Review
Cardiovascular disease in recent onset diabetes mellitus

Shoichi Yamagishi (MD, PhD) *

Department of Pathophysiology and Therapeutics of Diabetic Vascular Complications, Kurume University School of Medicine, Kurume 830-0011, Japan

Received 5 January 2011; accepted 6 January 2011
Available online 2 March 2011

KEYWORDS
Atherosclerosis; Diabetes; Oxidative stress; Postprandial hyperglycemia; AGEs

Summary
Diabetes is associated with a marked increased 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. Conventional risk factors, including hyperlipidemia, hypertension, smoking, obesity, lack of exercise, and a positive family history, contribute similarly to macrovascular complications in type 2 diabetic patients and non-diabetic subjects. The levels of these factors in diabetic patients are certainly increased, but not enough to explain the exaggerated risk for macrovascular complications in the diabetic population. Furthermore, recently, macrovascular complications of diabetes have been shown to start before the onset of diabetes. Indeed, several clinical studies have confirmed the increased risk of CVD in patients with impaired glucose tolerance (IGT). Since insulin resistance-related postprandial metabolic derangements are thought to play a central role in the development and progression of CVD in patients with IGT, amelioration of postprandial metabolic disturbance is a therapeutic target for the prevention of CVD in these high-risk patients. Therefore, in this paper, we review the molecular mechanisms for the increased risk of CVD in recent onset diabetes mellitus, especially focusing on postprandial dysmetabolism. We also discuss here the potential therapeutic strategies that specially target the mechanisms responsible for vascular alterations in diabetes.

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* Corresponding author. Tel.: +81 942 31 7873; fax: +81 942 31 7895.
E-mail address: shoichi@med.kurume-u.ac.jp

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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 the general population [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 the diabetic population. Therefore, diabetes-related specific risk factors should be involved in the excess risk in diabetic patients.

Macrovacular complications of diabetes have been shown to start before the onset of diabetes [3]. Several clinical studies have confirmed the increased risk of CVD in patients with impaired glucose tolerance (IGT) [4,5]. Insulin resistance could explain the increased risk for CVD in patients with IGT because insulin resistance is associated with IGT and postprandial hyperglycemia/hyperlipidemia [5]. Further, recently, insulin resistance-related postprandial dysmetabolism, including postprandial hyperglycemia/hyperlipidemia, was shown to be of greater importance in CVD in patients with type 2 diabetes [5]. These observations suggest that amelioration of postprandial metabolic derangements is a therapeutic target for preventing CVD in these patients. Therefore, in this review, we discuss the molecular mechanisms for accelerated atherosclerosis and increased risk for CVD in patients with recent onset diabetes mellitus, especially focusing on postprandial dysmetabolism. We also discuss here the potential therapeutic strategies that specially target the mechanisms responsible for vascular alterations in diabetes.

Postprandial dysmetabolism and CVD in diabetes

Epidemiological link

Several prospective studies have shown that hyperglycemia itself is clearly involved in predicting CVD [6]. In newly diagnosed type 2 diabetes, 10-year cardiovascular mortality increases three-fold by tertiles of blood glucose and glycated hemoglobin (Hb) A1c [7]. There is a significant increase in the risk of CVD death and all CVD events in type 2 diabetic subjects with HbA1c levels higher than 7.0% compared with diabetic subjects with lower HbA1c [8]. 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 Kingdom Prospective Diabetes Study (UKPDS) study, intensive blood glucose control effectively reduced microvascular complications in type 2 diabetic patients [9]. However, the risk of myocardial infarction was reduced slightly but not significantly by about 15%, and the risk reduction of myocardial infarction by control of blood glucose is less than that by the treatment of hypertension (21%) or hypercholesterolemia (31%). Since the reduction of hyperglycemia was small and the intervention period was relatively short, the beneficial effects of blood glucose control on CVD may be underestimated in this trial. Indeed, in the 10-year follow-up study of UKPDS, UKPDS80, despite an early loss of glycemic differences between the original intensive therapy group and the conventional one, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed [10]. These findings demonstrate that so-called ‘metabolic memory’ could cause chronic abnormalities and exert carry-over effects in diabetic vessels that are not easily reversed, even by subsequent, relatively good control of blood glucose. These observations suggest a long-term beneficial influence of early metabolic control, that is, legacy effects, on the risk of vascular complications and death in patients with diabetes [11].

