

Dipeptidyl Peptidase-4 Inhibitors – Emerging Player for Vascular Protection –

Kimio Satoh, MD, PhD

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors Improves Endothelial Dysfunction in Diabetic Patients With Coronary Artery Disease (CAD)

The development of atherosclerosis is initiated by activation of endothelial cells, leading to expression of adhesion molecules for inflammatory cells.¹ A critical step in the progression of atherosclerosis is the development of an oxidizing environment by activation of macrophages and vascular inflammation. These macrophages produce abundant reactive oxygen species (ROS) and secrete several inflammatory cytokines/chemokines that contribute to the progression of atherosclerosis.² It has been widely recognized that oxidative stress, generated by excessive ROS, promotes endothelial inflammation and atherosclerosis.³ ROS is increased in patients with hypertension, diabetes mellitus (DM), smoking, dyslipidemia, and advanced age, all of which are atherosclerotic risk factors in humans.⁴ Among them, the association between type 2 DM and cardiovascular events is apparent in the Japanese population.⁵ Approaches designed to reduce the inflammation and improve endothelial function may therefore be important in the prevention and treatment of atherosclerotic diseases, including CAD.

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DPP-4 inhibitors are novel drugs for the treatment of type 2 DM. They exert their action through inhibition of the catabolism of locally secreted incretins and glucose-dependent insulinotropic polypeptide (GIP) by inhibiting enzyme DPP-4. In addition to their antidiabetic action, recent experimental and clinical studies have demonstrated a pleiotropic cardiovascular protective effect of these agents (Figure). In this issue of the Journal, Matsubara et al⁶ test the hypothesis that sitagliptin, a DPP4 inhibitor, could improve endothelial dysfunction in DM patients with CAD. They and others have already reported that DPP-4 inhibitors prevent atherosclerosis in animal models.^{7,8} In their current study, 40 patients with uncontrolled DM and CAD were assigned to additional treatment with sitagliptin or aggressive conventional treatment for 6 months. Endothelial function was assessed by the reactive hyperemia peripheral arterial tonometry index (RHI) and the percent change in RHI was greater in the sitagliptin group than in the control group. This finding is of particular importance in the clinical setting.

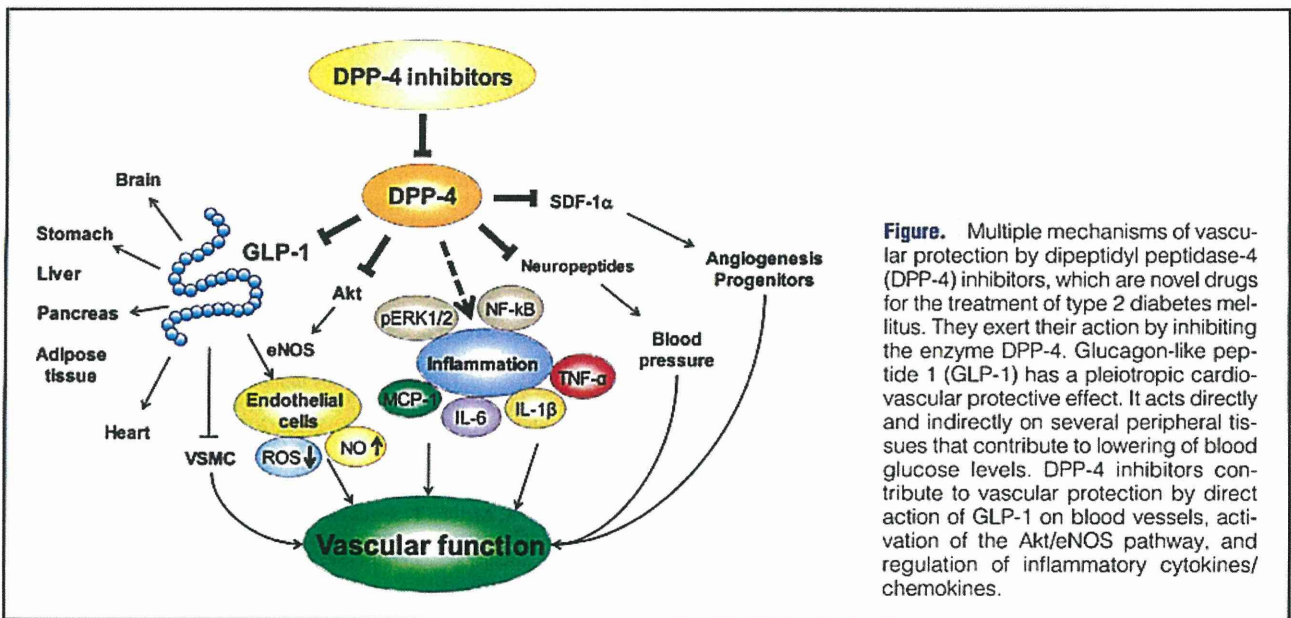


Figure. Multiple mechanisms of vascular protection by dipeptidyl peptidase-4 (DPP-4) inhibitors, which are novel drugs for the treatment of type 2 diabetes mellitus. They exert their action by inhibiting the enzyme DPP-4. Glucagon-like peptide 1 (GLP-1) has a pleiotropic cardiovascular protective effect. It acts directly and indirectly on several peripheral tissues that contribute to lowering of blood glucose levels. DPP-4 inhibitors contribute to vascular protection by direct action of GLP-1 on blood vessels, activation of the Akt/eNOS pathway, and regulation of inflammatory cytokines/chemokines.

