REVIEW

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Have dipeptidyl peptidase-4 inhibitors ameliorated the vascular complications of type 2 diabetes in large-scale trials? The potential confounding effect of stem-cell chemokines

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Abstract

Drugs that inhibit dipeptidyl peptidase-4 (DPP-4) are conventionally regarded as incretin-based agents that signal through the glucagon-like peptide-1 (GLP-1) receptor. However, inhibition of DPP-4 also potentiates the stem cell chemokine, stromal cell-derived factor-1 (SDF-1), which can promote inflammation, proliferative responses and neovascularization. In large-scale cardiovascular outcome trials, enhanced GLP-1 signaling has reduced the risk of atherosclerotic ischemic events, potentially because GLP-1 retards the growth and increases the stability of atherosclerotic plaques. However, DPP-4 inhibitors have not reduced the risk of major adverse cardiovascular events, possibly because potentiation of SDF-1 enhances plaque growth and instability, activates deleterious neurohormonal mechanisms, and promotes cardiac inflammation and fibrosis. Similarly, trials with GLP-1 agonists and sodium-glucose cotransporter 2 inhibitors have reported favorable effects on renal function, even after only 3–4 years of treatment. In contrast, no benefits on the rate of decline in glomerular filtration rate have been seen in trials of DPP-4 inhibitors, perhaps because the renal actions of DPP-4 inhibitors are primarily mediated by potentiation of SDF-1, not GLP-1. Experimentally, SDF-1 can promote podocyte injury and glomerulosclerosis. Furthermore, the natriuretic action of SDF-1 occurs primarily in the distal tubules, where it cannot utilize tubuloglomerular feedback to modulate the deleterious effects of glomerular hyperfiltration. Potentiation of SDF-1 in experimental models may also exacerbate both retinopathy and neuropathy. Therefore, although DPP-4 inhibitors have attractive clinical features, the benefits that might be expected from GLP-1 signaling may be undermined by their actions to enhance SDF-1.

Background

Drugs that inhibit dipeptidyl peptidase-4 (DPP-4) are conventionally regarded as incretin-based agents that enhance the actions of endogenous gastrointestinal hormones (glucose-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide) to promote the release of insulin from the pancreas [1, 2]. However, inhibition of DPP-4 also potentiates other substrates that are degraded by the enzyme, including several chemokines [3], particularly stromal cell-derived factor-1 (SDF-1) [4, 5]. This chemokine—also referred to as CXCL12 (C-X-C

motif chemokine 12)—is responsible for the mobilization of hematopoietic stem and progenitor cells by signaling through its receptor CXCR4, and it contributes importantly to tissue inflammation, vascularity, repair and regeneration [6]. This function is defective in type 2 diabetes [7–9], presumably because DPP-4 activity is enhanced in patients with glucose intolerance [9–11].

Potential role of stem-cell chemokines in type 2 diabetes

Experimentally, potentiation of SDF-1 can act to promote pancreatic β-cell genesis, differentiation and survival, and the chemokine may protect β cells from destruction as diabetes progresses [12, 13]. This chemokine may also play a protective role in the marshaling and recruitment

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of progenitor cells that could act to ameliorate ischemia, especially in peripheral limbs [14–17]. However, the ability of SDF-1 to promote repair involves both inflammation, angiogenesis and fibrosis, which could theoretically have adverse effects on the course of many of the macrovascular and microvascular complications of diabetes [18].

