Cardiovascular Disease in Diabetes

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Abstract: Diabetes is associated with a marked increase in the risk of atherosclerotic vascular disorders, including coronary, cerebrovascular, and peripheral artery disease. Cardiovascular disease (CVD) could account for disabilities and high mortality rates in patients with diabetes. In this paper, we review the molecular mechanisms for accelerated atherosclerosis in diabetes, especially focusing on postprandial hyperglycemia, advanced glycation end products (AGEs) and the renin-angiotensin system. We also discuss here the potential therapeutic strategy that specifically targets CVD in patients with diabetes.

Keywords: AGEs, atherosclerosis, diabetes, oxidative stress, renin-angiotensin system.

1. INTRODUCTION

Atherosclerotic arterial disease may be manifested clinically as cardiovascular disease (CVD). Diabetes is a major risk factor for cardiovascular morbidity and mortality. Indeed, the incidence of CVD is 2-4 times greater in diabetic patients than in general polulation [1]. CVD is responsible for about 70 % of all causes of death in patients with type 2 diabetes [2]. Conventional risk factors, including hyperlipidemia, hypertension, smoking, obesity, lack of exercise, and a positive family history, contribute similarly to CVD in type 2 diabetic patients and non-diabetic subjects [2]. The association rates of these factors in diabetic patients are certainly high, but not enough to explain the exaggerated risk for CVD in diabetic population [3]. Therefore, specific diabetes-related risk factors should be involved in the excess risk in diabetic patients. In this review, we discuss the molecular mechanisms for accelerated atherosclerosis in diabetes, especially focusing on postprandial hyperglycemia, advanced glycation end products (AGEs) and the renin-angiotensin system (RAS). We also discuss here the potential therapeutic strategy that specifically targets CVD in patients with diabetes (Fig. **1**).

2. ROLE OF POSTPRANDIAL HYPERGLYCEMIA IN CVD IN DIABETES

In the last decade, several prospective studies have shown that hyperglycemia itself is clearly involved in predicting CVD [4]. In newly diagnosed type 2 diabetes, 10-year cardiovascular mortality increases threefold by tertiles of blood glucose and HbA_{1c} [5]. There is a significant increase in the risk of CVD death and all CVD events in type 2 diabetic subjects with HbA_{1c} levels higher than 7.0 % compared with diabetic subjects with lower HbA_{1c} [6,7]. The conclusive answer to the question on the existence of cause-effect relationship between hyperglycemia and CVD may derive from intervention studies. In the United Kigdom Prospective Diabetes Study (UKPDS) study, intensive blood glucose control has effectively reduced microvascular complications in type 2 diabetic patients [8]. However, the risk of myocardial infarction has reduced slightly but not significantly by about 15 %, and less than treatment of hypertension (21 %) or hypercholesterolemia (31 %). Since the reduction of hyperglycemia is small in this trial, the role of hyperglycemia in preventing CVD may be underestimated.

It is believed that macrovascular complication starts before the development of diabetes. Several studies have confirmed the increased risk of CVD in patients with impaired glucose tolerance (IGT) [9-11]. Furthermore, there is a growing body of evidence that insulin resistance in the absence of overt diabetes has been associated with endothelial dysfunction [12,13]. Therefore, atherosclerotic process may actually begin earlier in the spectrum of insulin resistance.

Insulin resistance is one of the determinants of postprandial hyperglycemia [14]. Recently, postprandial hyperglycemia was shown to be of greater importance in CVD [15]. In the Funagata diabetes study, analysis of survival rates concluded that IGT, but not impaired fasting glucose, was a risk factor for CVD [16]. The DECODE study revealed that 2-h post-load hyperglycemia was associated with an increased risk of mortality from CVD, independent of fasting plasma glucose [17]. This study also showed that abnormalities in 2-h plasma glucose were better predictors of mortality from CVD and non-CVD than fasting glucose alone [17]. Furthermore, the Diabetes Intervention Study (DIS) identified postprandial hyperglycemia to be an independent risk factor for myocardial infarction and all-cause mortality [18]. Moreover, postprandial hyperglycemia has been shown to be associated with endothelial dysfunction and increased intima-media thickness (IMT) as well as a higher prevalence of atherosclerotic plaques of the common carotid arteries, thus suggesting that mild-to-moderate postprandial hyperglycemia is involved in early atherosclerosis [19-22].

