastolic volume.	[51]
Alagebrium	Factorial design, RCT	Physically inactive, elderly (n = 62) • Placebo and exercise • Placebo without exercise • 200 mg alagebrium and exercise • 200 mg alagebrium without exercise	1 year	• Alagebrium alone or in combination with exercise did not improve left ventricular function, stroke index and effective arterial elastance.	[54]

AGE: Advanced Glycation End Product; RCT: Randomised Controlled Trial; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.

has been demonstrated to rescue diabetic nephropathy in diabetic animal models via the reduction of albuminuria and renal vascular injury [44,45].

Nonetheless, a randomized controlled clinical trial (ACTION I) which involved 690 patients with Type 1 Diabetes Mellitus (T1DM) failed to establish beneficial effects of aminoguanidine on diabetic nephropathy as there was no significant delay in serum creatinine doubling time between treated and untreated individuals [46]. Aminoguanidine regimen did however, slow down the deterioration of glomerular filtration rate and reduce total urinary proteinuria [46]. Another similar trial, ACTION II, which was designed to study the effects of aminoguanidine on diabetic renal complications among the patients with type 2 diabetes mellitus, was subjected to early termination due to safety issues and low efficacy of the drug [47].

The use of aminoguanidine is associated side effects like autoantibody generation, anemia, flu-like symptoms and very rarely, crescentic glomerulonephritis [46]. These could be linked to other biological functions of aminoguanidine. Essentially, aside from being a dicarbonyl scavenger, aminoguanidine is also a potent inhibitor of inducible nitric oxide synthase and diamine oxidase as well as a strong scavenger for multiple metabolites including pyridoxal phosphate, pyruvate and glucose [43,48]. Flu-like symptoms may be attributable to histamine intolerance caused by the inhibitory effect on diamine oxidase. On the other hand, since aminoguanidine is a hydrazine derivative, this may trigger the induction of autoimmunity which contributes to the onset of glomerulonephritis [49]. In light of these adverse effects, the clinical use of aminoguanidine may not be feasible. In fact, the development of aminoguanidine as a therapy for diabetic neuropathy has been halted due to the aforementioned toxicity.

As for the AGE cross-link breaker, alagebrium, Randomized Controlled Trials (RCTs) has yielded mixed results on its efficacy. Treatment with alagebrium (200-210 mg) could reduce arterial and left ventricular stiffness [50,51], but failed to confer beneficial effect on overall cardiovascular health [52-54]. Two smaller and single-arm studies showed that the therapeutic effects of alagebrium on cardiovascular function were more prominent at much higher dosage (420 mg) [55,56]. Based on these findings, treatment with alagebrium seems to provide certain mechanical improvements to the heart and major blood vessels. This is linked to its selective AGE cross-links cleavage properties, which attenuates AGE accumulation and reduces existing AGE cross-links in the vascular wall and myocardium [57]. As a result, the reduction of AGE cross-links helps to restore vascular and ventricular elasticity. Nevertheless, the overall cardiovascular fitness remained largely unaffected by alagebrium. It is not unusual given that diabetes- or ageing-related cardiovascular disease is a multifactorial disease. This also suggests that the clinical role of AGE cross-link breaker should be adjunctive rather than primary.

Unlike aminoguanidine, there is no serious adverse effect associated with alagebrium. Another AGE cross-link breaker, TRC4186 which has undergone phase I clinical study, was also reported to be safe and well-tolerated in human subjects [58]. Unfortunately, like aminoguanidine, the development of alagebrium has been discontinued after the company incharge stopped their operation. Likewise, there is no further update about TRC4186 despite the completion of phase II clinical trial in diabetic patients with stable heart failure (Table 1).

Anti-hyperglycaemic medications

Many classes of antidiabetic drugs such as biguanides, Thiazolidinediones (TZDs), meglitinides, sulfonylureas and Dipeptidyl Peptidase 4 (DPP4) inhibitor, have been tested clinically for their inhibitory effects on AGE-RAGE axis (Table 2). All of them have demonstrated a promising AGE-lowering effect. This is plausible as the reduction of glucose level favors the reverse reaction of glycation and hence, lowering the formation and aggregation of AGEs. However, it is postulated that some of these drugs may suppress the AGE-RAGE axis independent of their glucose-lowering properties.

Considering the structural similarity to aminoguanidine, metformin is also thought to serve as a dicarbonyl scavenger apart from its insulin-sensitizing effect. Indeed, metforrmin is capable of reducing methylglyoxal *in vitro* [59] and in T2DM patients [60]. The combined effect of the two bioactivities may contribute to the significant decline in circulating AGE level [61,62]. Nevertheless, compared to other glucose-lowering drugs like pioglitazone and repaglinide, metformin did not perform better in reducing AGEs [63,64]. This implies that the glycaemic control plays a more predominant role than dicarbonyl scavenging in AGE-RAGE axis inhibition. Aside from AGE-lowering effect, treatment with metformin also restored antioxidant capacity of the serum, reduced proinflammatory biomarkers and enhanced nitric oxide level [63,64]. Hence, metformin may be an attractive candidate for further study about AGE-RAGE inhibition and diabetic vascular complications.

