Role of GLP-1 and DPP-4 in diabetic nephropathy and cardiovascular disease

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Abstract

Although there have been major advances in the understanding of the molecular mechanisms that contribute to the development of diabetic nephropathy, current best practice still leaves a significant treatment gap. The incidence of diabetes and associated nephropathy is increasing, with the main cause of mortality being related to cardiovascular causes. Novel therapies which are both ‘cardio-renal’ protective seem the logical way forward. In the present review, we discuss the GLP-1 (glucagon-like peptide-1) receptor agonists and DPP-4 (dipeptidyl peptidase-4) inhibitors (incretin-based therapies), which are novel antidiabetic agents used in clinical practice and their role in diabetic nephropathy with specific focus on renoprotection and surrogate markers of cardiovascular disease. We discuss the pleiotropic effects of the incretin-based therapies apart from glucose-lowering and highlight the non-GLP-1 effects of DPP (dipeptidyl peptidase) inhibition. Large-scale clinical studies with cardiovascular end points are underway; however, studies with renal end points are lacking but much needed.

Key words: dipeptidyl peptidase, cardiorenal disease, diabetic kidney disease, glucagon-like peptide, incretin

THE INCRETIN SYSTEM

The incretin hormones include GLP-1 (glucagon-like peptide-1) and GIP (gastrointestinal peptide), which are released from the gut in response to meals. Pro-glucagon is secreted by the intestinal mucosa and is then cleaved to GLP-1, levels of which are increased after a meal. GLP-1 acts on the GLP-1 receptor in the pancreas in a glucose-dependent manner and function to stimulate pancreatic insulin release and suppress glucagon secretion, with the net effect of regulating postprandial glucose excursions. These hormones have a very short half-life as they are rapidly degraded by DPP-4 (dipeptidyl peptidase-4), which cleaves two amino acids at the N-terminal end of peptides that have a proline (or less commonly an alanine) residue at the penultimate position. Hence GLP-1-(7–36)amide is cleaved to GLP-1-(9–36)amide, which is the major circulating form. GLP-1-(9–36) does not have insulinotropic effects.

Although the main role of DPP-4, also known as ADCP 2 (adenosine deaminase complexing protein 2) or T-cell activation antigen CD26 (EC 3.4.14.5.), is to terminate the action of GLP-1-(7–36), it is not exclusively so. DPP-4 is a serine exopeptidase belonging to the S9B protein family, members of which cleave X-proline dipeptides from the N-terminus of polypeptides, such as chemokines, neuropeptides and peptide hormones [1]. It is a 110-kDa type 11 integral membrane glycoprotein and is expressed ubiquitously in most organs and cell types. Importantly, DPP-4 is therefore able to cleave a host of other peptides and exert GLP-1-independent effects, which will be discussed in the present review. Additionally, DPP-4 exists in two forms (soluble and membrane-bound), both of which are capable of proteolytic activity. The soluble form in the circulation is thought to arise from shedding of the membrane forms and is responsible for the glucose-lowering effect of the DPP-4 inhibitors in clinical use. In contrast, the membrane-bound form of DPP-4, expressed on the surface of many cell types, including kidney tubular cells, endothelial cells and T-cells [2], is of major interest with respect to the pleiotropic actions of DPP-4. The GLP-1-dependent and -independent effects of DPP-4 (and of DPP-4 inhibitors) are shown in Figure 1.

INCRETIN-BASED THERAPIES

Incretin-based therapies in the treatment of patients with Type 2 DM (diabetes mellitus) are efficacious, have less risk of hypoglycaemia and do not promote weight gain [3]. This class of compounds include the orally active DPP-4 inhibitors and the
injectable GLP-1R (GLP-1 receptor) agonists, both of which stimulate insulin secretion and inhibit glucagon secretion. GLP-1R agonists are synthetic peptides that are not subjected to degradation/cleavage by DPP-4 and hence are more stable and have a longer half-life in the circulation. There are several DPP-4 inhibitors in clinical use, for example sitagliptin, saxagliptin, vildagliptin, alogliptin and linagliptin. They differ in their pharmacokinetic profiles and modes of excretion. Linagliptin is predominantly cleared by the liver, whereas saxagliptin is predominantly cleared by the kidney. The GLP-1R agonist exenatide is predominantly cleared by the kidney; however, liraglutide is not eliminated by the kidney and undergoes generalized proteolysis. There are currently no GIP analogues in clinical use [4].