The gene for SDF-1 has been identified through genome-wide association studies as one of the key loci associated with increased susceptibility to coronary artery disease [19, 20]. Increased levels of SDF-1 are associated with increased severity of coronary artery obstructions [21], and high levels of the chemokine are seen in patients with an acute coronary syndrome and forebode a worse prognosis and an increased risk of heart failure [22–24]. SDF-1 may also play a critical role in the genesis of retinopathy, which starts with damage to small blood vessels in the eye but whose progression depends on a neovascular response that can be exacerbated by SDF-1 [18, 25]. Similarly, although SDF-1 may ameliorate kidney injury and promote repair after nondiabetic ischemia [26], potentiation of the chemokine can contribute to a proliferative response that leads to glomerulosclerosis, podocyte loss, and albuminuria [27, 28], thus implicating SDF-1 in the pathogenesis of diabetic nephropathy. Experimental studies have also identified SDF-1 as a mediator of pain and neovascularization in diabetic neuropathy [29, 30].
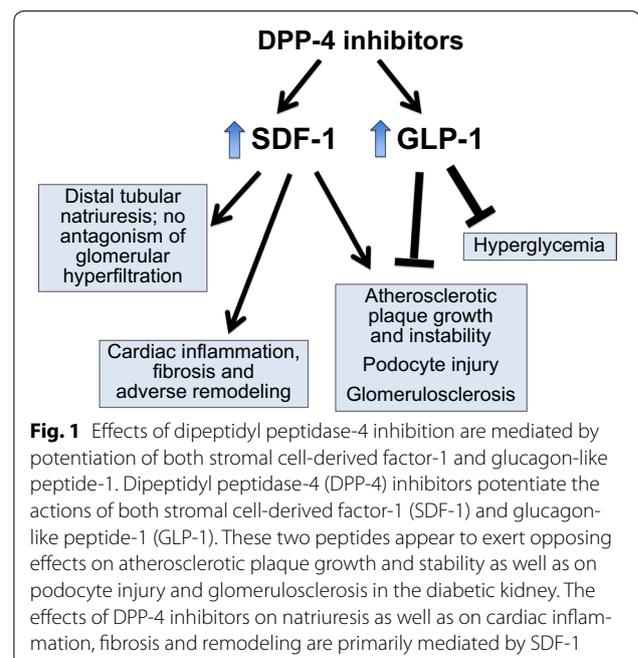
Despite their potential to potentiate SDF-1 and thereby exacerbate the vascular complications of type 2 diabetes, DPP-4 inhibitors have emerged as a popular choice for the treatment of the disease because of their ease of use, tolerability and ability to produce predictable and sustained lowering of blood glucose. Unlike older antidiabetic drugs [31–33], these drugs lower blood pressure and do not cause weight gain [34]; clinicians might expect such attributes to enhance the ability of these drugs to favorably modulate the risk of macrovascular and microvascular events [35, 36]. Furthermore, unlike long-acting GLP-1 analogs that also signal through the incretin pathway, DPP-4 inhibitors do not require parenteral administration, and their long-term use is associated with a low risk of gastrointestinal adverse effects and no meaningful increases in heart rate [37–40]. Use of these drugs is associated with a lower risk of hypoglycemia, when compared to insulin, sulfonylureas and thiazolidinediones [41, 42]. Additionally, unlike sodium-glucose transporter 2 (SGLT2) inhibitors, DPP-4 inhibitors do not adversely affect lipid metabolism or increase the risk of genitourinary infections [43]. The addition of DPP-4 inhibitors to patients already treated with metformin may seem particularly attractive, since both drugs may act to enhance circulating levels of GLP-1 and thus, may have synergistic effects on incretin receptor signaling [44–46].

However, the purpose of treating type 2 diabetes is not merely to lower levels of glycated hemoglobin, but to reduce the risk of the macrovascular and microvascular complications of the disease. Long-term outcomes trials with several different DPP-4 inhibitors have been performed, and their results are worth examining in order to understand both the mechanisms of action as well as the appropriate place of this class of drugs in diabetes care.

Effect of DPP-4 inhibitors on macrovascular events in landmark trials

Four large-scale prospectively-designed cardiovascular outcomes trials have been carried out with DPP-4 inhibitors. A trial of alogliptin (EXAMINE) was performed in 5380 patients with an acute coronary syndrome; the median duration of follow-up was 1.5 years [47]. A trial of sitagliptin (TECOS) enrolled 14,735 patients who had clinically stable type 2 diabetes; the median duration of follow-up in the study was 3.0 years [48]. A trial of saxagliptin (SAVOR-TIMI53) studied 16,492 patients with diabetes who were followed for a median of 2.1 years [49]. A trial of omarigliptin evaluated 4202 diabetic patients without acute ischemic disease, who were followed for a median of 1.8 years, before early termination of the trial [50]. In all four trials, treatment with the DPP-4 inhibitor produced meaningful decreases in glycated hemoglobin.

Despite a sustained benefit on glycemic control, treatment with the four different DPP-4 inhibitors did not reduce the risk of major adverse cardiovascular events. In all four major trials, despite substantial statistical power