Postprandial hyperglycemia induces oxidative stress generation via various biochemical pathways such as AGE formation, protein kinase C activation and stimulation of the

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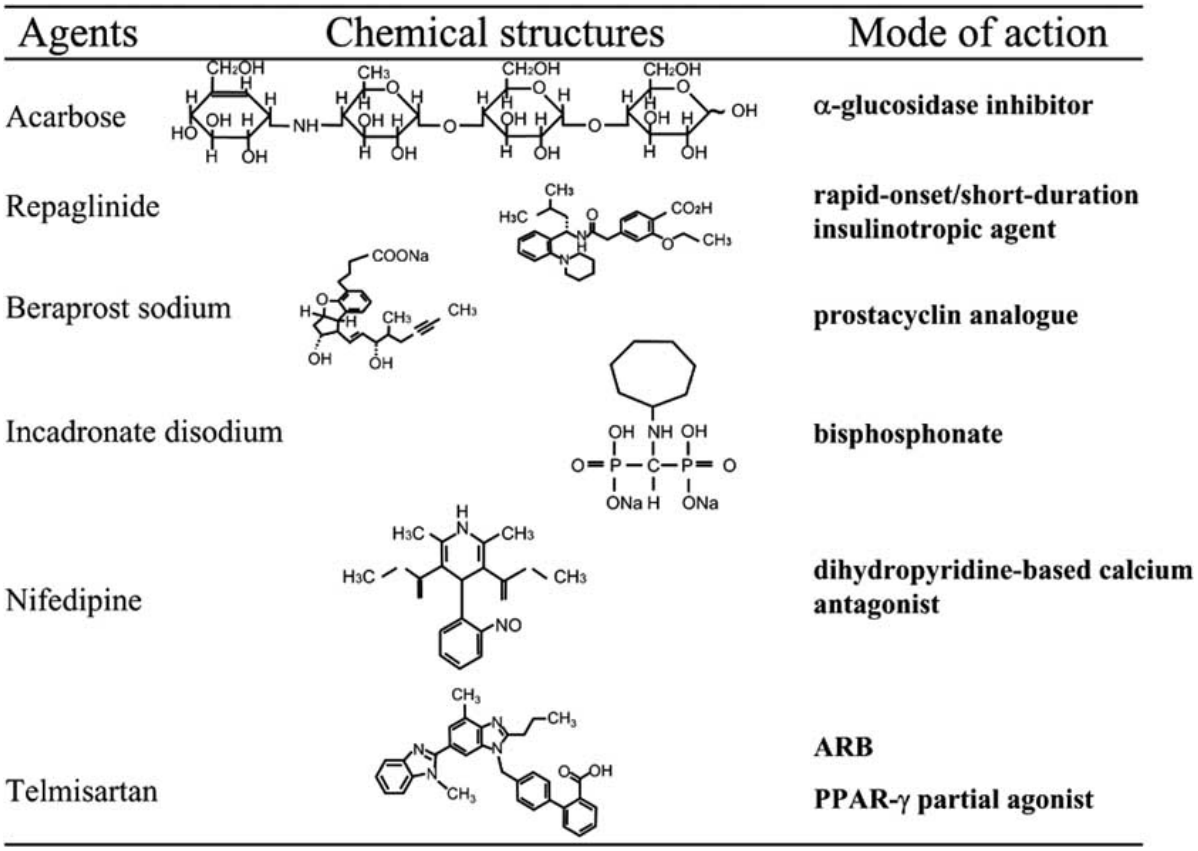

Fig. (1). Commercially available drugs for the treatment of CVD in diabetes.