Another anti-diabetic agent which has been rigorously tested is TZD. Fundamentally, TZDs like pioglitazone and rosiglitazone are Peroxisome Proliferator Activated Receptor (PPAR) agonist, with the highest preference for PPARγ isoform [65]. Studies revealed that the activation of PPARγ effectively down regulates the RAGE

Table 2: Clinical findings of the effectiveness of glucose-lowering medications on AGE-RAGE axis.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Metformin (Biguanides)	Observational	T2DM (n = 57) • Non-metformin (n = 27) • 500-2500 mg metformin (n = 30)	≥ 3 months	• High-dose (1500-2500 mg) metformin reduced plasma methylglyoxal compared to low-dose (≤ 1000 mg) and non-metformin treatment. • Detoxified methylglyoxal, D-lactate level increased with metformin treatment.	[60]
Metformin	RCT	T2DM (n = 99) • Lifestyle modification (n = 49) • 1000 mg metformin (n = 50)	3 months	• Metformin reduced AOPP, AGE and increased FRAP. • No difference in LCAT and PON.	[62]
Metformin	Double-blind RCT	T2DM (n = 208) • Placebo (n = 98) • 850-2000 mg metformin (n = 110)	24 weeks	• Metformin reduced ROS, AGEs and pentosidine, increased total thiol and NO levels, restored CRP, improved ATPase activity without affecting calcium and magnesium levels.	[61]
Metformin Pioglitazone (TZD)	RCT	T2DM (n = 129) • No medication (n = 49) • 30 mg pioglitazone (n = 30) • 1000 mg metformin (n = 50)	3 months	• Metformin increased FRAP. • Pioglitazone significantly restored LCAT and LPL enzymatic activity. • Both metformin and pioglitazone were equally effective at reducing AGE and AOPP.	[64]
Metformin Repaglinide (meglitinide)	Double-blind crossover study	T2DM (n = 96) • 6 mg repaglinide • 2 g metformin	4 months for each drug and 1 month washout	• Metformin reduced pro-inflammatory markers like TNF-α, plasminogen activator inhibitor-1 antigen, tissue-type plasminogen activator antigen, von Willebrand factor, soluble intercellular adhesion molecule-1 and soluble E-selectin. • Repaglinide reduced heart rate and Amadori products. • Both drugs had similar effects on IL-6, fibrinogen, VCAM-1, asymmetric dimethylarginine, AGEs and glycaemic level.	[63]
Pioglitazone Rosiglitazone (TZDs)	RCT	T2DM (n = 60) • Placebo (n = 21) • 30 mg pioglitazone (n = 19) • 4 mg rosiglitazone (n = 20)	12 weeks	• Pioglitazone increased sRAGE more significantly compared to other treatments.	[69]
Rosiglitazone (TZD) Glibenclamide/ Gliclazide (sulfonylurea)	Randomised, parallel group study	T2DM (n = 64) • 5 mg glibenclamide/80 mg gliclazide (n = 32) • 4 mg rosiglitazone (n = 32)	24 weeks	• Rosiglitazone or sulfonylurea reduced HbA1c, fasting glucose and AGE. • Only rosiglitazone increased sRAGE and esRAGE.	[68]
Pioglitazone (TZD) Glimepiride (sulfonylurea)	Randomised, parallel group study	T2DM (n = 57) • 15-30 mg pioglitazone (n = 27) • 0.5-2 mg glimepiride (n = 30)	24 weeks	• Pioglitazone led to higher increase in circulating plasma esRAGE and sRAGE. • Suppression of RAGE expression in mononuclear cells was more significant in pioglitazone-treated groups.	[75]

Alogliptin (DPP4 inhibitor)	Single-arm study	T2DM (n = 61) • 25 mg alogliptin	12 weeks	• Alogliptin reduced fasting glucose, glycoalbumin, HbA1c, sRAGE and urine albumin-to-creatinine ratio. • AGE level was reduced only in patients with high AGE level.	[74]

AGE: Advanced Glycation End Product; AOPP: Advanced Oxidation Protein Products; CRP: C-Reactive Protein; DPP4: Dipeptidyl Peptidase-4; esRAGE: Endogenous Secretory Receptor for Advanced Glycation End Product; FRAP: Ferric Reducing Antioxidant Power; IL-6: Interleukin-6; LCAT: Lecithin-Cholesterol Acyltransferase; LPL: Lipoprotein Lipase; NO: Nitric Oxide; PON: Paraoxonase; RCT: Randomised Controlled Trial; ROS: Reactive Oxygen Species; sRAGE: Soluble Receptor For Advanced Glycation End Product; T2DM: Type 2 Diabetes Mellitus; TNF-α: Tumour Necrosis Factor-α; TZD: Thiazolidinedione; VCAM-1: Vascular Cell Adhesion Molecule-1.

expression in the endothelial tissues [66,67]. This can further diminish NF-κB activation which helps to inhibit many downstream implications such as prothrombotic and proinflammatory responses of the blood vessels [3]. Two clinical trials reported significant increase in soluble RAGE (sRAGE) level with the treatment of rosiglitazone [68] and pioglitazone, in which the sRAGE-inducing effect of the latter was more prominent and rapid [69].

Principally, sRAGE originates from two sources, namely the proteolysis cleavage from membrane-bound RAGE [70] and the alternative splice variant of RAGE which is also known as endogenous secretory RAGE (esRAGE) [71]. Compared to the full-length RAGE isoform, sRAGE does not have the transmembrane and cytoplasmic signaling domains. As a result, ligand binding to sRAGE is unable to trigger signaling cascades. Such a distinctive feature makes sRAGE an effective decoy and competitive inhibitor of its membrane-bound counterpart which allows sRAGE to scavenge circulating AGEs, facilitate AGE detoxification and attenuate the pathological processes induced by RAGE activation [72]. Moreover, in T2DM patients, sRAGE was negatively correlated to RAGE expression, strongly indicative of a beneficial role of sRAGE in modulating AGE-RAGE axis [73]. Therefore, even though how exactly TZDs increase circulating sRAGE is largely unclear, such a bioactivity may mediate AGE disposal and suppress RAGE activation.