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Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

Mailing address: Kimio Satoh, MD, PhD, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine,

Sendai 980-8574, Japan. E-mail: satoh-k@cardio.med.tohoku.ac.jp

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The authors also report that treatment with sitagliptin resulted in a significant decrease in high-sensitivity C-reactive protein (hsCRP) levels in the DM patients, but not in the controls. Therefore, they concluded that sitagliptin significantly improved endothelial function and inflammatory state in patients with uncontrolled DM with CAD.

The new anti-type-2 DM drugs, including DPP-4 inhibitors and glucagon-like peptide 1 (GLP-1) analogs, improve glucose metabolism through activation of GLP-1 receptor signaling, which induces insulin secretion and suppresses glucagon secretion in the pancreas. Several studies have reported the beneficial effects of GLP-1 on the cardiovascular system. Because of these findings, it has been hypothesized that DPP-4 inhibitors would improve endothelial dysfunction in association with improvement of inflammation in DM patients with CAD. On this basis, Matsubara et al investigated whether additional treatment with the DPP-4 inhibitor, sitagliptin, improves endothelial dysfunction in patients with uncontrolled DM and CAD.⁶

The expression of hsCRP was significantly reduced in the sitagliptin group and the authors offer a plausible mechanism as to this important observation. Recently, they reported that sitagliptin reduced the mRNA expression levels of proinflammatory mediators, such as interleukin (IL)-6, IL-1 β , monocyte chemoattractant protein (MCP)-1 and tumor necrosis factor- α , in the aorta of apolipoprotein-E-deficient mice.⁷ In that study, they demonstrated that sitagliptin significantly increased GLP-1-induced cytosolic levels of cyclic adenosine monophosphate compared with GLP-1 alone, resulting in inhibition of phosphorylation of extracellular signal-regulated kinase 1/2 and nuclear factor- κ B p65 nuclear translocation, and suppression of proinflammatory cytokine and MCP-1 production in human cultured macrophages. They further demonstrated that sitagliptin significantly attenuated the expression of ICAM-1 and VCAM-1 and increased the phosphorylation of endothelial nitric oxide synthase in human cultured coronary endothelial cells.⁷ As elucidated by the authors, sitagliptin can suppress vascular inflammation, protect endothelial function and prevent the development of atherosclerosis (Figure).

Clinical Perspectives

In the present study, the authors found that sitagliptin significantly improved peripheral endothelial dysfunction associated with its anti-inflammatory effects in uncontrolled DM patients with CAD. The involvement of endothelial dysfunction in all stages of atherogenesis is generally accepted. The authors evaluated peripheral endothelial function by RH-PAT, which they have previously demonstrated can predict CAD, especially non-obstructive CAD associated with coronary endothelial dysfunction.⁹ Others have also demonstrated that the RH-PAT index predicts coronary endothelial dysfunction.¹⁰ Therefore, RH-PAT may be a useful marker for evaluating the therapeutic effects of cardiovascular medications. Importantly, Matsubara et al demonstrated that treatment with sitagliptin increased the RH-PAT index in DM patients with CAD.⁶

However, several issues remain regarding the interpretation of this study. First, the sample size was small, and the design was a single center study. Because of the small number of patients, the authors could not further investigate the effects of other drugs reported to influence endothelial function such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and statins. Second, as the authors did not measure the concentrations of GLP-1 and GIP, it is unclear whether the improvement of endothelial dysfunction by sitagliptin

depends on GLP-1. Third, the authors did not measure oxidative stress, which is an important marker for DPP-4-mediated vascular protection.¹¹ My group has previously demonstrated that the plasma level of cyclophilin A (CyPA), a novel oxidative stress marker, is significantly increased in patients with DM.¹² CyPA is secreted from vascular smooth muscle cells in a Rho-kinase-dependent manner^{2,13,14} and promotes endothelial dysfunction and apoptosis.³ It is well known that Rho-kinase is associated with activation of the NADPH oxidases, with resultant ROS production, which plays a crucial role in the development of cardiovascular diseases.¹⁵ Therefore, the correlation between the changes in endothelial function by RH-PAT and the oxidative stress marker should have been assessed in the DM patients with CAD. Further studies aimed at elucidating the mechanism with a large number of participants will provide important evidence for adding DPP-4 inhibitors to the conventional therapy for DM patients with CAD.

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