polyol pathway [23,24]. There is a growing body of evidence that oxidative stress generation is the pathogenic molecular mechanism linking postprandial hyperglycemia to endothelial dysfunction, an initial step of atherosclerosis [25]. Indeed, nitric oxide (NO) undergoes a rapid reaction with superoxide anions to form peroxynitrite, a toxic metabolite of NO, which could cause vascular damage [26]. Furthermore, the loss of NO permits increased activity of the redox-sensitive transcription factor nuclear factor-κB (NF-κB), which could lead to vascular inflammation and altered gene expression of cytokines and growth factors [27,28]. Moreover, postprandial hyperglycemia-elicited oxidative stress generation induces platelet activation and thrombin generation as well, thereby participating in the progression of atheroscleorsis in diabetes [29,30].

3. INHIBITORS OF POSTPRANDIAL HYPER-GLYCEMIA

The STOP-NIDDM trial revealed that acarbose, an α-glucosidase inhibitor, improved postprandial hyperglycemia and subsequently reduced the risk of diabetes in patients with IGT [31]. Recently, acarbose treatment was found to slow the progression of IMT of the carotid arteries and to reduce the incidence of CVD and newly diagnosed hypertension in IGT patients [32,33]. Acarbose significantly reduced body mass index and waist circumference in these patients over 3 years. Furthermore, a meta-analysis of seven double-blind placebo-controlled, randomized trials has shown that intervention with acarbose prevents myocardial infarction and CVD in type 2 diabetic patients [34]. In this analysis, glycemic control, triglyceride levels, body weight and systolic blood pressure was also significantly improved during acarbose treatment. These observations suggest that prevention of postprandial hyperglycemia by acarbose may be a promising therapeutic strategy for reducing the increased risk for diabetes, hypertension, dyslipidemia, obesity, and CVD in patients with diabetes or the metabolic syndrome. Acarbose is known to improve postprandial hyperglycemia by delaying the release of glucose from complex carbohydrates in the absence of an increase in insulin secretion. Therefore, improvement of postprandial hyperglycemia itself could be associated with amelioration in insulin sensitivity.

Recently, repaglinide, a rapid-onset/short-duration insulinotropic agent, was shown to decrease circulating inflammatory markers such as interleukin-6 and C-reactive proteins and regress carotid atherosclerosis by the control of postprandial hyperglycemia in patients with diabetes [35]. These observations suggest that control of excessive glucose excursions by glinides, especially in the postprandial state, may become a novel therapeutic strategy for the prevention of CVD in diabetic patients.

4. ROLE OF AGES IN CVD IN DIABETES

(i) Role of AGEs in the Development and Progression of Atherosclerosis

Reducing sugars can react non-enzymatically with the amino groups of proteins to initiate a complex series of rearrangement and dehydration reactions to produce a class of

irreversibly cross-linked, fluorescent moieties, termed AGEs [36]. The formation and accumulation of AGEs is a characteristic feature of aged or diabetic tissues. AGEs have been actually detected within atherosclerotic lesions in both extra- and intracellular locations [37,38].

A variety of molecular mechanisms underlying the actions of AGEs and their contribution to diabetic macrovascular complications have been proposed [39-41] (Figure **2**). AGEs formed on the extracellular matrix cause decreased elasticity of vasculatures, and quench NO, which could mediate defective endothelium-dependent vasodilatation in diabetes [42]. Reactive oxygen species (ROS) participate in the formation of AGEs that are by themselves a source of free radical superoxide generation [43]. Thus ROS productions and AGE formations are related each other, and may contribute to endothelial dysfunction, one of the initial steps of atherosclerosis, via inactivation of NO. AGE modification of low-density lipoprotein (LDL) exhibits impaired plasma clearance and contributes significantly to increased LDL concentrations *in vivo*, thus being involved in atherosclerosis [44]. Binding of AGEs to RAGE (receptor for AGEs) results in generation of intracellular ROS and subsequent activation of NF-κB in vascular wall cells. These molecules promote the expression of a variety of atherosclerosis-related genes, including intracellular adhesion molecule-1, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, tissue factor, and RAGE [45-49]. The interaction of the RAS and AGEs in the development of diabetic macrovascular complications has also been proposed. The AGE-RAGE interaction augments angiotensin II-induced smooth muscle cell proliferation and activation, thus promoting atherosclerosis in diabetes [50].