Despite the promising AGE-RAGE inhibitory effect of TZD, it is important to highlight that the sample size of the clinical trials was too small to draw a conclusive remark about its efficacy. Larger trials are therefore, warranted to fully elucidate the clinical prospect of TZDs in targeting AGE-RAGE axis. In addition to metformin and TZDs, the effects of repaglinide (meglitinide), glimepiride (sulfonylurea) and alogliptin (DPP4 inhibitor) on AGE-RAGE axis have also been examined [63,74,75]. Their AGE-lowering effect was encouraging and comparable to metformin and TZDs. However, the studies are also limited by their small sample sizes. In short, anti-hyperglycaemic drugs are potent AGE inhibitors in concordance to their glucose-lowering effects. Future studies are indispensable and should emphasize on their effectiveness on delaying the progression of diabetic micro- and macrovascular complications (Table 2).

Lipid-lowering drugs

Statins, notably atorvastatin, simvastatin, pravastatin and pitavastatin have been consistently found to inhibit AGE-RAGE axis. Briefly, HMG-CoA reductase inhibitor or so-called statin is one of the most commonly prescribed lipid-lowering medications for patients with hypercholesterolaemia due to its high efficiency to block conversion of HMG-CoA to mevalonic acid in cholesterol biosynthesis [76]. Recent trials (Table 3) ubiquitously reported a decline in circulating AGE level or elevation of sRAGE level following statin treatment [77-81]. AGE formation and RAGE expression in atherosclerotic plaques were also suppressed by simvastatin regimen [82].

The AGE-lowering effect by statins seems to be independent of glycaemic control because the glucose level and glycated Haemoglobin (HbA_{1c}) remained unchanged by statins in the studies outlined in Table 3. It is hypothesized that statins may induce RAGE shedding to facilitate increased sRAGE and AGE disposal [83]. Indeed, the results showed that statin stimulated proteolytic cleavage of membrane-bound RAGE by a disintegrin and metalloproteinase 10 (ADAM10) to yield sRAGE and this mechanism was proved to be strictly caused by cholesterol biosynthesis attenuation instead of isoprenylation inhibition [83]. Statin-induced RAGE shedding is not entirely a novel mechanism. Previous studies have pointed out that cellular cholesterol depletion can trigger ADAM10-facilitated shedding of interleukin-6 receptor [84], soluble amyloid precursor protein [85] and CD44 [86]. Proteolytic cleavage of these membrane-bound proteins correlates the roles of cellular cholesterol to inflammatory response, Alzheimer's disease prevention and suppression of tumor migration respectively. In this context, long term statin therapy may lead to cellular cholesterol depletion which in turn, promotes RAGE proteolytic shedding, although exact pathway remains uncertain. Consequently, circulating sRAGE level increases to scavenge AGEs and attenuate RAGE-mediated downstream signaling.

Table 3: Clinical studies of AGE-RAGE inhibitory effects of lipid-lowering drugs.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Atorvastatin	RCT	T2DM, hypercholesterolaemia (n = 25) • Diet therapy (n = 31) • 10 mg atorvastatin (n = 62)	4 weeks	• Atorvastatin significantly reduced AGE level, total cholesterol, LDL and triglycerides compared to diet control.	[77]
Atorvastatin	Single-arm	NASH, dyslipidaemia (n = 43) • 10 mg atorvastatin	12 months	• AGE levels were reduced, NAFLD activity was improved and serum glucose levels remained unchanged.	[79]
Atorvastatin	Double-blind RCT	T2DM, hypercholesterolaemia (n = 80) • Placebo (n = 41) • 10-20 mg atorvastatin (n = 39)	6 months	• Atorvastatin elevated serum esRAGE, but not sRAGE in comparison to placebo.	[80]
Atorvastatin	RCT	Acute myocardial infarction (n = 190) • 40 mg atorvastatin as loading dose, followed by 10 mg as maintenance dose prior to PCI (n = 98) • PCI only (n = 92)	30 days	• Atorvastatin improved left ventricular ejection fraction at 6 months post-infarction. • Atorvastatin lowered angiopoietin-like protein 2 and glyceraldehyde-derived AGEs 2 week post-infarction.	[96]
Atorvastatin Pravastatin	Single-arm	Hypercholesterolaemia (n = 20) • 20 mg atorvastatin/40 mg pravastatin	8 weeks	• Both statins reduced urinary 8-iso-PGF2α while only atorvastatin elevated sRAGE. • No significant change in ADMA levels for both statins.	[78]
Atorvastatin Pitavastatin	Single-arm	Acute coronary syndrome (n = 208) • 4 mg pitavastatin/20 mg atorvastatin	8-12 months	• Both statins significantly decreased AGE level without changing sRAGE.	[81]
Pravastatin Pitavastatin	Randomised, parallel group study	Angina pectoris, post PCI (n = 91) • 4 mg pitavastatin (n = 46) • 20 mg pravastatin (n = 45)	8 months	• Both statins did not affect circulating AGE level. • Both statins elevated sRAGE level which was negatively correlated with external elastic membrane volume and plaque volume.	[97]
Simvastatin	RCT	T2DM, asymptomatic carotid artery stenosis (n = 70) • AHA step I diet (n = 35) • AHA step I diet and 40 mg simvastatin (n = 35)	4 months	• Simvastatin reduced MPO, AGEs, RAGE, p65, COX-2, mPGES-1, MMP-2, MMP-9, lipids, oxLDL, gelatinolytic activity, macrophages, T-lymphocytes and HLA-DR + while increased procollagen 1 and collagen in plaques.	[82]

