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Review

Renal outcomes with dipeptidyl peptidase-4 inhibitors

A.J. Scheen [a,b,*], P. Delanaye [c]

[a] Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman (B35), 4000 Liège 1, Belgium
[b] Clinical Pharmacology Unit, CHU Liège, Center for Interdisciplinary Research on Medicines (CIRM), University of Liège, Liège, Belgium
[c] Division of Nephrology, Dialysis, Transplantation and Hypertension, Department of Medicine, CHU Liège (ULg-CHU), Liège, Belgium

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ABSTRACT

Dipeptidyl peptidase-4 inhibitors (DPP-4is) are increasingly being used in the management of type 2 diabetes (T2D). The present review summarizes the current knowledge of the effects of DPP-4is on renal outcomes by analyzing the experimental preclinical data, the effects of DPP-4is on urinary albumin–creatinine ratios (UACRs) and estimated glomerular filtration rates (eGFRs) from observational studies and clinical trials, and renal events (including kidney failure requiring renal replacement therapy) in recent large prospective cardiovascular outcome trials. Renal protection has been demonstrated in various animal models that have implicated different underlying mechanisms independent of glucose control, whereas prevention of new onset microalbuminuria and/or progression of albuminuria has been reported in some clinical studies, but with no significant effects on eGFR in most of them. The long-term clinical effects of DPP-4is on renal outcomes and the development of end-stage renal disease remain largely unknown and, thus, demand further investigations in prospective trials and long-term observational studies. In conclusion, despite promising results in animal models, data on surrogate biological markers of renal function and clinical renal outcomes remain rather scanty in patients with T2D, and mostly demonstrate the safety rather than true efficacy of DPP-4is.

Introduction

While cardiovascular complications have progressively decreased over the last three decades in patients with type 2 diabetes (T2D), end-stage renal disease (ESRD) has remained virtually unchanged. There is thus a medical need to avoid the progression of renal impairment in patients with T2D [1]. This objective requires a multirisk approach, targeting not only hyperglycaemia, but also other risk factors, such as hypertension and obesity [2,3]. Following a request by the US Food and Drug Administration (FDA) [4], the most recent prospective controlled trials of new glucose-lowering therapies have focused on outcomes of cardiovascular disease (CVD) rather than on renal outcomes, although some secondary analyses have provided interesting information regarding kidney function [5–7].

Dipeptidyl peptidase-4 inhibitors (DPP-4is) [8,9] and sodium–glucose cotransporter type 2 inhibitors (SGLT2is) [10,11] are two classes of oral glucose-lowering agents that have become increasingly more important over the past decade in the management of T2D [12–14]. They act through different, and potentially complementary, mechanisms of action [15]: DPP-4is are incretin enhancers that both stimulate insulin secretion and reduce glucagon secretion in a glucose-dependent manner [8,9]; whereas SGLT2is promote glucosuria, a renal action independent of insulin, and reduce glucose toxicity [10,11,16]. DPP-4is demonstrated non-inferiority vs. placebo (but no superiority) regarding cardiovascular outcomes in three major trials [17–19], as recently reviewed [20], whereas the SGLT2i empagliflozin produced a significant reduction in a composite endpoint of major cardiovascular events (MACEs), cardiovascular mortality, all-cause mortality and hospitalization for heart failure in the EMPA-REG OUTCOME trial [21]. Furthermore, in that landmark study, empagliflozin showed a marked (–49%) and significant ($P < 0.001$) reduction in a composite of renal outcomes in T2D patients with antecedents of CVD [5], while closely similar renal outcomes were recently reported with canagliflozin in the CANVAS Program [22]. These data suggest that SGLT2is may also be considered drugs of choice for preventing renal progression in patients with T2D and mild-to-moderate renal impairment, even though the underlying mechanisms of protection remain a matter of discussion [23,24]. However, because of their particular renal mechanism of action, SGLT2is have so far been contraindicated for patients with moderate-to-severe renal impairment [10,11,25]. In

* Corresponding author.
E-mail address: andre.scheen@chu.ulg.ac.be (A.J. Scheen).

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contrast, DPP-4is can be used in patients with any stage of chronic kidney disease (CKD), provided that the daily dose is appropriately adjusted according to eGFR reductions (except for linagliptin, which can be used at the same dosage whatever the eGFR because of its predominantly hepatic elimination) [26]. DPP-4is have been proven to be both efficacious and safe in several large well-designed trials specifically performed in T2D patients with moderate or severe CKD, including patients with ESRD [27–29].