Risk of CVD begins to increase before the onset of diabetes. Several studies have confirmed the increased risk of CVD in patients with IGT [3,4]. Furthermore, insulin resistance in the absence of overt diabetes has been associated with endothelial dysfunction, a surrogate marker of atherosclerosis [12,13]. Therefore, atherosclerotic process may actually begin earlier in the spectrum of insulin resistance. Insulin resistance-associated postprandial hyperglycemia may play a role in the development and progression of CVD in patients with recently diagnosed diabetes [5]. Indeed, in the Funagata diabetes study, analysis of survival rates concluded that IGT, but not impaired fasting glucose, was a risk factor for CVD [14]. 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 [15]. 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. Furthermore, the Diabetes Intervention Study (DIS) identified postprandial hyperglycemia to be an independent risk factor for myocardial infarction and all-cause mortality [16]. 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 [17–19]. 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 [20]. These observations suggest that the decrease of HbA1c levels could not necessarily reflect the reduction of...
postprandial hyperglycemia, especially in poorly controlled diabetic patients. This could partly explain why decreased HbA1c levels did not significantly lead to the reduction of the risk for CVD in the UKPDS trial.

There are several papers to suggest the link between postprandial hyperlipidemia and CVD in diabetic and non-diabetic subjects [21—23]. In a prospective cohort study of 7587 women and 6394 men from the general population of Copenhagen, elevated non-fasting triglyceride levels were associated with increased risk of myocardial infarction, ischemic heart disease, and death in both men and women [21]. Further, non-fasting serum triglycerides were reported to independently predict the incidence of coronary heart disease among Japanese men and women who possess low mean values of total cholesterol as well [22]. A recent meta-analysis of 27 prospective studies of western populations reported that non-fasting triglycerides were independently associated with CVD [23].

Possible molecular mechanisms underlying the link

In vitro, intermittent and constant high glucose have been shown to not only enhance apoptotic cell death, but also stimulate expression of adhesion molecules (intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin) as well as interleukin-6 (IL-6) in cultured endothelial cells through oxidative stress generation via both protein kinase C-dependent activation (IL-6) in cultured endothelial cells through oxidative stress generation. These observations suggest that postprandial hyperglycemic spike-activated oxidative stress generation may be involved in the development of vascular injury in diabetes.

Postprandial hyperglycemia induces oxidative stress generation in diabetic patients as well [26,27]. Monnier et al. reported that urinary excretion of an oxidative stress marker, 8-isoprostaglandin F2α, was independently associated with mean amplitude of glycemic excursions in type 2 diabetes, thus suggesting that glucose fluctuations during postprandial periods could exhibit a more specific triggering effect on oxidative stress generation than chronic sustained hyperglycemia [26]. Under oxidative stress conditions, nitric oxide (NO) undergoes a rapid reaction with superoxide anions to form peroxynitrite, a toxic metabolite of NO, which could cause endothelial dysfunction, an initial step of atherosclerosis [11,12]. 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 [11,12]. Moreover, postprandial hyperglycemia-elicited oxidative stress generation induces platelet activation and thrombin generation and inactivates fibrinolytic systems, thereby participating in the progression of atherosclerosis in diabetes [27,28].

Postprandial triglyceride-rich lipoproteins induce NF-κB activation in endothelial cells and subsequently up-regulate expression of several pro-inflammatory genes including ICAM-1, VCAM-1, monocyte chemoattractant protein-1 (MCP-1), and IL-6 [29]. In addition, postprandial hypertriglyceridemia has been shown to be independently associated with carotid IMT in patients with type 2 diabetes [30]. The positive relationships among postprandial lipemia, endothelial dysfunction, and oxidative stress were also reported in type 2 diabetic patients [31]. Further, postprandial hypertriglyceridemia was more prominent in type 2 diabetic patients with microalbuminuria, thus partly explaining the excess risk of CVD in these subjects [32]. Ceriello and colleagues have shown that postprandial hyperglycemia and/or hypertriglyceridemia are associated with an increase of plasma levels of nitrotyrosine and inflammatory and thrombogenic biomarkers such as IL-6, soluble ICAM-1, soluble VCAM-1 and prothrombin fragment 1+2 [27,28,33]. They showed that postprandial dysmetabolism was accompanied with oxidative stress and endothelial dysfunction in diabetic patients as well.

We have previously shown that glyceraldehyde can rapidly react with amino groups of proteins to form glyceraldehyde-derived advanced glycation end products (AGEs) in vivo, which elicit oxidative stress generation and evoke vascular inflammation and insulin resistance in patients with diabetes [34,35]. Further, we have recently found that serum levels of glyceraldehyde-derived AGEs rather than HbA1c could reflect cumulative postprandial hyperglycemia in oral hypoglycemic agent-naive type 2 diabetic patients [36]. In addition, increased production of methylglyoxal and 3-deoxyglucose, two highly reactive precursors of AGEs has been reported to occur with greater postprandial glycemic excursions in type 1 diabetic patients, whereas HbA1c does not reflect these differences [37]. Given the deleterious effects of glyceraldehyde-, methylglyoxal-, and 3-deoxyglucose-derived AGEs on CVD in diabetes [34,35], postprandial hyperglycemia may promote atherosclerosis partly via activation of AGEs-oxidative stress system.

