In the United States, nearly 13% of adults aged 20 years and older have type 2 diabetes mellitus (T2DM), and its prevalence is still increasing (1,2). Microvascular and macrovascular abnormalities are common in patients with T2DM and are related to the severity and duration of hyperglycemia (3–5). Thus, treatment of hyperglycemia is an important way to prevent or delay diabetic vascular complications.

Several clinical trials have been performed to examine whether intensive glucose lowering is effective for the prevention of cardiovascular events (6–8). However, intensive therapy targeting glycosylated hemoglobin levels lower than 6.0% for 3.5 years paradoxically increased all-cause mortality and did not significantly reduce major composite cardiovascular events compared with standard therapy (6). These findings disclose a previously unrecognized risk for intensive and rapid glucose lowering in high-risk patients with T2DM (6,9). However, it is also true that the same trials confirmed that the incidence of nonfatal myocardial infarction was significantly lower in the intensive glucose-lowering group compared with the standard therapy group (6,7,10). Moreover, the UKPDS 80 (United Kingdom Prospective Diabetes Study) demonstrated that better control of blood glucose was associated with continued risk reduction for microvascular complications, myocardial infarction, and all-cause death during 10 years of post-trial follow-up, a phenomenon called the “legacy effect” (4). Considering these clinical findings, it is desirable to use antidiabetic drugs that can effectively lower blood glucose levels but hardly induce hypoglycemia in patients with T2DM. One such ideal drug class is incretin-related drugs (11).

There are 2 main incretin hormones, glucose-dependent insulinotropic peptide (also known as gastric inhibitory peptide) and glucagon-like peptide (GLP)-1. Both hormones are secreted from endocrine cells located in the epithelium of the small intestine, triggered by an increase in the concentration of glucose in the intestinal tract (11). Incretins stimulate the pancreatic beta cells to secrete insulin but inhibit alpha cells from releasing glucagon. Thus, incretins reduce blood glucose levels in an orally taken glucose-dependent manner, and therefore these drugs hardly induce hypoglycemia. Both glucose-dependent insulinotropic peptide and GLP-1 are rapidly degraded by a serine protease, dipeptidyl peptidase (DPP)-4, and the fact that chemical inhibitors of DPP-4 prevented the degradation of glucose-dependent insulinotropic peptide and GLP-1 established the importance of DPP-4 as a critical determinant of incretin concentrations in vivo (12). Accordingly, 2 classes of incretin-related drugs have been developed; one is a GLP-1 analogue and the other a DPP-4 inhibitor.

Diabetic states augment reactive oxygen species, inflammatory responses, endothelial dysfunction, and lipid deposition in the vascular wall and thereby promote atherosclerosis (13). Thus, drugs that can not only control blood glucose levels but also inhibit cardiovascular complications are further desired. In this issue of the Journal, Matsubara et al. (14) report that a DPP-4 inhibitor, des-fluoro-sitagliptin (DFS), significantly inhibits atherosclerotic lesion formation in apolipoprotein E–deficient mice. DFS treatment lowered blood glucose levels during oral glucose tolerance testing, restored endothelial function ex vivo, and decreased endothelial cell senescence and apoptosis in vitro. DFS suppressed inflammatory cytokine production in cultured macrophages by enhancing the GLP-1–mediated cyclic adenosine monophosphate signaling cascade (14). The investigators’ data clearly indicate that DFS has both glucose-dependent and glucose-independent actions for antiatherosclerosis.

GLP-1 receptor is expressed in various tissues of the cardiovascular system (15), and previous studies have shown that GLP-1 analogues have not only glucose-lowering but also direct cardioprotective actions (16–18). A GLP-1 analogue, exendin–4, reduced macrophage accumulation in the arterial wall and thereby inhibited atherosclerotic lesion formation in apolipoprotein E–deficient mice (16), a similar animal model used by Matsubara et al. (14). GLP-1 also protected against myocardial ischemia and reperfusion injury in both animals and humans (17,18). These studies collectively support the concept that GLP-1 analogues and their elevating agents, DPP-4 inhibitors, may have direct cardioprotective actions independent of glucose-lowering (Fig. 1).
Another interesting aspect of DPP-4 inhibitors may be incretin-independent actions. In other words, DPP-4 has several important endogenous substrates other than incretins (19). For example, chemokine stromal cell–derived factor (SDF)-1 and substance P have been known to be cleaved by DPP-4, and their endogenous concentrations are significantly affected by DPP-4 inhibitors (19). SDF-1 has been known to induce angiogenesis in ischemic tissues and can recruit cardiac or endothelial progenitor cells from the bone marrow to injured cardiovascular tissues (20–22). Interestingly, the expression of SDF-1 is decreased within bone marrow to injured cardiovascular tissues (20–22). However, SDF-1 and substance P, which may elicit antiatherosclerotic and cardioprotective actions as well through a variety of mechanisms. However, the latter possibilities of biological action of DPP-4 inhibitors need further investigation.

Fact that the prevalence of T2DM is more common in patients with coronary artery disease compared with those without (26). However, it is still unknown whether plasma GLP-1 level is a major determinant of atherosclerotic disease burden in patients with T2DM. Although the investigators show a significant inverse correlation between plasma GLP-1 activity and the area of atherosclerotic lesions in the apolipoprotein E–deficient mice (14), this relation is still unknown for humans. Clearly, additional basic research and clinical studies are necessary to further address the antiatherogenic efficacy of DPP-4 inhibitors.

**REFERENCES**

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