Fig. 1 Effects of dipeptidyl peptidase-4 inhibition are mediated by potentiation of both stromal cell-derived factor-1 and glucagon-like peptide-1. Dipeptidyl peptidase-4 (DPP-4) inhibitors potentiate the actions of both stromal cell-derived factor-1 (SDF-1) and glucagon-like peptide-1 (GLP-1). These two peptides appear to exert opposing effects on atherosclerotic plaque growth and stability as well as on podocyte injury and glomerulosclerosis in the diabetic kidney. The effects of DPP-4 inhibitors on natriuresis as well as on cardiac inflammation, fibrosis and remodeling are primarily mediated by SDF-1

to detect a clinically meaningful treatment effect, the administration of sitagliptin, saxagliptin, alogliptin and omarigliptin did not reduce the combined risk of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke [47–50]. This lack of benefit stands in contrast with the significant or nearly-significant reduction in macrovascular risk reported with liraglutide, semaglutide and exenatide [51–53], which also enhance signaling through the GLP-1 receptor [54]. The findings with DPP-4 inhibitors also differ from the responses reported with SGLT2 inhibitors, which (in two trials) were reported to reduce major adverse cardiovascular events, especially the risk of new-onset heart failure [55, 56]. By comparison, the DPP-4 inhibitors, saxagliptin and alogliptin, carry a regulatory warning about the finding of an increased risk of hospitalization for heart failure in treated patients enrolled in large-scale trials carried out with these drugs [57].

The reasons for the lack of benefit of DPP-4 inhibitors on major cardiovascular outcomes could theoretically be related to the relatively short duration of follow-up in the landmark trials. However, this possibility seems unlikely, because over comparable periods of time, treatment with GLP-1 receptor agonists (which also enhance signaling through the GLP-1 pathway) reduced the risk of atherosclerotic ischemic events [51, 52]. Similarly, when given for treatment periods less than 4 years, SGLT2 inhibitors have had favorable effects on the risk of cardiovascular death, heart failure and nephropathy [55, 56, 58].

How then can these contrasting results be reconciled? In experimental studies, augmentation of the actions of GLP-1 retards the growth and increases the stability of atherosclerotic plaques, thus minimizing the likelihood of plaque rupture [59, 60]. Such an effect is mediated by an action of GLP-1 signaling to reduce the inflammatory response to vascular injury [59–62]. However, such a benefit might not be seen with DPP-4 inhibitors, since these drugs primarily potentiate levels of GLP-1 in the gastrointestinal tract and have modest effects on GLP-1 receptors in the systemic circulation [4]. Furthermore, DPP-4 inhibitors potentiate the actions of SDF-1 [5, 63], which acts as a proinflammatory chemokine to promote plaque growth and instability [2, 64–66]. The potentiation of endogenous SDF-1 by DPP-4 inhibitors could negate the benefits on atherosclerotic ischemic events that might be expected from enhanced GLP-1 signaling [59, 60] (Fig. 1).

Interestingly, SDF-1 can increase the number of circulating progenitor cells and direct the homing of stem cells to the heart in experimental myocardial injury [16, 17, 67–69]. However, in the absence of acute injury, SDF-1 signaling may impair cardiac contractility [70, 71]. Circulating levels of SDF-1 and the expression of receptors for SDF-1 are already increased in patients with heart failure, in the absence of DPP-4 inhibition [72, 73]. Further potentiation of SDF-1 could activate deleterious neurohormonal systems [74, 75], interact unfavorably with concurrently administered beta-adrenergic receptor blockers [71, 76], and promote progenitor cell infiltration, cardiac inflammation and adverse cardiac remodeling [77–79]. Is it possible that SDF-1 potentiation might explain the increased risk of heart failure reported in trials of DPP-4 inhibitors? [80, 81].

Effect of DPP-4 inhibitors on microvascular events in landmark trials

An adequate assessment of the effect of antidiabetic drugs on the risk of microvascular events requires trials that evaluate durations of glucose-lowering treatments administered for a decade or longer. Interventions that lower blood glucose for 10 years have been shown to reduce the risk of retinopathy and nephropathy [82, 83]; changes in course of neuropathy may require more prolonged therapy. DPP-4 inhibitors have not been tested for such extended periods of time, and large-scale cardiovascular outcomes trials have not been designed to evaluate the effects of treatment with these drugs on microvascular risk.

Nevertheless, many of the large-scale cardiovascular trials have reported the effects of DPP-4 inhibitors on aspects of diabetic nephropathy, specifically changes in urinary protein excretion, in glomerular function over time, and in the risk of progression to end-stage renal disease [47, 48, 84]. In its large-scale trial, saxagliptin produced a sustained but modest effect on albuminuria [84]. Such an effect was not unexpected; hyperglycemia acts directly on glomerular podocytes to increase their permeability to albumin [85, 86], and its correction should reduce urinary protein excretion. However, a favorable effects of DPP-4 inhibitors on albuminuria has not been a consistent finding in clinical trials [87], possibly because potentiation of SDF-1 in podocytes may aggravate proteinuria, and thus, may oppose the benefits expected from glycemic control [28].