(ii) Role of AGEs in Plaque Instability

Plaque neovascularization is comprised of a network of capillaries that arise from adventitial vasa vasorum and extend into the intimal layer of atherosclerotic lesions [51]. They are found in areas rich in inflammatory cells such as macrophages and T cells, and have been considered to function as conduits for the entry of leukocytes and nutrients into the artery wall [52,53]. Plaque vessels are often associated with plaque rupture and intraplaque hemorrhage as well [54,55]. Furthermore, recently, inhibition of plaque angiogenesis is found to reduce macrophage accumulation and suppress plaque growth in apolipoprotein E-deficient mice [56,57]. These observations suggest that angiogenesis may be involved in plaque growth and lesion instability in atherosclerosis. Among various angiogenic factors, vascular endothelial growth factor (VEGF), a specific mitogen for endothelial cells, has been recently shown to enhance plaque formation and progression in atherosclerosis in animal models [58]. AGEs stimulate the production of VEGF by vascular wall cells [59-61]. Moreover, the expression level of VEGF is increased in human atheromatous plaque [62]. Taken together, these findings suggest that AGEs, which exist in atherosclerotic plaque, could play a role in plaque instability by promoting plaque angiogenesis via VEGF overproduction.

Vascular calcification is a common feature in advanced atherosclerosis [63] and also a predictor of future cardiovascular events such as unstable angina and myocardial infarction [64]. Although vascular calcification has long been regarded as an end-stage, degenerative process, recent works by Demer *et al.* revealed that it was an actively regulated process involving a subpopulation of artery wall cells, called calcifying vascular cells (CVC) [65,66]. They also showed that CVC had the potential to differentiate along with other mesenchymal lineages such as osteoblasts, and their immunochemical characters were identical to those of pericytes [65-67].

AGEs have the ability to induce the osteoblatic differentiation of pericytes, thus contributing to the development of vascular calcification in atherosclerosis [68]. Pericytes have been known to possess the plasticity to

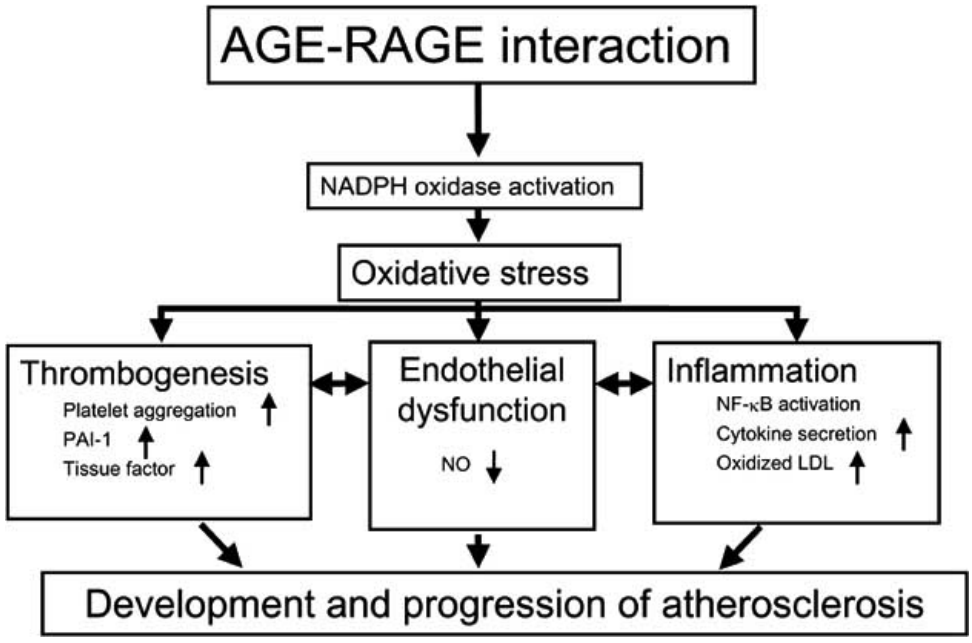

Fig. (2). Possible participation of AGE-RAGE system in the development and progression of atherosclerosis.