8-iso-$PGF_{2\alpha}$: 8-iso Prostaglandin $F_{2\alpha}$; ADMA: Asymmetric Dimethylarginine; AGE: Advanced Glycation End Product; AHA: American Heart Association; COX-2: Cyclooxygenase-2; esRAGE: Endogenous Secretory Receptor For Advanced Glycation End Product; LDL: Low Density Lipoprotein; MMP-2: Matrix Metalloproteinase-2; MMP-9: Matrix Metalloproteinase-9; mPGES-1: Membrane-Associated Prostaglandin E2 Synthase-1; MPO: Myeloperoxidase; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; oxLDL: Oxidised Low Density Lipoprotein; PCI: Percutaneous Coronary Intervention; RAGE: Receptor for Advanced Glycation End Product; RCT: Randomised Controlled Trial; sRAGE: Soluble Receptor for Advanced Glycation End Product; T2DM: Type 2 Diabetes Mellitus.

It is widely acknowledged that oxidative stress plays a critical role in the formation of advanced glycoxidation and lipoxidation end products [87]. In this context, statins also possesses antioxidant properties. It has been demonstrated that statin can inhibit superoxide generation from NADPH oxidase via the transcriptional suppression of NADPH oxidase subunits and blockade of NADPH oxidase activation [88-90]. Furthermore, treatment with statins could also alleviate AGE-induced cellular signaling pathways like NF-κB and MAPK which resulted in reduced reactive oxygen species production [91]. As a result, the reduced oxidative stress may inhibit AGE formation and RAGE-mediated proinflammatory signaling, which contribute to the beneficial effects observed in clinical studies.

As opposed to statins, the effect of fibrates (another class lipid-lowering drug) on AGE-RAGE axis is poorly under-

stood. Thus far, no clinical evidence is available. *In vitro* and *in vivo* studies on this aspect is also limited. However, fibrates have been demonstrated to attenuate AGE-induced NF-κB activation in glomerular microvascular endothelial cells [92]. Such an inhibitory on NF-κB activation was also found in atherosclerosis-prone, diabetic mice, but whether or not the effect was AGE-dependent is unclear [93]. Nevertheless, two recent randomized controlled trials (ACCORD Eye study and FIELD study) unraveled the promising therapeutic effect of fibrates on diabetic retinopathy although the underlying mechanism remains unclear [94,95]. These exciting clinical findings justify future investigations of fibrates on AGE-RAGE axis.

Table 4: Clinical studies of AGE-RAGE inhibitory effects of anti-hypertensive drugs.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Eprosartan (ARB)	Randomised, parallel group study	Hypertension, diastolic dysfunction (n = 97) • 600 mg eprosartan (n = 47) • Other hypertensive drugs (n = 50)	6 months	• No beneficial treatment effect was detected in CML, CEL and pentosidine levels.	[104]
Irbesartan (ARB)	Double-blind RCT	T2DM, microalbuminuria (n = 264) • Placebo (n = 125) • 300 mg irbesartan (n = 139)	2 years	• No beneficial treatment effect was detected in CML and CEL.	[103]
Valsartan (ARB)	Single-arm	T2DM, hypertension (n = 15) • 40 mg valsartan	6 months	• AGE level and urine microalbumin level were decreased but oxidative markers remained unchanged.	[101]
Valsartan (ARB)	Single-arm	T2DM, microalbuminuria, hypertension (n = 12) • 80-160 mg valsartan	6 months	• Plasma and urinary pentosidine, CML and 15-F2t-isoprostanes were reduced. • Plasma and urinary malondialdehyde was unchanged.	[99]
Olmesartan (ARB) Telmisartan (ARB)	Randomised, parallel group study	Hypertensive, on dialysis (n = 24) • 20 mg olmesartan (n = 12) • 40 mg telmisartan (n = 12)	24 weeks	• Olmesartan decreased systolic blood pressure, pentosidine and CML compared to telmisartan.	[100]
Ramipril (ACE inhibitor)	Nonrandomised, parallel group study	Non-diabetic nephropathy (n = 19) • 2.5-5 mg ramipril (n = 12) • Other anti-hypertensive drugs (n = 7)	2 months	• AGE fluorescence, AOPP decreased and malondialdehyde by ramipril therapy but CML remained unchanged.	[118]
Irbesartan (ARB) Amlodipine (CCB)	Double-blind RCT	T2DM, nephropathy (n = 196) • Placebo (n = 70) • 300 mg irbesartan (n = 65) • 10 mg amlodipine (n = 61)	2 years	• No beneficial treatment effect was detected in pentosidine and CML levels for ARB and CCB.	[102]
Azelnidipine (CCB) Amlodipine (CCB)	Randomised, parallel group study	Non-diabetic chronic kidney disease (n = 30) • 16 mg azelnidipine (n = 15) • 5 mg amlodipine (n = 15)	6 months	• Azeldipine decreased AGE, sRAGE, proteinuria and urinary levels of liver-type fatty acid binding protein but not amlodipine.	[120]
Nifedipine-Telmisartan combined therapy	Single-arm	Hypertensive, microalbuminuria (n = 262) • 20 mg nifedipine-80 mg telmisartan combined therapy	24 weeks	• Significant increase in plasma sRAGE was observed.	[121]

ACE: Angiotensin Converting Enzyme; AGE: Advanced Glycation End Product; AOPP: Advanced Oxidation Protein Product; ARB: Angiotension II Receptor Blocker; CCB: Calcium Channel Block; CEL: Carboxyethyllysine; CML: Carboxymethyllysine; RCT: Randomised Controlled Trial; sRAGE: Soluble Receptor for Advanced Glycation End Product; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus.

