Role of postprandial hyperglycaemia in cardiovascular disease in diabetes

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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 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 hyperlipidaemia, 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 diabetic population. 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 hyperglycaemia. We also discuss here the potential therapeutic strategy that specifically targets CVD in patients with diabetes.

Role of postprandial hyperglycaemia in CVD in diabetes

Epidemiological link between postprandial hyperglycaemia and CVD

In the last decade, several prospective studies have shown that hyperglycaemia 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 HbA1c (5). 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 (6,7). The conclusive answer to the question on the existence of cause-effect relationship between hyperglycaemia and CVD may derive from intervention studies. In the United Kingdom 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 hypercholesterolaemia (31%). As the reduction of hyperglycaemia is small...
in this trial, the role of hyperglycaemia 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 hyperglycaemia (14). Recently, postprandial hyperglycaemia 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 postload hyperglycaemia 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 identified postprandial hyperglycaemia to be an independent risk factor for myocardial infarction and all-cause mortality (18). Moreover, postprandial hyperglycaemia 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 hyperglycaemia is involved in early atherosclerosis (19–22). 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 (23). These observations suggest that the decrease of HbA1c levels could not necessarily reflect the reduction of postprandial hyperglycaemia, 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 UKPDS.

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, vascular cell adhesion molecule-1 and E-selectin) as well as interleukin-6 in cultured endothelial cells through oxidative stress generation via protein kinase C-dependent activation of NADPH oxidase and mitochondrial electron transport chain (24,25). The deleterious effects are even more evident in intermittent high glucose. These observations suggest that postprandial hyperglycaemic spike may be involved in the development of vascular injury in diabetes.

Postprandial hyperglycaemia induces oxidative stress generation via various biochemical pathways such as advanced glycation end product formation, protein kinase C activation and stimulation of the polyol pathway (26,27). There is a growing body of evidence that oxidative stress generation is the pathogenic molecular mechanism linking postprandial hyperglycaemia to endothelial dysfunction, an initial step of atherosclerosis (Figure 1) (28). Indeed, nitric oxide (NO) undergoes a rapid reaction with superoxide anions to form peroxynitrite, a toxic metabolite of NO, which could cause vascular damage (29). Furthermore, the loss of NO permits increased activity of the redox-sensitive transcription factor nuclear factor-kB (NF-kB), which could lead to vascular inflammation and altered gene expression of cytokines and growth factors (30,31). Moreover, postprandial hyperglycaemia-elicited oxidative stress generation induces platelet activation and thrombin generation as well, thereby participating in the progression of atherosclerosis in diabetes (32,33).

Inhibitors of postprandial hyperglycaemia

Administration of acarbose, an α-glucosidase inhibitor, for 12 weeks in non-obese type 2 diabetic rats improved postprandial hyperglycaemia, postprandial insulin level, triglyceride and fatty acid levels (34). 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 hyperglycaemia in diabetes.

The metabolic syndrome, also called insulin resistance syndrome, is a clustering of coronary risk factors, such as high triglyceride, low high-density lipoprotein (HDL) cholesterol and hypertension (35,36). It is well known that these metabolic abnormalities can be induced in rats by fructose-rich diets (37). Indeed, we have previously shown that hyperinsulinaemia and hypertriglyceridaemia with lowered HDL-cholesterol levels developed in rats that were fed a high fructose diet for 4 weeks (37). Acarbose treatment improved insulin resistance in fructose-fed rats. The treatment also increased HDL levels and inhibited the elevation of systolic blood pressure. Furthermore, oral administration of acarbose decreased serum levels of monocyte chemoattractant protein-1 (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 (38), and its expression is found to be elevated in human atherosclerotic plaques (39). Moreover, recently, the selective targeting of CCR2, the receptor for MCP-1, was shown to decrease markedly atheromatous lesion formation in apoE knockout mice (40). Therefore, our present study suggests that acarbose may also play a protective role against atherosclerosis by suppressing MCP-1 overexpression in patients with insulin resistance. Recently, a single administration of acarbose has been reported to improve postprandial glucose excursion and endothelial dysfunction in type 2 diabetic patients as well (41).

The STOP-NIDDM trial revealed that acarbose improved postprandial hyperglycaemia and subsequently reduced the risk of diabetes in patients with IGT (42). Recently, 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 (43,44). 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, randomised trials has shown that intervention with acarbose prevents myocardial infarction and CVD in type 2 diabetic patients (45). In this analysis, glycaemic control, triglyceride levels, body weight and systolic blood pressure was also significantly improved during acarbose treatment. These observations suggest that prevention of postprandial hyperglycaemia by acarbose may be a promising therapeutic strategy for reducing the increased risk for diabetes, hypertension, dyslipidaemia, obesity and CVD in patients with diabetes or the metabolic syndrome. Acarbose is known to improve postprandial hyperglycaemia by delaying the release of glucose from complex carbohydrates in the absence of an increase in insulin secretion. Taken together, improvement of postprandial hyperglycaemia 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 hyperglycaemia in patients with type 2 diabetes (46). Administration of another rapid insulinotropic agent, mitiglinide, significantly decreased oxidative stress markers including nitrotyrosine and oxidised low-density lipoprotein (LDL) levels and preserved total radical-trapping antioxidant capacity in diabetic patients as well (47). In addition, as compared with regular insulin, short-acting insulins such as insulin aspart reduced the area under the curve for postprandial hyperglycaemia and nitrotyrosine, and preserved flow-mediated vasodilation (48,49). These observations 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 CVD in diabetic patients.

Conclusions

The recently published Collaborative Atorvastatin Diabetes Study (CARDS), a multicentre-randomised placebo-controlled trial, revealed that 10 mg daily atorvastatin was efficacious in reducing the risk of first cardiovascular events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol (50). In this study, the benefit from atorvastatin treatment was independent of age, sex, basal levels of lipids and blood pressure or HbA₁c. These data were keeping with the diabetic subanalysis of Heart Protection Study (51), thus suggesting that there is no threshold of LDL levels at which type 2 diabetic patients should be initiated on statin therapy. Furthermore, a recent analysis by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC) revealed that any commonly-used BP-lowering regimen also reduced the risk of total major cardiovascular events, and larger reductions in BP produced larger reductions in the risk, especially in diabetic patients (52). As described above, postprandial hyperglycaemia induces 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 aggressive treatment for conventional risk factors including postprandial hyperglycaemia could reduce the risk of CVD in patients with diabetes or the metabolic syndrome.

Acknowledgements

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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Paper received August 2006, accepted September 2006