differentiate into other mesenchymal cell types under various circumstances, and may function as resting stem cells to be converted into smooth muscle cells, macrophage-like phagocytes or osteoblasts [69,70]. Indeed, under hypoxic conditions, pericytes are capable of exhibiting phenotypic characteristics ascribed to osteoblasts [71]. These observations suggest that AGEs and hypoxia may be main inducers of osteoblastic differentiation of pericytes. The finding that vascular calcification is often associated with plaque angiogenesis suggests the active participation of microvascular pericytes in plaque instability in atherosclerosis [72].

Recently, serum levels of AGEs were found to be elevated in diabetic patients with coronary heart disease [73], and were associated with endothelial dysfunction [74], one of the initial steps of atherosclerosis, further supporting the clinical relevance of AGEs in CVD in patients with diabetes.

5. INHIBITORS OF THE AGE-RAGE SYTSEM

In animal models, Schmidt *et al.* has demonstrated that diabetic apoE null animals receiving soluble RAGE (sRAGE) display a dose-dependent suppression of advanced atherosclerosis in these mice [75]. Lesions that formed in animals receiving sRAGE appeared largely arrested at the fatty streak stage; the number of complex atherosclerotic lesions was strikingly reduced in diabetic apoE null mice. The tissue and plasma AGE burden was suppressed in diabetic apoE null mice receiving sRAGE, suggesting that the AGE-RAGE-induced oxidative stress generation might participate in AGE formation themselves. These observations suggest the active involvement of AGE-RAGE interaction in the pathogenesis in accelerated atherosclerosis in diabetes. The same group has recently reported that the AGE-RAGE system contributes to atherosclerotic lesion progression as well, and that RAGE blockade stabilizes the lesions in these mice [76]. Another study shows a correlation between AGE levels and the degree of atheroma in cholesterol-fed rabbits, and that aminoguanidine has an anti-atherogenic effect in these rabbits by inhibiting AGE formation [77].

There is a growing body of evidence that hypertension is an independent risk factor for the incidence and progression of diabetic vascular complications and that strict blood pressure control achieves a clinically important reduction in the risk of progression of these devastating disorders [78,79]. Nifedipine is one of the widely used dihydropyridine-based calcium antagonists (DHPs) for treatments of patients with hypertension [80]. We have recently found that nifedipine inhibited RAGE overexpression in AGE-exposed ECs by suppressing ROS generation [81]. Since RAGE is a signal-transducing receptor for AGEs and that engagement of RAGE by AGEs elicits vascular and inflammatory cell perturbation, blockade of RAGE expression by nifedipine may have therapeutic potentials in treatment of patients with various AGE-related disorders including diabetic vascular complication [82,83].

Recently, food-derived AGEs are reported to induce oxidative stress and enhance inflammatory cytokine production [84]. Dietary glycotoxins promote diabetic atherosclerosis in apoE-deficient mice [85]. The marked atheroprotective effects of an AGE-restricted diet in these models may provide the basis for relevant clinical studies.