As such, our knowledge about the effect of fibrates on the glycation pathway is lacking, but recent clinical studies may suggest possible therapeutic effects. Conversely, statins are well-studied and have a huge potential to be AGE-lowering agents. The RAGE shedding mechanism is also unique to HMG-CoA reductase inhibitors. Clinically, statins are known to associate with very few side effects. Hence, all these favorable features make statins a practical and excellent choice to be developed as a therapeutic intervention targeting AGE-RAGE axis in diabetic vasculopathy (Table 3).

Anti-hypertensive agents

Table 4 summarizes clinical studies on AGE-inhibiting effects of anti-hypertensive drugs of different pharmacological classes like Angiotensin Receptor Blockers (ARBs), Angiotensin Converting Enzyme (ACE) inhibitors and Calcium Channel Blockers (CCBs). Among the three classes, ARBs are the most extensively studied drugs on AGE-RAGE axis. Basically, angiotensin II receptors play an integral role in Renin-Angiotensin-Aldosterone System (RAAS), a hormone system that regulates blood pressure, electrolyte and water balance. Blocking the receptor results in vasodilation, reduction in aldosterone and catecholamine secretion as well as reduced water reabsorption which collectively lower blood pressure [98].

Regarding the inhibitory effect of ARBs on AGE-RAGE axis, clinical trials produced mixed results. Small and short (6 months) trials indicated that Carboxylmethyllysine (CML) and pentosidine were significantly reduced in hypertensive patients by valsartan and olmesartan [99,100]. This is further supported by another single-arm study which reported decreased serum AGEs after valsartan therapy in Japanese T2DM patients with hypertension [101]. In contrast, larger RCTs with longer follow-up duration (2 to 4 years) concluded that treatment with ARBs did not lower AGEs and other AGE adducts like CML and pentosidine [102-104]. Nonetheless, ARBs could efficaciously delayed kidney failure progression [105,106], reduced the severity and risk of retinopathy in diabetic patients [107,108]. These findings support the use of ARBs for the management and prevention of diabetic vascular complications.

Various mechanisms have been proposed to explain ARB-facilitated AGE reduction. It is speculated that ARBs are potential PPARγ agonist that can exert glycaemic control and AGE-lowering effect similar to TZDs [109]. However, this is somewhat unlikely because ARB therapy has no apparent effect on fasting blood glucose and HbA_{1c} level [101,110]. Another putative mechanism is by the restoration of glyoxalase-I activity. Basically, glyoxalase-I is a key enzyme in the detoxification of AGE precursors, namely glyoxal, methylglyoxal and 3-deoxyglucosone [111]. Candesartan was capable of rescuing glyoxalase-I mRNA expression and activity which were otherwise, impaired by angiotensin II [112]. Overexpression of glyoxalase I has been shown to cause a markedly low intracellular AGE level, suggesting that ARBs could promote detoxification of AGE precursors which reduces AGE accumulation [113]. Additionally, ARBs may also possess transition metal chelating ability which allows them to cease a number of oxidative reactions involved in the glycation pathway and dicarbonyl generation [114]. Collectively, these mechanisms could contribute to the AGE-lowering effect following ARB therapy.

Apart from AGE-lowering effect, ARB-treated diabetic patients showed decent improvements in various inflammatory and oxidative stress markers, namely, high-sensitive C-reactive protein, interleukins-6 and -18 [110,115]. This suggests possible inhibition of RAGE-associated cellular signaling as evidenced by the suppression of RAGE activation upon ARB treatment [116,117]. To date, the evidence about the inhibitory activity of ARBs on AGE-RAGE axis is fairly limited and so, such a bioactivity remains inconclusive. However, clinical studies did show beneficial effects of ARBs to retard diabetic microvascular disease progression which makes ARBs a desirable therapeutic candidate. Further investigations are necessary to delineate the possible underlying mechanisms of ARBs on AGE-RAGE axis.

Like ARBs, ACE inhibitors also act on RAAS. Instead of blocking the receptor, they inhibit the conversion of angiotensin I to angiotensin, thereby preventing the activation of angiotensin II type I receptor. One trial showed that ramipril could reduce AGE level [118] while another work demonstrated comparable therapeutic effect between enalapril and telmisartan in delaying diabetic nephropathy deterioration [106]. Like ARBs, it is proposed that ACE inhibitors can chelate the transition metals that catalyse AGE formation [114]. Nevertheless, the AGE-inhibiting effect of ACE inhibitors is still inconclusive due to inadequate evidence.

