Do DPP-4 inhibitors improve endothelial cell function?

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Abstract

DPP-4 inhibitors have been used to treat patients with type 2 diabetes mellitus. These agents not only provide glycemic control, but also have other favorable effects, including the prevention of atherosclerosis. However, it has not been determined whether these agents can improve or maintain endothelial cell function. We previously reported the results of two prospective studies assessing the effects of incretin agents on flow-mediated dilation in patients with type 2 diabetes mellitus without severe atherosclerotic diseases. These studies showed that both the DPP-4 inhibitor sitagliptin and the GLP-1 analogue liraglutide did not improve endothelial cell function. This report discusses the effects of sitagliptin on early-stage atherosclerosis and beta-cell function.

Keywords: DPP-4 inhibitor, Endothelial cell function.

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Introduction

Patients with type 2 diabetes mellitus are at a markedly higher risk of cardiovascular events than individuals without diabetes [1]. Therefore, prevention and improvement of atherosclerosis in patients with diabetes are as important as maintaining favorable blood glucose control. Fluctuations in blood glucose levels have been reported to be closely related to endothelial cell damage [2], known to be the first stage of atherosclerosis. Flow-mediated dilation of the brachial artery (FMD) reflects endothelial nitric oxide bioavailability and is widely used as a marker of endothelial cell function and early atherosclerosis [3].

In recent years, several hypoglycemic agents with noble mechanisms have been used to treat type 2 diabetes mellitus. One class of incretin drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors, has been found to inhibit glucose fluctuation and avoid hypoglycemia by suppressing insulin secretion and disinhibiting suppression of glucagon secretion under normoglycemic and hypoglycemic conditions.

These agents have been reported to not only have favourable effects on glucose metabolism but also to have anti-atherosclerotic effects *in vitro* and in animal models. Several recent clinical trials have reported that DPP-4 inhibitors affect FMD, a marker of early atherosclerosis, but their results are inconsistent [4,5].

We describe here the results of an open-label, prospective, randomized, parallel-group comparison study assessing whether the DPP-4 inhibitor sitagliptin improves endothelial cell function [6].

Effects of Sitagliptin on Endothelial Cell Function

Among the clinically available tools to assess endothelial cell function is measurement of FMD. This parameter is frequently selected because of its ease of performance, non-invasiveness and plasticity. Moreover, improvements in FMD have been associated with reduced risks of cardiovascular outcomes [7].

Although previous clinical studies have reported that DPP-4 inhibitors have beneficial effects on FMD [8,9], these studies had several drawbacks, including those related to control groups, study duration, subject populations and accuracy of FMD measurements. In this 26-week, multicenter, open-label, prospective, randomized, parallel-group comparison study, we therefore focused on early phase atherosclerosis in patients with type 2 diabetes mellitus. In addition, FMD was measured by a well-trained technician blinded to study assignment. The original study results are illustrated in Table 1.

Table 1: Summary of the original study (SAIS-1).

	Sitagliptin (50 mg/day)	Glimepiride (0.5-2.0 mg/day)
Levels of HbA1c	Improved	Improved
%FMD	Not changed	Not changed
Inflammatory cytokine (TNF-α)	Improved	Not changed

Anti-oxidant responses (SOD, BAP)	Improved	Not changed
Lipid profiles (adiponectin, HDL-C)	Improved	Not changed
Beta-cell functions (SUIT, C-peptide index)	Improved	Improved

Although glycemic control improved equally in patients treated with 50 mg/day sitagliptin or 0.5–2.0 mg/day glimepiride for 26 weeks, neither group showed improvements in FMD, even after adjustment for confounding factors [6]. Similar results were observed with another method of evaluating endothelial function, the Endo-PAT, with reactive hyperemia index being similar in the two groups. These results indicated that sitagliptin had no effect on endothelial cell function, as assessed by FMD.

The effects of DPP-4 inhibitors on atherosclerosis were thought to be partially due to augmented GLP-1 signaling, but it is not clear whether endothelium expresses the GLP-1 receptor [10]. Moreover, another randomized clinical trial showed that long-term treatment with the GLP-1 analogue liraglutide, which possess more potent GLP-1 action, also did not ameliorate FMD [11]. Taken together, these findings suggest that GLP-1 may not have a direct effect on endothelial cell function. However, because continuous infusion of supraphysiologic concentrations of GLP-1 improved FMD [12], we could not exclude the possibility that GLP-1 has indirect action on systemic blood vessels.

Possible Effects of DPP-4 Inhibitors on Atherosclerosis

A recent prospective study showed that treatment with sitagliptin for 104 weeks significantly ameliorated intima-media thickness in patients with type 2 diabetes mellitus [13]. DPP-4 is thought to exert anti-atherosclerotic effects through pathways that increase GLP-1 signaling, inhibit the accumulation of macrophages, suppress macrophage-related inflammation and inhibit DPP-4-induced smooth muscle proliferation [14]. Our secondary analysis also showed that sitagliptin treatment for 26 weeks improved inflammatory, anti-inflammatory and anti-oxidant responses, as measured by concentrations of tumor necrosis factor (TNF)-α and super oxide dismutase (SOD) and by biological antioxidant potential, respectively. TNF-α has been reported involved in the onset and progress of atherosclerosis, and may induce endothelial cell dysfunction and apoptosis [15]. SOD, which plays a critical role in inhibiting the oxidative inactivation of nitric oxide, has been reported to prevent peroxynitrite formation and endothelial and mitochondrial dysfunction [16]. We also found that augmentation index, an independent predictor of cardiovascular events [17], tended to improve, but not significantly. Although we could not verify the direct action on endothelial function, managing such pro-/anti-inflammatory factors may result in prevention of atherosclerosis after long term treatment.

Beta-Cell Protection by Incretin Agents

Pancreatic beta-cells, which express relatively low levels of anti-oxidant enzymes, such as SOD, catalase and glutathione peroxidase, are sensitive to oxidative stresses [18]. Our study revealed that both sitagliptin and glimepiride improved not only HbA1c levels but also surrogate markers of beta-cell function, including C-peptide index and secretory units of islet transplantation [6]. Moreover, as described above, sitagliptin treatment improved SOD and biological antioxidant potential, quantitative measures of total antioxidant stress activity. Many *in vitro* studies have reported that DPP-4 inhibitors have protective effects on pancreatic beta-cells, reducing cell apoptosis [19,20] and anti-oxidant responses [21], suggesting our results may be reasonable. Moreover, DPP-4 inhibitors stabilize glucose fluctuations, which are closely related to endothelial cell damage [2], by inhibiting postprandial glucose and modifying fasting glycemia [22], these agents may be beneficial not only for glucose metabolism but for management of atherosclerosis.

Summary

In summary, our results indicated that incretin-agents, including DPP-4 inhibitors, did not directly improve endothelial function in patients with diabetes. However, DPP-4 inhibitors had beneficial effects on beta-cell function and anti-oxidant potentials. These results should be confirmed using other DPP-4 inhibitors and different treatment periods. The long-term efficacy of DPP-4 inhibitors in patients with atherosclerotic diseases should be assessed in future.

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