DPP-4is improve glucose control without inducing hypoglycaemia or weight gain, but have limited effects, if any, on blood pressure and lipid profiles [8,9]. Nevertheless, early promising results on cardiovascular surrogate parameters have been reported [30–32] that may also be of potential interest for renal protection [15,33–35]. DPP-4is increased levels of glucagon-like peptide-1 (GLP-1), and GLP-1 receptor agonists have been shown to exert favourable effects on renal outcomes, especially liraglutide in the LEADER study [36], but also in other experimental and clinical studies, as recently reviewed [37]. Furthermore, the kidney is the organ in which DPP-4 activity is at its highest level per organ weight, and one preclinical analysis suggested that DPP-4is might even ameliorate kidney fibrosis [38]. Microalbuminuria represents an important early sign of kidney damage in humans, and DPP-4is have been found to reduce the onset and progression of microalbuminuria [39]. Effects of DPP-4is may be both GLP-1-dependent and -independent, and not necessarily directly related to improvement of glucose control and reduction of blood pressure. Other substrates of DPP-4, such as brain natriuretic peptide and stromal cell-derived factor (SDF)-1α, may also play a role in potential renoprotection [40]. Experimental studies in various animal models have suggested that the underlying nephroprotective properties of DPP-4is may include reduction of oxidative stress and inflammation, and improvement of endothelial dysfunction (Fig. 1, Table 1) [39,41]. In one large retrospective observational cohort study, administration of DPP-4is (sitagliptin, linagliptin, saxagliptin, vildagliptin, gemigliptin) reduced urine albumin excretion after 1 year and mitigated the reduction of eGFR after 4 years in Japanese T2D patients [42]. However, in a recent meta-analysis of 36 double-blind randomized controlled trials (RCTs) with DPP-4is and a total of 54,664 patients, there were no significant differences in renal failure on comparing DPP-4is with placebo or other, active glucose-lowering agents (RR: 1.06, 95% CI: 0.88–1.27) [20].

Table 1
Mechanisms of nephroprotective effects of dipeptidyl peptidase (DPP)-4 inhibitors explored in experimental studies of various animal models.

Mechanisms	References
Upregulation of GLP-1 and GLP-1 receptors	[50,54]
Inhibition of renal DPP-4 activity	[55,75,80]
Reduction of inflammation	[52,53,58,77,83]
Attenuation of activation of NLRP3/ASC inflammasome	[77]
Reduction of oxidative stress	[52,53,58]
Reduction of mitochondrial dysfunction and apoptosis	[58]
Suppression of connective tissue growth factor	[60,94]
Regulation of preglomerular vascular smooth muscle and mesangial cell proliferation	[61]
Restoration of renal myogenic function	[106]
Reduction of tubulointerstitial fibrosis and renal sclerosis	[76,79,94,106]
Upregulation of stromal cell-derived factor-1	[87]
Suppression of advanced glycation end-products	[91]
Reduction of blood pressure	[62]

Several effects were independent of glucose and blood pressure reduction, but only some were evaluated and confirmed in humans; GLP-1: glucagon-like peptide-1; NLRP3: nucleotide-binding domain leucine-rich repeat-containing receptor family, pyrin-domain-containing 3; ASC: apoptosis-associated speck-like protein containing a caspase-recruitment domain.

Thus, the objective of this narrative review is to analyze renal outcomes with DPP-4is by considering data from animal models, mechanistic human studies and phase II/III clinical trials, and the results of recent large prospective cardiovascular outcome studies, including secondary analyses of renal outcomes. What is not discussed here are the pharmacokinetic characteristics as well as efficacy and safety of DPP-4is in patients with mild, moderate or severe renal impairment, as these have already been analyzed in recent general reviews of antihyperglycaemic medications [43–45] and in specific reviews devoted to incretin-based therapies [26,46] or, more specifically, DPP-4is [47,48]. The present review focuses only on the five commercially available DPP-4is worldwide

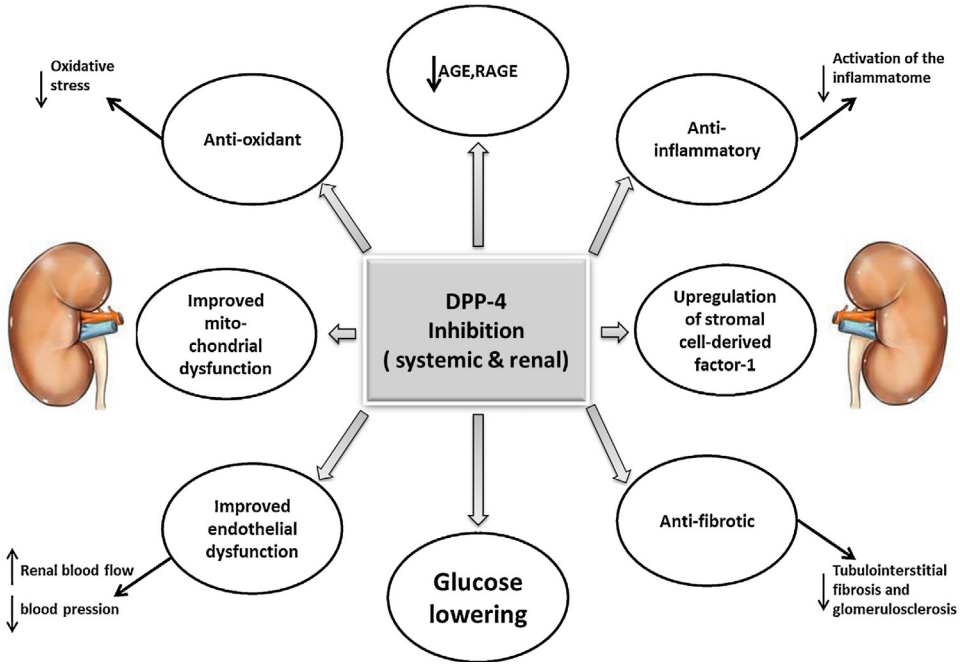

Fig. 1. Potential mechanisms of action of dipeptidyl peptidase-4 (DPP-4) inhibitors that could positively affect renal outcomes in patients with type 2 diabetes. AGE: advanced glycation end-product. RAGE: advanced glycation end-product receptor.

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