Another class of anti-hypertensive, CCBs including azelnidipine, amlodipine and nifedipine have also been tested for their AGE-RAGE inhibitory effect. Unlike ARBs and ACE inhibitors, CCBs do not target RAAS but instead, directly antagonize the calcium influx into muscle tissues to cause arterial dilation and decline in blood pressure [119]. Treatment with amlodipine failed to lower AGE level [102] whereas azelnidipine could [120]. Combined therapy with nifedipine and telmisartan significantly elevated sRAGE level, but whether or not such a beneficial effect was conferred by nifedipine is unknown [121]. CCBs are also found to repress RAGE expression *in vitro* by acting as PPARγ agonist [122]. However, clinically, such a RAGE modulatory effect of CCBs via PPARγ activation is unlikely as no impact on glycaemic parameters was observed [120]. On the other

hand, AGE exposure has been shown to prolong calcium decay time in the cardiomyocytes which might induce abnormal contraction of the cardiac muscles [123]. Furthermore, CML-treated vascular smooth muscle cells had increased calcium release from the sarcoplasmic reticulum and calcium entry, contributing to the onset of enhanced contractility and hypertension [124]. The use of CCBs may be able to alleviate the adverse effects of AGE-RAGE axis on calcium regulation in muscle tissues. As such, like other antihypertensive agents, the inhibitory effects of CCBs on AGE-RAGE axis lack strong support from clinical evidence. Further clarifications on its mechanisms and efficacy are required to justify its clinical value in AGE-RAGE inhibition and managing diabetic complications (Table 4).

Vitamins B and its derivatives

Basically, the AGE-RAGE inhibitory effect of two types of vitamin B, namely vitamins B1 (thiamine and benfotiamine) and B6 (pyridoxine and pyridoxamine), have been examined. The clinical findings are summarized in Table 5. Some common pitfalls of the clinical trials are short treatment duration and small sample size. Generally, the studies reported mixed results on the AGE-RAGE inhibitory effect of vitamin B derivatives. Some studies detected beneficial AGE-lowering effect by benfotiamine [125,126] and by pyridoxamine [127] whereas others found no such activity [128-130].

Despite being in the same vitamin group, vitamins B1 and B6 are thought to have very distinct inhibitory mechanism on the AGE-RAGE axis. By supplying an essential cofactor of transketolase which is thiamine pyrophosphate, thiamine and benfotiamine enhance transketolase activity to channel fructose-6-phosphate and glyceraldehydes-3-phosphate from glycolysis into pentose phosphate pathway [131]. As this is also the rate-limiting step in pentose phosphate pathway, the activation of transketolase can effectively prevent the aggregation of the two metabolites which will otherwise be driven into dicarbonyl and AGE formation [132].

Conversely, pyridoxamine and pyridoxine can bind

Table 5: Clinical studies of AGE-RAGE inhibitory effects of vitamins B and its derivatives.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Benfotiamine	Non-randomised crossover study	T2DM (n = 13) • High AGE content meal with and without 1050 mg benfotiamine pre-treatment	3 days	• High AGE content meal increased AGE level, endothelial dysfunction and oxidative stress markers which were reduced by benfotiamine.	[125]
Benfotiamine	Single-arm	T1DM (n = 9) • 600 mg benfotiamine-1200 mg α-lipoic acid	28 days	• Benfotiamine treatment together with α-lipoic acid normalised angiopoietin-2, monocyte hexosamine-modified proteins, prostacyclin synthase activity and AGE formation.	[126]
Benfotiamine	Double-blind RCT	T2DM, microalbuminuria (n = 82) • Placebo (n = 43) • 900 mg benfotiamine (n = 39)	12 weeks	• Benfotiamine did not decrease urinary albumin excretion and tubular damage marker, kidney injury molecule-1.	[128]
Benfotiamine	Double-blind RCT	T2DM, microalbuminuria (n = 82) • Placebo (n = 43) • 900 mg benfotiamine (n = 39)	12 weeks	• Benfotiamine had no effect on plasma and urinary CML, CEL and MG-H1 as well as other endothelial dysfunction and low-grade inflammatory markers.	[129]
Pyridoxamine	Double-blind RCT	DM, overt nephropathy (n = 212) • Placebo (n = 90) • 100-500 mg pyridoxamine (n = 122)	24 weeks	• Pyridoxamine reduced serum creatinine, urinary TGF-β1, CML and CEL.	[127]
Thiamine-Pyridoxine combined therapy	RCT	On haemodialysis (n = 50) • Placebo (n = 25) • 250 mg thiamine-200 mg pyridoxine combined therapy (n = 25)	8 weeks	• No beneficial treatment effect was observed in the serum albumin, plasma hsCRP, IL-6, AOPP, pentosidine and 8-hydroxy-2'-deoxyguanosine of the combined treatment.	[130]

AGE: Advanced Glycation End Product; AOPP: Advanced Oxidation Protein Product; CEL: Carboxyethyllysine; CML: Carboxymethyllysine; DM: Diabetes Mellitus; hsCRP: High Sensitive C-Reactive Protein; IL-6: Interleukin-6; MG-H1: Methylglyoxal-Derived Hydroimidazolone 1; RCT: Randomised Controlled Trial; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; TGF-β1: Transforming Growth Factor-β1.

to catalytic redox metal ions which are vital to convert Amadori products to AGEs in the glycation pathway [133]. The post-amadori inhibition effectively prevents the formation of AGEs and hence, a new term "Amadorin" was coined to describe drugs behave similarly to vitamin B6 in the inhibition of AGE-RAGE axis [134]. However, the clinical prospect of both the vitamin B1 and B6 in alleviating the AGE-RAGE-mediated pathogenesis requires further investigation in light of the contradictions from the available studies (Table 5).

