Involvement of the Toxic AGEs (TAGE)-RAGE System in the Pathogenesis of Diabetic Vascular Complications: A Novel Therapeutic Strategy

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Abstract: Diabetic vascular complications are leading causes of acquired blindness, end-stage renal failure, a variety of neuropathies, and accelerated atherosclerosis, which may be involved in the disabilities and high mortality rates suffered by diabetic patients. Continuous hyperglycemia is involved in the pathogenesis of diabetic micro- and macrovascular complications via various metabolic pathways, and numerous hyperglycemia-induced metabolic and hemodynamic conditions exist, including increased generation of various types of advanced glycation end-products (AGEs). Recently, we demonstrated that glyceraldehyde-derived AGEs (Glycer-AGEs), the predominant components of toxic AGEs (TAGE), play an important role in the pathogenesis of angiopathy in diabetic patients. Moreover, a growing body of evidence suggests that the interaction of TAGE with the receptor for AGEs (RAGE) alters intracellular signaling, gene expression, and the release of pro-inflammatory molecules and elicits oxidative stress generation in numerous types of cells, all of which may contribute to the pathological changes observed in diabetic vascular complications. Therefore, the inhibition of TAGE formation, blockade of TAGE-RAGE interaction, and the suppression of RAGE expression or its downstream pathways are promising targets for therapeutic interventions against diabetic vascular complications. In this review, we discuss the pathophysiological role of the TAGE-RAGE-oxidative stress system and related therapeutic interventions for preventing the development and progression of diabetic vascular complications.

Keywords: Diabetic vascular complications, advanced glycation end-products (AGEs), toxic AGEs (TAGE), receptor for AGEs (RAGE), oxidative stress, soluble RAGE (sRAGE), renin-angiotensin system (RAS), pigment-epithelium-derived factor (PEDF).

INTRODUCTION

Diabetic vascular complications are leading causes of end-stage renal failure, acquired blindness, a variety of neuropathies, and cardiovascular disease (CVD) and may be involved in the disability and high mortality rates suffered by patients with type 1 or type 2 diabetes mellitus (DM) [1]. Although various hyperglycemia-induced metabolic and hemodynamic conditions are proposed to contribute to vascular complications in DM [2, 3], recent clinical studies have suggested that the concept of “hyperglycemic memory” plays a role in the pathogenesis of vascular injury in DM [4-6]. Indeed, the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) Study demonstrated that the reduced risk of progressive retinopathy and nephropathy brought about by intensive therapy in patients with type 1 DM persisted for at least eight years, despite increasing hyperglycemia [4, 5]. The intensive therapy administered during the DCCT resulted in decreased progression of intima media thickness (IMT) and had reduced the risk of nonfatal myocardial infarction, stroke, or death from CVD by 57% by 11 years after the end of the trial [6].

Furthermore, a recent follow-up study, the United Kingdom Prospective Diabetes Study (UKPDS), also demonstrated that the benefits of intensive therapy in patients with type 2 DM were sustained after the cessation of the trial [7]. In this study, despite the early loss of glycemic differences between the patients administered the intensive and conventional therapies, a continued reduction in microvascular risk and emergent reductions in the risks of myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up [7]. These observations indicate that intensive therapy aimed at controlling blood glucose levels has long-term beneficial effects on the risk of diabetic retinopathy, nephropathy, CVD, and death in patients with type 1 or type 2 DM, strongly suggesting that so-called “metabolic memory” causes chronic damage to diabetic vessels that is not easily reversed, even by subsequent, relatively good control of blood glucose. Among the various pathways activated under DM, the biochemical nature of advanced glycation end-products (AGEs) and their mode of action are the most compatible with the theory of “hyperglycemic memory” [8, 9].

There is a growing body of evidence to suggest that continuous hyperglycemia under diabetic conditions enhances the formation of AGES, which are senescent macroprotein derivatives, through non-enzymatic glycation (which is known as the “Maillard reaction”). There is also
accumulating evidence that the binding of the receptor for AGEs (RAGE) with AGEs elicits oxidative stress generation and subsequently evokes inflammatory and/or thrombogenic responses in various types of cells, thus participating in the development and progression of diabetic angiopathies [10-18]. Recently, we demonstrated that glyceraldehyde-derived AGEs (GlycER-AGEs), a predominant component of toxic AGEs (TAGE), play an important role in the pathogenesis of angiopathy in diabetic patients [10, 19, 20]. Furthermore, there is a growing body of evidence to suggest that the interaction of TAGE with the RAGE alters intracellular signaling, gene expression, and the release of pro-inflammatory molecules and elicits oxidative stress generation in numerous types of cells, all of which may contribute to the pathological changes associated with diabetic vascular complications. Therefore, the inhibition of TAGE formation, blockade of TAGE-RAGE interactions, and the suppression of RAGE expression or its downstream pathways are promising targets for therapeutic interventions against diabetic vascular complications.

In this review, we discuss the pathophysiological role of the TAGE-RAGE-oxidative stress system and related therapeutic interventions against the development and progression of diabetic vascular complications.

**INTERACTION OF AGES-RAGE IN VIVO**

AGEs are formed by the Maillard reaction, a non-enzymatic reaction between the aldehyde or ketone groups of reducing sugars (such as glucose, fructose, and trioses etc.) and the amino groups of proteins, and contribute to the aging of proteins and to the pathological complications of DM [10-13, 19-24]. In the hyperglycemia elicited by DM, this process begins with the conversion of reversible Schiff base adducts to more stable, covalently bound Amadori rearrangement products. Over the course of days to weeks, these Amadori products undergo further rearrangement reactions to form irreversibly bound moieties known as AGEs. AGEs were originally characterized by their yellow-brown fluorescent color and their ability to form cross-links with and between amino groups, but the term is now used for a broad range of advanced products of the glycation process, including N-(carboxymethyl)lysine (CML) and pyrraline, which do not display color or fluorescence and are not cross-linked proteins [8, 21-25]. The formation of AGEs in vivo is dependent on the turnover rate of the chemically modified target, the time available, and the sugar concentration. The structures of the various cross-linked AGEs that are generated in vivo have not yet been completely determined. Due to their heterogeneity and the complexity of the chemical reactions involved, only some AGEs have been structurally characterized in vivo. The structural identity of AGEs with cytotoxic properties also remains unknown.