Compared to the strategy of preventing the AGE-RAGE interaction, the manupulation of the AGE signaling pathways as a therapeutic option in diabetic macrovascular complications remains much less developed. However, our recent findings that the AGE-RAGE interaction elicited vascular inflammation by NADPH oxidase-mediated ROS generation and the subsequent NF-κB activation via Ras-mitogen activated protein kinase (MAPK) pathway [36,60] may provide a novel therapeutic option for CVD in diabetes. Indeed, we have recently found that cerivastatin or incardronate disodium blocked the AGE-signaling in endothelial cells by suppressing protein prenylation of small G proteins Rac and Ras [60,86]. Furthermore, cyclic AMP elevating agents such as beraprost sodium also blocked the AGE-signaling by inhibiting NADPH oxidase activity [87]. These observations suggest that NADPH oxidase activated by AGEs may be a promising molecular target for the treatment of CVD in diabetes. In addition, we have very recently found that pigment epithelium-derived factor (PEDF), one of the superfamily of serine protease inhibitors with potent neuronal differentiating activity in human retinoblastoma cells, inhibited the AGE-elicited endothelial cell activation by suppressing NADPH oxidase-induced ROS generation as well [88].

6. ROLES OF THE RAS AND ITS INHIBITION IN CVD IN DIABETES

The metabolic syndrome is strongly associated with insulin resistance and consists of a constellation of factors such as hypertension and hyperlipidemia that raise the risk for cardiovascular diseases and diabetes mellitus [89]. Hypertension occurs approximately twice as frequently in patients with diabetes compared with in non-diabetic controls [90-92]. Conversely, recent data suggest that hypertensive patients are more likely to develop diabetes than normotensive persons [90-92]. The association of diabetes with hypertension increases its risk of cardiovascular morbidity and mortality. Indeed, up to 75% of CVD in diabetic patients can be attributed to hypertension [90-92]. Therefore, the primary goals of treating the metabolic syndrome are prevention of type 2 diabetes and cardiovascular events.

There is widespread agreement that the RAS plays a pivotal role in the pathogenesis of insulin resistance and CVD in diabetes and that large clinical trials have demonstrated substantial benefit of the blockade of this system for end-organ protection [93-95]. Interruption of the RAS with angiotensin-coverting enzyme inhibitors (ACEIs) or angiotensin II type 1 receptor blockers (ARBs) has been recently shown to prevent the onset of diabetes in hypertensive patients and to reduce cardiovascular and renal disease progression in diabetic patients with hypertension [93-95].

On the basis of these findings, the American Diabetes Association currently recommends ARBs as first-line therapy for hypertensive type 2 diabetic patients with micro- or macroalbuminuria. Among various ARBs, telmisartan was recently reported to act as a partial agonist of

peroxisome proliferator-activated receptor-γ (PPAR-γ), thus reducing glucose, insulin, and triglyceride levels in rats fed a high-fat, high-carbohydrate diet [96,97]. PPAR-γ influences the gene expression involved in carbohydrate and lipid metabolism, and pioglitazone and rosiglitazone, ligands for PPAR-γ, improve insulin resistance in diabetic patients [98,99]. Furthermore, there is a growing body of evidence to show that activators of PPAR-γ exert anti-inflammatory, anti-oxidative and anti-proliferative effects on vascular wall cells, thus decreasing the risks for atherosclerosis in insulin resistant patients [98,99]. These observations suggest that that due to its unique PPAR-γ-modulating activity, telmisartan would become a promising 'cardiometabolic sartan', that targets both diabetes and CVD in patients with the metabolic syndrome. Ongoing clinical trial (ONTARGET) has been designed to study the efficacy of telmisartan with an ACEI, ramipril, alone or in combination [100]. This randomized, double-blind, multicenter international study will provide further information whether telmisartan can actually improve insulin resistance and subsequently reduce the development of diabetes and CVD in high-risk hypertensive patients.

We have recently found that angiotensin II augmented the AGE-signaling in vascular wall cells by up-regulating RAGE expression and that telmisartan completely blocked the crosstalk between the RAS and AGE-RAGE system (unpublished data).

CONCLUSIONS

Postprandial hyperglycemia, increased levels of AGE formation and the activated RAS induce adhesion molecules and coagulation factors in vascular wall cells via oxidative stress generation, thus being involved in the pathogenesis of endothelial dysfunction and atherosclerosis. Further large clinical studies will clarify whether commercially available drugs mentioned in this review could actually reduce the risk of CVD in patients with diabetes.

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