Other Investigational Interventions and Future Drug Development

In addition to the aforementioned five major classes of pharmacological agents, a few other drugs, including azeliragon (RAGE inhibitor), epalrestat (aldose reduc-

Table 6: Other clinical trials that investigate the inhibitory effect of other pharmacological interventions on AGE-RAGE axis.

Therapeutic drug	Experimental design	Patient characteristics and treatment groups	Treatment duration	Major findings	Reference
Azeliragon (RAGE inhibitor)	Double-blind RCT	≥ 50-years-old, Alzheimer's disease, dementia (n = 60) • Placebo (n = 10) • Low-dose Azeliragon: 30 mg starting dose; 10 mg maintenance (n = 25) • High-dose Azeliragon: 60 mg starting dose; 20 mg maintenance (n = 25)	10 weeks	• Low-dose regimen was more tolerable than high-dose regimen. • No significant difference in terms of vital signs, plasma level of amyloid β, proinflammatory cytokines and cognitive performance between groups.	[152]
Azeliragon (RAGE inhibitor)	Double-blind RCT	≥ 50-years-old, Alzheimer's disease (n = 399) • Placebo (n = 133) • Low-dose Azeliragon: 15 mg starting dose; 5 mg maintenance (n = 131) • High-dose Azeliragon: 60 mg starting dose; 20 mg maintenance (n = 135)	18 months	• High-dose arm was terminated prematurely due to increased adverse event like confusion, falls and cognitive decline. • Low-dose regimen was well-tolerated and delayed cognitive decline. • No significant difference in CSF levels of amyloid β, total tau protein and phospho-tau-181 between groups.	[137]
Azeliragon (RAGE inhibitor)	Double-blind RCT	≥ 50-years-old, Alzheimer's disease (n = 399) • Placebo (n = 133) • Low-dose Azeliragon: 15 mg starting dose; 5 mg maintenance (n = 131) • High-dose Azeliragon: 60 mg starting dose; 20 mg maintenance (n = 135)	18 months	• Low-dose regimen slowed down cognitive decline among the patients with mild Alzheimer's disease.	[138]
Epalrestat (Aldose reductase inhibitor)	Observational study	T2DM and nondiabetic (n = 66) • Nondiabetic (n = 12) • Untreated T2DM (n = 38) • 150 mg epalrestat (n = 16)	≥ 2 months	• Treatment with epalrestat was associated with lower erythrocyte CML, 3-DG, triosephosphates, fructose and sorbitol.	[139]
Epalrestat (Aldose reductase inhibitor)	Observational study	T2DM (n = 74) • Untreated T2DM (n = 36) • 150 mg epalrestat (n = 38)	2 years	• Epalrestat reduced CML and slowed down the deterioration of diabetic peripheral neuropathy.	[140]
1, 25 dihydroxyvitamin D3 (Vitamin D)	Observational study	Vitamin D deficit women w/o PCOS (n = 67) • Untreated (n = 16) • 50000 IU vitamin D3 (n = 51)	8 weeks	• Vitamin D3 supplementation increased circulating sRAGE in women with PCOS, but not in those without PCOS.	[153]

Vitamin E	RCT	Nondiabetic patients on haemolysis (n = 16) • Conventional SMC membrane (n = 8) • Vitamin E-coated dialyzer (n = 8)	42 weeks	• Dialysis with vitamin E-coated membrane lowered pentosidine and AGEs in the bloodstream.	[154]
α-lipoic acid	Single-arm	T1DM (n = 9) • 1200 mg α-lipoic acid plus 600 mg benfotiamine	28 days	• α-lipoic acid plus benfotiamine normalised angiopoietin-2, monocyte hexosamine-modified proteins, prostacyclin synthase activity and AGE formation.	[126]
α-lipoic acid	RCT	Diabetic nephropathy (n = 34) • Placebo (n = 17) • 800 mg α-lipoic acid plus 80 mg pyridoxine (n = 17)	12 weeks	• α-lipoic acid plus pyridoxine lowered urinary albumin, serum malonyldialdehyde and systolic blood pressure and enhanced circulating nitric oxide compared to placebo. • Supplemented group showed significant decline in pentosidine and CML at the end of the experiment compared to baseline.	[146]

3-DG: 3-Deoxyglucosone; AGE: Advanced Glycation End Product; CML: Carboxymethyllysine; CSF: Cerebrospinal Fluid; PCOS: Polycystic Ovarian Syndrome; RAGE: Receptor for Advanced Glycation End Product; RCT: Randomised Controlled Trial; T1DM: Type 1 Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; SMC: Synthetic Modified Cellulose Membrane.

tase inhibitor), vitamin D and vitamin E, have also been tested clinically for their AGE-RAGE inhibitory effects as summarised in Table 6.

In this context, it is worth noting that RAGE-induced pathogenesis, particularly upon the interaction with amyloid β, is well-implicated in neurodegenerative diseases like Alzheimer's disease [135]. Therefore, azeliragon or PF-04494700 or TTP488, which is a small-molecule RAGE antagonist, has been developed as an investigational drug against Alzheimer's disease and diabetic neuropathy. Unfortunately, the development of the drug for the latter has been discontinued. For Alzheimer's disease, a preclinical study using transgenic mice that overexpressed human amyloid precursor proteins demonstrated an excellent, dose-dependent therapeutic efficacy of azeliragon in terms of the amyloid plaque formation, proinflammatory response, cerebral glucose utilisation and behavioural impairment [136]. However, in human clinical trials, at higher dosages (≥ 20 mg/day), the drug seemed to accelerate cognitive dysfunction [137]. Low-dose regimen, on the other hand, might confer some protection against cognitive deterioration, notably among the patients with mild Alzheimer's disease [138]. Currently, two phase 3 clinical studies are on-going to explore the short- and long-term efficacy and safety of azeliragon. Positive findings from these trials may support the use of azeliragon in diabetic vasculopathy.