Recent studies have suggested that AGEs arise not only from reducing sugars, but also from carbonyl compounds derived from the autoxidation of sugars and other metabolic pathways [26-28]. Indeed, we have demonstrated that glucose, α-hydroxyaldehydes (glyceraldehyde and glycolaldehyde), and dicarbonyl compounds (methylglyoxal, MGO; glyoxal, GO; and 3-deoxyglucosone, 3-DG) are actively involved in protein glycation [21, 29-31]. Six immunochromically distinct classes of AGEs (glucose-derived AGEs, Glc-AGEs; glyceraldehyde-derived AGEs, GlycER-AGEs; glycolaldehyde-derived AGEs, Glycol-AGEs; MGO-derived AGEs, MGO-AGEs; GO-derived AGEs, GO-AGEs; and 3-DG-derived AGEs, 3-DG-AGEs) are present in the sera of type 2 diabetic patients on hemodialysis [21, 29-31]. Based on these findings, we proposed a pathway for the formation of distinct AGEs involving the Maillard reaction, sugar autoxidation, and sugar metabolic pathways in vivo, as shown in Fig. (1).

Such receptors may play a critical role in AGEs-related biology and the pathology of diabetic vascular complications and aging disorders. Several types of AGEs binding proteins and/or receptors for AGEs such as RAGE [32-36]; oligosaccharyl transferase-48 (AGE-R1) [37]; galectin-3 (AGE-R3) [38]; CD36 [39]; macrophage scavenger receptors 1 and 2 (MSR-1 & -2) [40]; and fasciin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptors 1 and 2 (FEEL-1 & -2) [41] have been reported. The relative pathogenic contributions of these receptors to diabetic vascular complications are poorly defined, although RAGE is by far the best characterized, and mechanistic in vitro and in vivo studies on AGEs and their regulatory fragments such as soluble form of RAGE (sRAGE) have indicated that they play important roles in pathobiology [36, 42]. RAGE is normally expressed in a variety of cells, including endothelial cells (EC), pericytes, neurons, and microglia [32-34]. We have recently found that glyceraldehyde rapidly reacts with the amino groups of proteins to form GlycER-AGEs both in vitro and in vivo [19, 21, 30]. Furthermore, GlycER-AGEs have the strongest binding affinity for RAGE and subsequently elicit oxidative stress generation and vascular inflammation and are therefore implicated in accelerated atherosclerosis in DM [43, 44]. Recently, we also demonstrated that GlycER-AGEs, the predominant component of toxic AGEs (TAGE), play an important role in the pathogenesis of angiopathy in diabetic patients [19, 20]. Moreover, there is a growing body of evidence to suggest that the interaction of TAGE with RAGE elicits oxidative stress generation in numerous types of cells, all of which may contribute to the pathological changes associated with diabetic vascular complications [10, 19, 20].

The administration of a recombinant sRAGE consisting of its extracellular ligand-binding domain has recently been shown to not only suppress the development of atherosclerosis but also stabilize established atherosclerosis in diabetic apolipoprotein E-null mice [45, 46]. The blockade of the AGEs-RAGE axis by the administration of sRAGE reduces the development of acellular capillaries and pericyte ghosts in experimental diabetic retinopathy [47]. Furthermore, Kaji et al. have also shown that attenuating the RAGE axis by injecting sRAGE inhibits retinal leukostasis and blood-retinal barrier breakdown in diabetic RAGE-transgenic mice, which are accompanied by decreased expression of vascular endothelial growth factor (VEGF) and intercellular adhesion molecule 1 (ICAM-1) in the retina [48]. These observations suggest that exogenously administered sRAGE captures and eliminates circulating AGEs, thus protecting against AGEs-elicted tissue damage by acting as a decoy for AGEs.
PATHWAY OF GLYCER-AGES (TOXIC AGES; TAGE) FORMATION IN VIVO

Glyceraldehyde is derived from two distinct pathways in vivo, 1) the glycolytic pathway and 2) the fructose metabolism pathway [19, 20, 49]. 1) The glycolytic intermediate glyceraldehyde-3-phosphate (G-3-P) is normally catabolized by the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). With a decline in GAPDH activity, G-3-P accumulates intracellularly. G-3-P metabolism then shifts to another route, and the amount of glyceraldehyde is increased, which leads to an increase in the formation of TAGE. This suggests a positive feedback mechanism; i.e., TAGE-RAGE interactions have been postulated to play a role in the development and progression of diabetic microvascular disease in DM.

2) Under hyperglycemic conditions, the increased intracellular glucose concentration stimulates the polyol pathway to generate fructose in insulin-independent tissues such as the lens and kidney, nerve tissue, brain, and red blood cells [50-52]. Furthermore, fructose, a component of table sugar and high-fructose corn syrup, is present in the daily diets of many individuals [53]. Fructose is phosphorylated to fructose-1-phosphate (F-1-P) and then catabolized to glyceraldehyde and dihydroxyacetone phosphate by aldolase B [52-55]. The newly synthesized glyceraldehyde is then transported or leaks passively across the plasma membrane. Glyceraldehyde promotes the formation of TAGE both intracellularly and extracellularly (Fig. 2).

DIABETIC MICROVASCULAR COMPLICATIONS

The formation and accumulation of AGEs progresses at an accelerated rate in diabetes, thereby implicating it in diabetic vascular complications [10-18]. Indeed, a variety of molecular mechanisms underlying the actions of TAGE and their contribution to EC dysfunction have been proposed [10, 12, 19, 20]. TAGE-RAGE interactions have been postulated to play a role in the development and progression of microvascular disease in DM.

1) Diabetic Retinopathy

Diabetic retinopathy is one of the most important microvascular complications in DM and is a leading cause of acquired blindness among people of occupational age [56]. Hyperglycemia damages retinal microvascular cells and causes various changes in retinal tissues such as enhanced vascular permeability due to pericyte loss, followed by microvascular occlusion in the retina [57, 58]. Pericytes are elongated cells of mesodermal origin, which wrap around and along the EC of small vessels [59]. As pericytes contain
contractile muscle filaments on their EC side, they are regarded as microvascular counterparts of smooth muscle cells and are considered to be involved in the maintenance of capillary tone [60, 61]. AGEs have been postulated to play a role in the development and progression of microvascular disease in DM. VEGF, which is also known as vascular permeability factor, is a specific mitogen to EC and is generally thought to be involved in the pathogenesis of proliferative diabetic retinopathy. Indeed, clinical observations have demonstrated that the VEGF level in ocular fluid is positively correlated with the amount of neovascularization in diabetic retinopathy [62, 63].