Potential therapeutic strategies for postprandial dysmetabolism

Administration of acarbose, an α-glucosidase inhibitor, for 12 weeks in non-obese type 2 diabetic rats improved postprandial hyperglycemia, postprandial insulin level, triglyceride, and fatty acid levels [38]. Furthermore, acarbose efficiently reduced the number of monocytes adherent to aortic endothelial layer, improved acetylcholine-dependent vasodilation, and reduced intimal thickening of the aorta. These findings may suggest that acarbose could exert atheroprotective properties, at least in part, by suppressing monocyte adhesion to endothelial cells via the inhibition of repetitive postprandial hyperglycemia in diabetes.

It is well known that postprandial metabolic abnormalities can be induced in rats by fructose-rich diets [5]. Indeed, we have previously shown that hyperinsulinemia and hypertriglyceridemia with lowered high-density lipoprotein (HDL)-cholesterol levels developed in rats that were fed a high fructose diet for 4 weeks [5]. Acarbose treatment improved insulin resistance in fructose-fed rats [5]. The treatment also increased HDL-cholesterol levels and inhibited the elevation of systolic blood pressure. Furthermore, oral administration of acarbose decreased serum levels of MCP-1 and its expression in aorta in fructose-fed rats. MCP-1 has been postulated to play an important role in the early
phase of atherosclerosis by initiating monocyte recruitment to the vessel wall, and its expression is found to be elevated in human atherosclerotic plaques [39]. Moreover, the selective targeting of CCR2, the receptor for MCP-1, was shown to markedly decrease atheromatous lesion formation in apoE knockout mice [39]. In addition, MCP-1 has contributed to insulin resistance by evoking inflammatory reactions in adipose tissues as well [40]. Taken together, these observations suggest that acarbose may play a protective role against atherosclerosis and insulin resistance in diabetes by suppressing MCP-1-induced inflammatory reactions via amelioration of postprandial dysmetabolism.

In patients with type 2 diabetes, acarbose treatment was shown to not only increase serum lipoprotein lipase mass levels [41], but also decrease circulating levels of oxidized low-density lipoprotein (LDL)-cholesterol, plasminogen activator inhibitor-1 and fibrinogen [42]. Further, a single administration of acarbose has been reported to improve postprandial glucose excursion and endothelial dysfunction in type 2 diabetic patients as well [43]. Acarbose also attenuated several of the characteristic hepatic alterations of non-alcoholic steatohepatitis, a hepatic manifestation of insulin resistance: there was less steatosis and inflammation with a significant reduction in tumor necrosis factor-α expression [5].

The STOP-NIDDM trial revealed that acarbose improved postprandial hyperglycemia and subsequently reduced the risk of diabetes in patients with IGT [44]. Acarbose treatment was also 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 [45]. Acarbose significantly reduced body weight and increased HDL-cholesterol levels 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 [5]. 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. Improvement of postprandial hyperglycemia itself could be associated with amelioration in insulin sensitivity.

Repaglinide, a rapid-onset/short-duration insulinotropic agent, has been shown to decrease circulating inflammatory markers such as IL-6 and C-reactive protein and regress carotid atherosclerosis by the control of postprandial hyperglycemia in patients with type 2 diabetes [46]. Administration of another rapid insulinotropic agent, mitiglizide, significantly decreased oxidative stress markers including nitrotyrosine and oxidized LDL levels and preserved total radical-trapping anti-oxidant capacity in diabetic patients as well [47]. In addition, as compared with regular insulin, short-acting insulin such as insulin aspart reduced the area under the curve for postprandial hyperglycemia and nitrotyrosine and preserved flow-mediated vasodilation [17]. We have recently found that combination therapy with nateglinide and telmisartan could ameliorate insulin resistance in Zucker fatty rats by suppressing the AGES-oxidative stress axis in the liver [48]. These findings suggest that control of excessive glucose excursions by glinides or aspart, especially in the postprandial state, may also become a novel therapeutic strategy for the prevention of insulin resistance and CVD in diabetes.

Conclusions

As mentioned above, recent clinical studies have substantiated the concept of ‘metabolic memory’ in the pathogenesis of CVD in diabetes [34,35]. The biochemical nature of AGES and their mode of actions are most compatible with the theory ‘metabolic memory’ [34,35,49]. Further large clinical studies are needed to clarify whether aggressive treatment for postprandial dysmetabolism could reduce the risk of CVD in patients with recent onset diabetes by blocking the AGES-oxidative stress axis.

Acknowledgments

This work was supported in part by Grants of Collaboration with Venture Companies Project from the Ministry of Education, Culture, Sports, Science and Technology, Japan (S.Y.).

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