Despite an ability to reduce albuminuria, treatment with DPP-4 inhibitors has not been accompanied by beneficial changes in the clinical course of diabetic nephropathy. A meta-analysis of trials with linagliptin reported favorable effects on renal outcomes; however, the median duration of treatment was less than 6 months, and the benefit was driven primarily by a reduction in albuminuria [88]. In large-scale longer-term cardiovascular outcomes trials [47, 48, 84], long-term DPP-4 inhibition was associated with no change or a small decline in glomerular function that persisted during the entire duration of follow-up (up to 4 years). Furthermore, treatment with

sitagliptin and saxagliptin did not diminish the risk of serious adverse renal events, as measured by a doubling of serum creatinine or the need for renal replacement therapy. In contrast, treatment with the GLP-1 receptor agonist liraglutide yielded a small improvement in kidney function at the end of the follow-up period [89], and in two large-scale trials, the use of SGLT2 inhibitors was accompanied by a meaningful and durable improvement in glomerular function and a reduction in the risk of serious adverse renal events [56, 58]. The advantages of SGLT2 inhibitors over DPP-4 inhibitors cannot be ascribed to differences in their antihyperglycemic effects, since in the large-scale trials, the two classes of drugs produced similar decreases in blood glucose during long-term treatment.

To the extent that hyperglycemia contributes to renal injury and nephropathy, the antihyperglycemic effects of long-term DPP-4 inhibition might be expected to slow the rate of decline of glomerular function, if this benefit can be sustained for prolonged periods of time [83, 84]. However, in the large-scale cardiovascular outcomes trials, the benefits of GLP-1 receptor agonists and SGLT2 inhibitors on renal function were seen relatively early in treatment, within only 3–4 years [56, 58]. Why did DPP-4 inhibitors not exert favorable renal effects when administered over these relatively short periods of time?

There are two possibilities. First, although the experimental data are conflicting [90], it is possible that potentiation of SDF-1 by DPP-4 inhibitors may enhance the inflammatory and proliferative responses to kidney injury and may thereby aggravate the course of diabetic nephropathy [27, 28]. This adverse effect may negate any benefit on renal function that might be achieved through GLP-1 receptor signaling [91, 92]. Second, kidney injury in diabetes appears to be related to glomerular hyperfiltration [93, 94], which is likely related to an excessive reabsorption of sodium in the proximal tubule, leading diminished delivery of sodium to the macula densa, and (via tubuloglomerular feedback) to afferent arteriolar dilatation [95, 96]. Both GLP-1 receptor agonists and SGLT2 inhibitors act directly on the proximal tubule to block sodium hyper-reabsorption [97, 98]; this effect, which is independent of their action on blood glucose, may underlie the early favorable actions on the kidney seen with these drugs in large-scale trials. In contrast, DPP-4 inhibitors exert a natriuretic effect by acting primarily on distal segments, apparently by enhancing the effects of SDF-1 [99] (Fig. 1). However, because this distal site of action that cannot utilize tubuloglomerular feedback to ameliorate glomerular hyperfiltration [95, 96], DPP-4 inhibition does not appear to exert early benefits on renal function in type 2 diabetes. If DPP-4 inhibitors exert any effect to inhibit sodium transport in the proximal tubule, this action does not appear to be mediated by potentiation of GLP-1 and or by pathways linked to the GLP-1 receptor [98–101]. The totality of evidence suggests that the effects of DPP-4 inhibitors on the kidney may be primarily mediated through potentiation of SDF-1 rather than of GLP-1.

Summary and conclusions

DPP-4 inhibitors represent an attractive therapeutic option for the control of hyperglycemia in patients with type 2 diabetes due to their ease of use, tolerability and safety profile. However, unlike other newer antidiabetic drugs, DPP-4 inhibitors do not appear to exert meaningful effects on macrovascular or microvascular risk, at least when administered for periods of 3–4 years. This lack of early benefit may be related to the fact that the clinical profile of DPP-4 inhibitors may be dominated by the potentiation of endogenous peptides other than GLP-1 [1]. Many of the effects of DPP-4 inhibitors in large-scale clinical trials, including their effects on atherosclerotic ischemic events, heart failure, sodium excretion, albuminuria and glomerular function may be meaningfully influenced by their actions to enhance of the endogenous stem-cell chemokine, SDF-1. Only the antihyperglycemic effect of these drugs appears to be clearly related to the potentiation of incretins (i.e., GLP-1 and glucose-dependent insulinotropic polypeptide) [102, 103], possibly because such potentiation is confined to the gastrointestinal tract and may not be manifest systemically [63]. Given the complexity of the clinical effects exhibited by DPP-4 inhibitors in diabetes, it may not be entirely informative to refer to them solely as incretin-based drugs.

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