Retinal pericytes accumulate AGEs during diabetes [64], which is expected to have a detrimental effect on pericyte survival and function [65]. We have found that TAGE cause the apoptosis of retinal pericytes and induce the expression of VEGF by interacting with RAGE, indicating the involvement of TAGE in the pathogenesis of diabetic retinopathy, especially in the early stages [66-68]. TAGE also induce VEGF expression, DNA synthesis, and angiogenesis in EC. These changes are the hallmarks of proliferative diabetic retinopathy [69, 70]. These findings suggest that TAGE-RAGE interaction facilitates angiogenesis by two distinct mechanisms: by relieving the restriction on EC growth caused by the apoptotic cell death of pericytes, and by autocrine and paracrine induction of VEGF proteins by vascular wall cells. Although the molecular mechanisms of the VEGF overexpression elicited by TAGE are not fully understood, our recent investigation suggested that TAGE-RAGE interaction increases VEGF gene transcription in EC by NADPH oxidase-mediated reactive oxygen species (ROS) generation and the subsequent activation of nuclear factor κB (NF-κB) via the Ras-mitogen activated protein kinase pathway [69, 70].

The abovementioned effects of TAGE strongly suggest a pathological role for these senescent macroproteins in diabetic vascular complications. Furthermore, Glc-AGEs and TAGE are present in human serum, and the levels of both AGEs are elevated in types 1 and 2 DM [71-74]. These AGEs, especially TAGE-epitopes, elicit angiogenesis at the concentrations present in the sera of diabetic patients. These results suggest the involvement of TAGE-epitopes in pathologic angiogenesis in vivo. Recently, we demonstrated that the vitreous levels of both TAGE and VEGF were significantly higher in diabetic patients than in control subjects and that these levels were correlated with the

Fig. (2). In vivo glyceraldehyde-derived AGES (Glycer-AGEs) production routes. The glycolytic intermediate glyceraldehyde-3-phosphate (G-3-P) is normally catabolized by the enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH). With a decline in GAPDH activity, G-3-P accumulates intracellularly. G-3-P metabolism then shifts to another route, and the amount of glyceraldehyde is increased, which leads to an increase in the formation of TAGE. Fructose is phosphorylated to fructose-1-phosphate (F-1-P) and then catabolized to glyceraldehyde and dihydroxyacetone phosphate by aldolase B. The newly synthesized glyceraldehyde is then transported or leaks passively across the plasma membrane. Glyceraldehyde promotes the formation of TAGE both intracellularly and extracellularly. TAGE, toxic AGEs (glyceraldehyde-derived AGES); RAGE, receptor for AGES; ROS, reactive oxygen species; HFCS, high-fructose corn syrup; AR, aldose reductase; SDH, sorbitol dehydrogenase; FK, fructokinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; * TAGE.
severity of neovascularization in diabetic retinopathy. In addition, we also found a significant correlation between vitreous TAGE and VEGF levels [75, 76].

While many of the reported studies investigating diabetic retinopathy measured a range of ill defined AGEs moiety, others evaluated defined adducts such as CML, pentosidine, and crossline [77, 78]. However, some groups have reported that they found no correlation between AGE levels and retinopathy in diabetic patients [77, 79], although the apparent disparity between the findings of the various studies may be related to differences in the patient populations and/or the non-uniform assays used for plasma AGEs-quantification. Our studies suggest that an elevated TAGE level in DM patients is important for the initiation and progression of retinopathy. Therefore, the inhibition of TAGE formation and the blockade of TAGE-RAGE interactions are potential therapeutic strategies for the prevention of diabetic retinopathy.

2) Diabetic Nephropathy

Nephropathy is one of the most common complications of DM. The disease is characterized by an increased glomerular basement membrane thickness, a decreased glomerular filtration rate, and an expanded mesangial volume [80-82]. Diabetes-induced changes in the physical and biochemical properties of the glomerular basement membrane can result in proteinuria. However, the involvement of these changes in the development of the early phase of diabetic nephropathy has not been fully elucidated. Mesangial cells occupy a central anatomical position in the glomerulus, playing crucial roles in maintaining the structure and function of glomerular capillary tufts [83]. They also provide structural support for capillary loops and modulate glomerular filtration via smooth muscle activity [83-85].

We have found that TAGE disturb glomerular homeostasis by inducing apoptotic cell death in human mesangial cells. Cell growth is also strongly inhibited by TAGE. Furthermore, TAGE stimulate the secretion of VEGF and monocyte chemoattractant protein-1 (MCP-1). Hyperfiltration and microalbuminuria occur subsequently, suggesting the involvement of TAGE in the pathogenesis of the early phase of diabetic nephropathy [86]. More recently, we found that the serum levels of TAGE were significantly higher in diabetic patients with nephropathy than in diabetic patients without clinically evident nephropathy (unpublished data). These results suggest that the effects of TAGE on pericytes are similar to their effects on mesangial cells, supporting the notion that attacks on vascular wall cells by TAGE are involved in the early phase of diabetic vascular complications.

RAGE-overexpressing diabetic mice have been found to show progressive glomerulosclerosis and renal dysfunction compared with diabetic littermates lacking the RAGE transgene [87]. Myint et al. reported that inactivation of the RAGE gene in a mouse model of diabetic nephropathy resulted in significant suppression of kidney changes, including kidney enlargement, increased glomerular cell number, mesangial expansion, advanced glomerulosclerosis, increased albuminuria, and increased serum creatinine compared with wild-type diabetic mice [88]. They also showed that low-molecular weight heparin treatment significantly prevented albuminuria and increased glomerular cell number, mesangial expansion, and glomerulosclerosis by antagonizing RAGE [88]. We have recently found that treatment with telmisartan or olmesartan inhibits TAGE-evoked inflammatory responses in EC via the downregulation of RAGE expression [89-93]. These observations suggest that the blockade of TAGE-RAGE signaling pathways by renin-angiotensin system (RAS) inhibitors may be clinically relevant to the prevention of diabetic vascular complications.