Next, as mentioned previously, reactive carbonyl species which is AGE precursors can be derived from the polyol pathway. Therefore, blocking the pathway is an attractive choice to reduce AGE formation. In fact, the reduction of dicarbonyl compounds like CML and 3-deoxyglucosone with the use of epalrestat which is an aldose reductase inhibitor, is strongly supported by clinical evidence [139,140]. The inhibition of aldose reductase and blockade of polyol pathway is further translated into other beneficial effects, most notably the delayed progression of diabetic retinopathy, nephropathy and neuropathy [141,142]. Thus far, the clinical results of aldose reductase inhibitor, especially in diabetic cardiovascular autonomic neuropathy, are exceedingly favourable [143], making it a valuable drug for the therapy of diabetic complications.

The inhibitory effect of vitamins D and E on AGE-RAGE axis have also been examined in non-diabetic patients, both of which showed a certain extent of beneficial effects by increasing sRAGE or lowering circulating AGEs respectively. The actual mechanism remains unclear, but may be partially explained by their antioxidant properties [144,145]. Speaking of antioxidant activity, α-lipoic acid which is a potent antioxidant can also confer AGE-lowering effect in diabetic patients when it is used together with other potential AGE inhibitors like benfotiamine and pyridoxine [126,146]. However, these studies did not include an "α-lipoic acid only" cohort and hence, its effect on AGE-RAGE axis independent from the interaction with other compounds is unclear. It is worth mentioning that α-lipoic acid has been extensively tested in diabetic patients and consistently shown to alleviate oxidative stress, improve lipid and glucose

homeostasis and most importantly, enhance the peripheral neurological function in patients with diabetic polyneuropathy [147,148]. This points to a promising clinical prospect of α-lipoic acid in diabetes and its related vasculopathy.

In regard to the development of specific RAGE inhibitors, increasing efforts and resources are channelled into synthetic medicine. One of the earlier examples is FPS-ZM1, which is a high-affinity synthetic RAGE inhibitor that binds to the V domain of the receptor [149]. FPS-ZM1 also readily crosses the blood-brain-barrier, inhibits β-secretase and production of amyloid β peptide, making it a potential therapy for Alzheimer's disease [149]. Han, et al. also reported successful synthesis of a 2-aminopyrimidine-based small molecule that can inhibit ligand-RAGE interaction and confers similar therapeutic effects to FPS-ZM1 in transgenic mouse models with Alzheimer's disease [150]. With the assistance of molecular docking, the small molecule was also predicted to bind to the V-domain of RAGE. In fact, with the advancement in computational technology, it is entirely possible to screen a wide arrays of molecular structures for promising RAGE inhibitors with well-designed algorithms. For instance, one such molecule, Compound 62, has been identified to demonstrate excellent bioavailability, minimal mutagenicity and carcinogenicity besides having the highest affinity to RAGE compared to many pre-existing specific RAGE inhibitors, all with the use of computational tools [151]. Even though further experimental validation is necessary, it is undeniable that computational advancement could significantly revolutionise not only the AGE-RAGE and diabetes research, but also many other aspects in medicine and drug development in the near future (Table 6).

Conclusion

As the AGE-RAGE axis is reckoned to be one of the major driving forces to the onset of diabetic vascular complications, potent AGE-RAGE inhibitory agents are therefore, highly sought after. However, aside from glucose- and lipid-lowering medications, the clinical studies of most AGE-RAGE inhibitors yielded mixed results in terms of their clinical efficacy and practicality. This is strongly indicative of a few arguments: (1) Current understanding of AGE-RAGE-mediated pathogenesis is incomplete; (2) Inhibition of AGE-RAGE axis may be better as adjunctive instead or primary therapy; (3) RAGE ligands other than AGE could play a predominant role in RAGE-mediated signal transduction; (4) The clinical trials were not empowered to detect minor beneficial effects. In light of the complex pathogenesis and multifactorial nature of diabetes- and cardiovascular-associated comorbidities, such mixed and confusing clinical findings are not entirely surprisingly. However, this does not imply that targeting AGE-RAGE axis is a futile attempt. In fact, recent breakthrough in Alzheimer's disease with the use of specific RAGE inhibitor (azeliragon) points out that blockade of RAGE could indeed confer positive impacts, particularly at the early stage of the disease. Likewise, targeting AGE-RAGE axis during pre-diabetic state may help to slow down the progression of diabetic vascular complications. As for currently available drugs, metformin, TZDs and statins show great potential to be developed as AGE-RAGE inhibitors as supported by concrete clinical evidence. Aldose reductase inhibitors are also promising candidates but the clinical evidence on AGE-RAGE axis is limited. As such, AGE-RAGE antagonists remain as an interesting clinical option for the treatment of diabetes-associated complications. Despite the contradictory results, exploratory studies that identify the specific patient populations whom will be benefited from the treatment is highly recommended.

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Conflicts of Interest

None.

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