3) Diabetic Neuropathy

DM is a major cause of peripheral neuropathy, which commonly manifests as distal symmetrical polyneuropathy [94]. In human diabetic nerves, the major pathology involves fiber loss, axonal degeneration and demyelination, and microangiopathic changes [95, 96]. The sural, peroneal, and saphenous nerves of human diabetic subjects contain AGEs in the perineurium, EC, and pericytes of endoneurial microvessels as well as in myelinated and unmyelinated fibers [97]. AGEs accumulation in the nerves of diabetics and the inhibition of AGEs formation by anti-glycation agents improved the neuropathic changes suffered by experimental diabetic rats [98]. However, the pathologic mechanisms behind the actions of AGEs in diabetic neuropathy are poorly understood. We investigated the effects of TAGE on the viability, replication rate, and cytokine production of cultured Schwann cells. Cell viability, replication, and the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) were significantly affected by TAGE in Schwann cells [99]. The finding of TAGE-associated toxicity in Schwann cells is consistent with the results of previous reports investigating the effects of TAGE on other types of cells such as neuronal, vascular, and mesangial cells [66, 86, 100].

DIABETIC MACROVASCULAR COMPLICATIONS

It is well known that postchallenge and postprandial hyperglycemia are related to the development and progression of diabetic macrovascular disease [101, 102]. Type 2 DM is a major risk factor for CVD morbidity and mortality, and the incidence of CVD is 2-4 times greater in diabetic patients than in the general population [103]. There is a growing body of evidence to suggest that postprandial hyperglycemia plays an important role in the pathogenesis of CVD [104, 105]. Indeed, the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study revealed that 2-h post-load hyperglycemia was associated with an increased risk of mortality from CVD, independent of fasting plasma glucose (FPG) [101]. Furthermore, the Diabetes Intervetion Study identified postprandial hyperglycemia to be an independent risk factor for myocardial infarction and all-cause mortality [104]. Moreover, postprandial hyperglycemia has been shown to be associated with endothelial dysfunction and increased IMT as well as a higher prevalence of atherosclerotic plaques of the common carotid arteries [105]. These findings suggest that postprandial hyperglycemia would make a good a therapeutic target for preventing CVD in type 2 DM. However, there is no convenient biomarker that reflects cumulative postprandial hyperglycemia in DM.
We have recently found that glycidaldehyde rapidly reacts with the amino groups of proteins to form TAGE, which causes vascular inflammation and endothelial dysfunction and is therefore implicated in accelerated atherosclerosis in DM [10, 19]. More recently, we examined whether the TAGE concentration was able as a biomarker that reflects cumulative postprandial hyperglycemia in Goto-Kakizaki (GK) rats, a rat model of type 2 DM, that were fed twice a day [106]. At 8 weeks of age, the GK rats were divided into 2 groups: either the vehicle or 50 mg/kg of nateglinide, a rapid-acting insulin secretagogue, was administered twice daily just before each meal. After 6 weeks, nateglinide treatment was found to not only prevent postprandial hyperglycemia, but also reduce TAGE levels in the GK rats. However, there was no significant difference in HbA1c or GIC-AGE levels between the two groups. The present study demonstrated for the first time that TAGE, but not HbA1c or GIC-AGEs, can be used as biomarkers that reflect cumulative postprandial hyperglycemia in diabetic rats.

This may partly explain why decreased HbA1c levels did not lead to a significant reduction in the risk of CVD in the UKPDS, thus further strengthening the importance of identifying a biomarker that reflects cumulative postprandial hyperglycemia in DM [107]. Since TAGE have the strongest binding affinity for RAGE [43, 44] and exert deleterious effects on diabetic vessels through their interaction with RAGE [10, 19, 20], TAGE may partly account for the increased risk of CVD in diabetic and impaired glucose tolerant patients with postprandial hyperglycemia. Taken together, our present study also suggests that TAGE are a novel therapeutic target for preventing CVD in DM patients [106].

Furthermore, we have recently found that serum TAGE levels are positively correlated with the levels of thrombogenic markers in humans. Plasminogen activator inhibitor-1 (PAI-1) and fibrinogen levels are positively associated with serum TAGE levels [108]. These results suggest the relevance of TAGE-epitopes to pathologic angiogenesis and thrombogenesis in humans.

THERAPEUTIC AGENTS THAT COULD BLOCK THE TAGE-RAGE AXIS

Several therapeutic strategies such as the inhibition of TAGE formation, the blockade of TAGE-RAGE interactions, and the suppression of RAGE expression or its downstream pathways are promising for the treatment of vascular complications in DM.

1) Pimagedine

Double-blinded, placebo-controlled, randomized clinical trials of aminoguanidine (AG, Pimagedine) (ACTION; A Clinical Trial In Overt Nephropathy) were designed to evaluate the safety and efficacy of AG in retarding the rate of progression of renal disease in patients with overt diabetic nephropathy. Pimagedine therapy reduced 24-hour total urinary proteinuria and prevented decreases in the glomerular filtration rate in patients with type 1 diabetes [109]. In addition, compared with those receiving placebo, fewer pimagedine-treated patients experienced a three-step or greater progression of diabetic retinopathy [109]. However, the effects of pimagedine on serum creatinine doubling were not significant; serum creatinine doubled in 26% of the placebo-treated patients and in 20% of those who received pimagedine ($p=0.099$). This study is noteworthy as it provides the first clinical proof that inhibiting AGE formation can result in a clinically important attenuation of the serious complications of diabetes. However, as the reported side effects of AG in clinical therapy included gastrointestinal disturbance; abnormalities in liver function tests; flu-like symptoms; and the development of anuclear antibody, pernicious-like anemia, and a rare form of vasculitis [109], further clinical trials of AG were terminated due to safety concerns.

2) Inhibition of TAGE Formation

Although many agents improve overall glycemic control, including postprandial plasma glucose levels, several pharmacologic therapies specifically target postprandial hyperglycemia.

More recently, we investigated the effects of nateglinide, which has been shown to improve postprandial hyperglycemia, on HbA1c, GIC-AGE, and TAGE levels in GK rats [106]. After 6 weeks, nateglinide treatment was found to not only prevent postprandial hyperglycemia, but to also reduce TAGE levels in GK rats. However, there were no significant differences in HbA1c or GIC-AGE levels [106]. This study suggests that TAGE are formed more rapidly than HbA1c, a precursor of GIC-AGEs, under postprandial hyperglycemic conditions and show potential as novel markers of cumulative postprandial hyperglycemia. In this study, although we did not clarify the exact molecular mechanism by which TAGE were formed under postprandial hyperglycemic conditions, hyperglycemia-induced oxidative stress-mediated inhibition of GAPDH may lead to the elevation of glycidaldehyde levels and subsequently enhance the formation of TAGE during the postprandial period [110]. The relative contribution of postprandial glucose decreased progressively from the lowest to the highest quintile of HbA1c, whereas, the relative contribution of fasting glucose increased gradually with increasing levels of HbA1c [111]. These observations suggest that a decrease in HbA1c levels does not necessarily reflect a reduction in postprandial hyperglycemia, especially in poorly controlled diabetic patients.

Acarbose, an α-glucosidase inhibitor, which delays the absorption of carbohydrates from the small intestine, reduces postprandial hyperglycemia in patients with type 2 DM [112]. Recently, acarbose treatment was reported to slow the progression of IMT of the carotid arteries and to reduce the incidence of CVD in patients with impaired glucose tolerance or type 2 DM [112], thus suggesting that acarbose treatment inhibits the development and progression of CVD by suppressing postprandial hyperglycemia.

We have previously shown that glycidaldehyde reacts rapidly with the amino groups of proteins to form TAGE in vivo, which evoke vascular inflammation and oxidative stress generation, thereby implicating them in accelerated atherosclerosis in DM [10, 19, 20]. Furthermore, we recently found that the serum levels of TAGE rather than HbA1c reflect cumulative postprandial hyperglycemia in type 2 diabetic rats [106]. These observations led us to speculate...
that acarbose treatment reduces the serum levels of TAGE, which may contribute to its cardioprotective properties in vivo. Thirteen oral hypoglycemic agent (OHA)-naive Japanese type 2 diabetic patients without microangiopathy, coronary artery disease, or any active inflammatory disease were enrolled in this study. The patients were treated with 50 mg acarbose three times a day for 12 weeks. Their TAGE levels and those of other biochemicals were measured before and after treatment with acarbose [113]. After 12 weeks, acarbose treatment was found to have significantly reduced the TAGE and free fatty acid levels of the diabetic patients. Acarbose treatment also decreased their postprandial plasma glucose (PPG) levels, but its effects on PPG were not statistically significant because of the high variability in the data and the small number of subjects enrolled in the study. Acarbose did not affect other anthropometric or metabolic variables; i.e., there were no significant differences in body mass index, blood pressure, HbA1c, FPG, or lipid parameters between before and after treatment with acarbose. This study demonstrated for the first time that acarbose treatment reduced the serum levels of TAGE in OHA-naive type 2 diabetic patients [113]. Our observations suggest that HbA1c levels do not necessarily reflect reductions in postprandial hyperglycemia by acarbose and that TAGE levels may be a biomarker that reflects cumulative postprandial hyperglycemia in type 2 DM. Given the deleterious effects of TAGE on CVD [10, 20], the reduction of TAGE concentrations by acarbose is a novel therapeutic strategy for preventing CVD in patients with type 2 DM.

3) Blocker of the TAGE-RAGE Interaction: the Soluble Form of RAGE

Recently, endogenous sRAGE has been identified in humans [43]. Endogenous sRAGE may be generated from the cleavage of cell surface full-length RAGE or novel splice variants of RAGE (the C-truncated splice isoform of secretory RAGE, esRAGE) [43]. Endogenous total sRAGE levels are elevated in patients with types 1 and 2 DM [114-117]. Furthermore, we, along with others, have recently demonstrated that total serum sRAGE levels are positively, rather than inversely, associated with TAGE levels in both non-diabetic and diabetic subjects [117, 118]. Age-, sex-, and body mass index-adjusted TAGE levels are also significantly increased in proportion to the increased level of sRAGE in non-diabetic subjects [117, 118]. These findings suggest that the sRAGE pool is not able to efficiently capture and eliminate the circulating TAGE in vivo by acting as a decoy receptor. Since TAGE is a positive regulator of the expression of RAGE, circulating sRAGE levels may reflect RAGE expression at the tissue level and be elevated in parallel with serum TAGE levels as a counter-system against TAGE-elicited tissue damage [119-122].

The serum levels of esRAGE are also correlated with the levels of circulating AGEs such as CML and pentosidine in type 1 DM patients [123]. However, in contrast to the case for total sRAGE, circulating esRAGE levels are decreased, rather than increased, in both type 1 and 2 diabetic patients. Katakami et al. reported that the serum levels of esRAGE were significantly decreased in Japanese patients with type 1 DM compared with those in non-diabetic subjects [124] and that esRAGE levels were significantly lower in type 1 diabetic patients with retinopathy than in those without retinopathy [124, 125]. Decreased esRAGE levels were also found to be an independent risk factor for carotid atherosclerosis [126]. Indeed, Koyama et al. reported that esRAGE levels were decreased in Japanese type 2 diabetic patients compared with non-diabetic subjects and that low levels of esRAGE were associated with the components of metabolic syndrome and carotid atherosclerosis [126]. These observations were contrary to the findings of previous reports that demonstrated that total sRAGE levels were associated with conventional coronary risk factors including inflammatory markers and were independent determinants of coronary artery disease in DM [115, 119, 120]. Therefore, the kinetics and role of sRAGE and esRAGE in DM may differ [121]. Decreased levels of esRAGE may be associated with comorbidities such as diabetic retinopathy and atherosclerosis via mechanisms other than acting as a decoy because esRAGE levels are approximately 3-4 fold lower than total sRAGE levels and may not be sufficient to efficiently eliminate circulating AGEs in humans. Furthermore, sRAGE, but not esRAGE, levels were recently found to be independently correlated with albuminuria in type 2 diabetic patients [127].

On the contrary, other groups have found that total sRAGE levels were inversely correlated with lipid concentrations [128]. Basta et al. recently reported that total plasma sRAGE levels were decreased in diabetic patients. In a subgroup of 26 diabetic and 24 non-diabetic subjects of similar age, they found that total sRAGE levels were inversely associated with the level of S100A12, a non-AGEs ligand for RAGE and that low sRAGE and high S100A12 concentrations were strongly associated with an increased risk of CVD [128].

There is still some controversy over the therapeutic modulation of sRAGE. Forbes et al. reported that treatment with ramipril, an angiotensin-converting enzyme inhibitor (ACEI), restored the decreased plasma levels of total sRAGE in diabetic rats [129]. Similarly, they also found that there was a significant increase in total plasma sRAGE levels in patients who had type 1 DM and were treated with the ACEI perindopril [129]. Nakamura et al. reported that telmisartan, an angiotensin II type 1 receptor blocker (ARB), inhibited sRAGE generation by angiotensin-II-exposed EC and decreased the serum levels of total sRAGE in patients with essential hypertension [130].

4) Inhibitors of the Renin-Angiotensin System (RAS)

The interaction of the RAS and TAGE-RAGE systems has also been proposed. We have found that angiotensin II potentiates the deleterious effects of TAGE in pericytes by inducing RAGE protein expression [68]. In vivo, TAGE-injection stimulated RAGE expression in the eyes of spontaneously hypertensive rats, which was blocked by telmisartan. In vitro, angiotensin II-type 1 receptor-mediated ROS generation elicited RAGE gene expression in retinal pericytes through NF-kB activation. Furthermore, angiotensin II augmented TAGE-induced pericyte apoptosis, the earliest hallmark of diabetic retinopathy. Telmisartan also blocks angiotensin II-induced RAGE expression in EC [130].
Recently, there has been increasing interest in the role of inflammatory reactions and immune phenomena in the pathogenesis of diabetic vascular complications [131-133]. Indeed, leukocyte adhesion to diabetic retinal vasculature is considered to be a critical early event in diabetic retinopathy, the development of which is mainly mediated by VEGF, ICAM-1, and MCP-1 expression [131-133]. ICAM-1 and MCP-1 are essential chemokines that mediate the recruitment of leukocytes to mesangial lesions [134, 135]. The selective targeting of ICAM-1 or MCP-1 was also shown to markedly decrease albuminuria and renal injury in experimental diabetic nephropathy [134, 135]. Furthermore, several experimental studies have supported the pathological role of VEGF in diabetic nephropathy: antibodies raised against VEGF have been reported to improve hyperfiltration and albuminuria in diabetic rats [136, 137]. In addition, atherosclerosis is also an inflammatory-proliferative disease [138], and the administration of VEGF is reported to enhance atherosclerotic plaque progression in animals [139]. We have recently found that treatment with telmisartan or olmesartan inhibits TAGE-evoked inflammatory responses in EC via the downregulation of RAGE expression [89-93]. These observations suggest that the blockade of the TAGE-RAGE signaling pathways by RAS inhibitors is clinically relevant to the prevention of diabetic vascular complications.

As for the underlying molecular mechanisms, telmisartan may downregulate RAGE expression through its unique peroxisome proliferator-activated receptor-γ (PPAR-γ)-modulating ability on the basis of the following observations [89-91]: (1) telmisartan downregulated RAGE mRNA levels and subsequently inhibited superoxide generation as well as MCP-1 expression in mesangial cells, all of which were prevented by GW9662, an inhibitor of PPAR-γ [90]; (2) another ARB, candesartan, did not suppress TAGE-induced superoxide generation in mesangial cells; (3) the antioxidant N-acetylcysteine (NAC) inhibited MCP-1 production by TAGE-exposed mesangial cells; (4) telmisartan, but not candesartan, decreased TAGE-induced RAGE expression, ROS generation, and the subsequent C-reactive protein (CRP) expression in human Hep3B hepatoma cells [91]; (5) GW9662 also blocked the inhibitory effects of telmisartan on RAGE expression and its downstream signaling in Hep3B cells; (6) troglitazone and ciglitazone, full agonists of PPAR-γ, mimicked the effects of telmisartan on Hep3B cells; and (7) treatment with anti-oxidants or curcumin, an inhibitor of NF-κB, blocked the TAGE-induced upregulation of CRP mRNA levels in Hep3B cells. There is accumulating evidence to suggest that telmisartan is a promising cardiometabolic sartan due to its unique PPARγ-modulating ability [89, 140]. Furthermore, thiazolidinediones have been reported to reduce the endothelial expression of RAGE via NF-κB suppression [141]. Taken together, these observations suggest that telmisartan works as an anti-inflammatory agent against TAGE-signaling by suppressing RAGE expression in EC, mesangial cells, and the liver via PPAR-γ activation and that it plays a protective role against diabetic vascular complications by limiting the susceptibility of these cells to pro-inflammatory TAGE effects.

We should also describe other possible mechanisms by which RAS inhibitors such as ARB and ACEI suppress the TAGE-RAGE system. ACEI and ARB were recently found to inhibit the formation of reactive carbonyl precursors of AGEs in vitro by chelating transition metals and inhibiting various oxidative steps, including the formation of carbon-centered and hydroxyl radicals, at both the pre- and post-Amadori steps [142]. In animal models, the ACEI ramipril also reduced the accumulation of renal and serum AGEs, probably via effects on oxidative pathways [143]. Long-term treatment with the ARB losartan seemed to exert salutary effects on AGE levels in a rat remnant kidney model, probably by improving renal function [144]. Furthermore, candesartan, another ARB, reduced AGEs accumulation and the subsequent albuminuria by downregulating the expression of the NADPH oxidase component p47phox and inducible nitric oxide synthase (iNOS) and by attenuating RAGE expression in type 2 diabetic KK/Tz mouse kidneys [145]. In addition, the infusion of AGEs into rats induced tubular and glomerular hypertrophy and AGES accumulation, which were antagonized by valsartan [146]. The administration of olmesartan medoxomil was found to inhibit increases in systolic and diastolic blood pressure and urinary N-acetyl-beta-D-glucosaminidase activity in exogenous TAGE-injected rats [147], and olmesartan medoxomil treatment prevented glomerulosclerosis in TAGE-treated rats [147]. In humans, the administration of ramipril has recently been shown to result in a mild decline in the concentrations of fluorescent non-CML-AGEs and malondialdehyde in non-diabetic nephropathy patients [148]. In type 2 diabetic subjects, low-dose valsartan treatment was reported to decrease serum TAGE levels in a blood pressure-independent manner [149].

5) Nifedipine, a Dihydropyridine-Based Calcium Channel Blocker

We have recently found that nifedipine inhibits RAGE expression in TAGE-exposed EC by suppressing ROS generation [150]. Therefore, the blockade of RAGE expression by nifedipine may have therapeutic potential for the treatment of patients with CVD in DM. Furthermore, nifedipine also inhibits TAGE-induced MCP-1 expression in human cultured mesangial cells [151]. Since diphenylethylene iodonium, an inhibitor of NADPH oxidase, was found to mimic the effects of nifedipine, nifedipine may prevent MCP-1 expression-related AGES-signalizing in mesangial cells, probably by suppressing NADPH oxidase activity. We have previously found that nifedipine inhibited TNF-α-induced MCP-1 expression in EC by blocking NADPH oxidase-mediated ROS generation [152], further supporting the concept that NADPH oxidase is a molecular target of nifedipine in TAGE-exposed mesangial cells. The redox-sensitive transcription factor NF-κB modulates the gene expression of pro-inflammatory chemokines such as MCP-1, thus playing a central role in the pathogenesis of diabetic nephropathy [153]. Therefore, it is conceivable that nifedipine decreases TAGE-elicted MCP-1 overexpression in mesangial cells by inhibiting ROS generation as well as reducing the subsequent NF-κB activation by suppressing NADPH oxidase activity.

6) Pigment-Epithelium-Derived Factor (PEDF)

PEDF is a glycoprotein that belongs to a superfamily of serine protease inhibitors with complex neurotrophic, neuroprotective, anti-angiogenic, anti-oxidative, and anti-inflammatory properties, any of which could potentially be exploit-
ed as a therapeutic option for the treatment of vascular complications in DM [154, 155]. PEDF inhibits TAGE-induced ROS generation and subsequently prevents apoptotic cell death in pericytes by restoring downregulation of the gene expression of the anti-apoptotic factor bcl-2 [156]. Furthermore, PEDF also inhibits TAGE-induced ICAM-1, VEGF, and MCP-1 upregulation as well as NO suppression in EC by blocking NADPH oxidase-mediated ROS generation [157-162]. In vivo, the administration of PEDF or pyridoxal phosphate, an AGES inhibitor, decreased the retinal levels of 8-hydroxydeoxyguanosine (8-OHdG), an oxidative stress marker, and subsequently suppressed ICAM-1 gene expression and retinal leukostasis in diabetic rats [163]. Moreover, intravenous administration of TAGE to normal rats increased ICAM-1 gene expression and retinal leukostasis, which were blocked by PEDF [163]. PEDF also inhibited diabetes- or TAGE-induced RAGE gene expression by blocking superoxide-mediated NF-κB activation [164]. In addition, we have recently found that intravenous administration of TAGE to normal rats not only increased retinal vascular permeability by stimulating VEGF expression, but also decreased retinal PEDF levels [165]. Simultaneous treatment with PEDF inhibited TAGE-elicited VEGF-mediated permeability by downregulating the mRNA levels of p22phox and gp91phox, membrane components of NADPH oxidase, and subsequently decreasing the retinal levels of the oxidative stress marker 8-OHdG. PEDF also inhibited TAGE-induced vascular hyperpermeability (as measured by transendothelial electrical resistance) by suppressing VEGF expression and decreased ROS generation in TAGE-exposed EC by suppressing NADPH oxidase activity via the down-regulation of p22phox and gp91phox mRNA expression. This led to blockade of TAGE-elicited Ras activation and NF-κB-dependent VEGF gene induction in EC. These results indicate that the central mechanism of PEDF inhibition of vascular permeability-related TAGE-signaling is the suppression of NADPH oxidase-mediated ROS generation and subsequent VEGF expression [165].

The PEDF levels in the aqueous humor and vitreous are decreased in diabetic patients, especially in those with proliferative retinopathy, suggesting that loss of PEDF in the eye contributes to the pathogenesis of proliferative diabetic retinopathy [166, 167]. We have also found significantly higher vitreous levels of TAGE and VEGF in diabetic patients than in control subjects [75] as well as a significant correlation between vitreous TAGE and VEGF levels. Total anti-oxidant status was also decreased in the vitreous in patients with diabetes. Furthermore, both TAGE and VEGF levels (inversely) and the PEDF level (positively) were associated with the total anti-oxidant status of the vitreous [168, 169]. These observations further support the concept that PEDF is an endogenous anti-inflammatory and anti-oxidative agent that blocks the TAGE-VEGF axis, thereby protecting against the progression of diabetic retinopathy.

7) Statins and Bisphosphonates

We have found that protein prenylation is crucial for TAGE-RAGE signaling in EC [69, 70]. Cerivastatin completely prevented the TAGE-induced increases in NF-κB activity and VEGF expression and the resultant increases in DNA synthesis and tube formation in microvascular EC [70]. Since mevalonate blocked the growth-inhibitory effects of cerivastatin on TAGE-exposed EC and that FTI-276, an inhibitor of farnesyltransferase, mimicked the effects of cerivastatin, cerivastatin may block TAGE-RAGE signaling involved in vascular hyperpermeability and angiogenesis via the suppression of protein prenylation. Furthermore, we have recently found that atorvastatin dose-dependently inhibited TAGE-induced ROS generation in Hep3B cells [170]. Atorvastatin as well as the anti-oxidant NAC was found to suppress CRP expression in TAGE-exposed Hep3B cells at both the mRNA and protein levels [170]. These results demonstrate that atorvastatin is able to block CRP expression-associated TAGE-signaling through its anti-oxidative action. Taken together, these observations suggest that statins have vasculoprotective effects and act by inhibiting the deleterious effects of TAGE via the suppression of their downstream signaling.

Bisphosphonates are potent inhibitors of bone resorption and are widely used for the treatment of osteoporosis, osteolytic bone metastasis, and tumor-associated hypercalcemia [171-173]. These compounds have a high affinity for calcium ions and therefore target bone mineral, where they are internalized by bone-resorbing osteoclasts and inhibit osteoclast function. Recently, farnesyl pyrophosphate synthase has been shown to be a molecular target of nitrogen-containing bisphosphonates such as incardronate disodium and minodronate, and the inhibition of the post-translational prenylation of small molecular weight G proteins including Ras and Rac-1 is probably involved in their anti-resorptive activity in osteoclasts [171-173]. Since the protein prenylation of GTP-binding proteins is associated with various cellular functions such as cell growth and differentiation [171-173], nitrogen-containing bisphosphonates may exert pleiotropic effects by blocking the synthesis of isoprenoid intermediates. Indeed, incardronate disodium was found to inhibit TAGE-induced increases in NF-κB activity and VEGF expression as well as the proliferation and tube formation of EC [69]. Furthermore, we have recently found that minodronate inhibits TAGE-induced NF-κB activation and subsequently suppresses VCAM-1 gene expression by reducing ROS generation in EC [171]. In addition, geranylgeranyl pyrophosphate reversed the anti-oxidative properties of minodronate in TAGE-exposed EC [171]. Taken together, these findings suggest that nitrogen-containing bisphosphonates are able to inhibit TAGE-elicited inflammatory-proliferative changes in EC by suppressing NADPH oxidase-derived ROS generation, probably via the inhibition of the geranylgeranylation of Rac-1, a component of endothelial NADPH oxidase [172, 173].

8) Kremezin

Recently, dietary AGEs were reported to induce oxidative stress and promote inflammatory signals [174]. Heat processing of foods containing sugars and proteins may generate AGEs [174]. Nutrient composition, temperature, and the method of cooking can affect the formation of AGEs in food. Recent human studies have revealed that approximately 10% of dietary AGES were absorbed, two-thirds of which remained in the body, and only one-third of which was excreted in urine within 2 days of ingestion [175]. In diabetic patients, especially those with advanced renal
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disease, the urinary elimination of absorbed dietary AGEs is markedly impaired, and the elevation of serum AGEs persists for longer than 48 h post-ingestion [175]. These observations suggest that dietary AGEs play a role in the pathogenesis of vascular complications in DM and that inhibiting the absorption of dietary AGEs may be a therapeutic target for treating these devastating disorders.

More recently, we have demonstrated that hepatic RAGE and VEGF expression were increased in rats administered Glc-AGE-rich beverages, indicating a novel association of dietary AGEs with the hepatic expression of genes closely related to liver fibrosis [176]. Furthermore, immunohistochemical analysis detected Glc-AGEs- and TAGE-positive cells in the livers of the Glc-AGE-rich beverage-administered rats [176]. These results suggest that Glc-AGE-rich beverages increase hepatic RAGE and VEGF expression as well as Glc-AGEs and TAGE accumulation, bringing about TAGE-RAGE interactions. The Glc-AGEs content of foods should be taken into consideration for disease prevention, particularly in individuals at a high risk of developing DM, CVD, or chronic kidney disease (CKD).

Kremezin, a prominent oral adsorbent that consists of porous spherical carbonic particles, attenuates the progression of chronic renal failure (CRF) by removing uremic toxins such as precursors of indoxyl sulfate from the intestine [177]. Indeed, Kremezin shows a superior adsorption ability to activated charcoal for certain organic compounds (uremic toxins) that are known to be precursors of substances that accumulate in patients with CKD and are believed to accelerate the decline in kidney function [177]. Kremezin is approved in Japan as a treatment for prolonging the time to hemodialysis therapy and improving uremic symptoms in patients with CKD. Kremezin is also reported to reduce carotid IMT and arterial stiffness, a surrogate marker of atherosclerosis, in CRF patients before dialysis [178]. Furthermore, recent multicenter and randomized trials have revealed that 12 weeks Kremezin treatment (9 g/day) was well tolerated and did not adversely affect the general status of patients with CKD [179]. Since AGEs represent an important class of uremic toxins and that, as described above, dietary AGEs may play an important role in atherogenesis, we investigated whether Kremezin treatment was able to decrease the serum levels of AGEs in non-diabetic CRF patients. The administration of Kremezin (6 g/day) for 3 months significantly decreased the serum levels of Glc-AGEs and TAGE in non-diabetic CRF patients; whereas, both AGE levels remained unchanged in age-and

Fig. (3). The TAGE-RAGE-oxidative stress system and related therapeutic interventions against the development and progression of diabetic micro- and macrovascular complications. There is a growing body of evidence to suggest that the interaction of TAGE with RAGE alters intracellular signaling, gene expression, and the release of pro-inflammatory molecules and elicits oxidative stress generation in numerous types of cells, all of which may contribute to the pathological changes associated with diabetic vascular complications. Since TAGE have the strongest binding affinities for RAGE and exert deleterious effects on diabetic vessels through their interaction with RAGE, TAGE may partly account for the increased risk of cardiovascular disease (CVD) in diabetic and impaired glucose tolerance (IGT) patients with postprandial hyperglycemia. Glc-AGE-rich beverages increase hepatic RAGE and VEGF expression as well as the accumulation of Glc-AGEs and TAGE, bringing about TAGE-RAGE interactions. The Glc-AGEs content in foods should be taken into consideration for disease prevention, particularly in individuals at high risk of developing DM, CVD, or chronic kidney disease (CKD). Taken together, our present study also suggests that TAGE are novel therapeutic targets for preventing CVD in DM patients. Therefore, the inhibition of TAGE formation, blockade of TAGE-RAGE interactions, and the suppression of RAGE expression or its downstream pathways are promising targets for therapeutic interventions against diabetic vascular complications. TAGE, toxic AGEs; RAGE, receptor for AGEs; PEDF, pigment-epithelium-derived factor.
renal function-matched CRF patients who were not treated with Kremezin [180]. In addition, the patient sera obtained after Kremezin treatment showed significantly reduced mRNA levels of RAGE, MCP-1, and VCAM-1 in EC compared with the sera collected before treatment. These findings suggest that the renoprotective and anti-atherosclerotic properties of Kremezin can be ascribed, at least in part, to its AGES-lowering effects mediated via the inhibition of dietary Glc-AGEs absorption and that the inhibition of dietary AGES absorption by Kremezin is a promising therapeutic strategy for the treatment of vascular complications in DM.

CONCLUSION

Two recent large prospective clinical studies, DCCT and UKPDS, have shown that intensive blood glucose control effectively reduces vascular complications among patients with DM [181, 107]. However, strict control of hyperglycemia is often very difficult to maintain and may increase the risk of severe hypoglycemia in diabetic patients. There is accumulating evidence that the TAGE-RAGE-oxidative stress system is actively involved in the pathogenesis of diabetic vascular complications. Inhibition of TAGE formation, blockade of TAGE-RAGE interactions, and the suppression of RAGE expression or its downstream pathways by the agents discussed here are promising novel therapeutic strategies for the treatment of patients with diabetic vascular complications (Fig. 3) [69, 70, 74, 106, 113, 130, 147, 150, 156, 157, 170, 171, 174, 176, 180]. Further clinical studies are needed to clarify whether the use of these agents reduces the risk of diabetic vascular complications beyond blood glucose-, blood pressure-, or cholesterol-lowering effects.

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