DIABETIC NEPHROPATHY

Diabetic nephropathy occurs in approximately one-third of patients with DM. A treatment gap exists in preventing progressive kidney disease in patients with DM. Current standard care, although effective, only partially has an impact on the loss of kidney function and a reduction in cardiovascular risk. As cardiovascular complications represent the main cause of mortality in patients with DM, it is imperative that we improve our understanding of the renal and cardiovascular consequences of GLP-1 augmentation and DPP-4 inhibition. Continued investigations into mechanisms of kidney failure in patients with DM that will lead to the finding of novel strategies to limit cardiovascular and renal disease are imperative. Hence investigating the effects of incretins on cardiovascular and renal pathology is highly relevant, and strategies to simultaneously target glucose control, cardiovascular disease and renal pathology are inherently attractive in the treatment of patients with DM.

In nephropathy complicating both Type 1 and Type 2 DM, chronic hyperglycaemia is central to the development of renal pathology [5]. Although glomerular lesions are characteristic, it is increasingly recognized that the pathology within the tubulointerstitium, for example fibrosis, tubular atrophy and ischaemic damage, are ultimately more predictive of the renal outcome [6]. Brownlee [7] has postulated that four main molecular mechanisms initiated by hyperglycaemia ultimately converge in the development of microvascular complications in diabetes. The four mechanisms are increased flux through the polyol and hexosamine pathways, increased AGE (advanced glycation end-product) formation and activation of PKC (protein kinase C). More recently, there has been increasing interest in alternative mechanisms of glucose toxicity resulting in nephropathy, including lipotoxicity, activation of inflammatory pathways and disruption of mitochondrial DNA bioenergetics among others. Among the cytokines, most prominent in the development of diabetic nephropathy are the pro-fibrotic cytokines TGF (transforming growth factor) β1 and CTGF (connective tissue growth factor). They synergistically promote cell hypertrophy and extracellular matrix deposition, leading to glomerulosclerosis, arteriolar thickening and tubulointerstitial fibrosis [8] and ultimately resulting in a loss of renal function. Although historically considered as a largely ‘non-inflammatory’ disease process, it has been recently demonstrated that inflammatory processes play a significant role in the development and progression of diabetic nephropathy [9]. Activation of innate immunity with the development of a chronic low-grade inflammatory response is a recognized factor in the pathogenesis of diabetic nephropathy [10]. Stimuli inherent in the diabetic milieu that activate these pathways and hence are considered to be integral to the development of diabetic nephropathy include hyperglycaemia [11,12], AGE formation [13,14], oxidative stress [7,15], mechanical stretch [16], glucosamine overproduction [17], AngII (angiotensin II) [18], endothelin [19] and thromboxane [20]. Progressive proteinuria coupled with extracellular matrix (fibronectin and collagen) expansion and inflammation lead to scarring that ultimately compromises renal function. In considering novel therapies, the complex and multifactorial basis of this disease process needs to be fully appreciated and integrated.

Cellular sodium and water transport are also dysregulated in DM. Mechanistically this is thought to be due to altered tubuloglomerular feedback arising from the increased glucose and sodium reabsorption through the SGLT2 (sodium–glucose co-transporter 2) receptor [21]. There is also in vitro data to suggest that glucose stimulates the EGFR (epidermal growth factor receptor) and downstream Sgk1 (serum glucocorticoid regulated kinase 1), resulting in increased sodium reabsorption in the proximal tubule by increasing the activity of the NHE3 (sodium/hydrogen exchanger 3) receptor [22].
GLP-1 AND DIABETIC NEPHROPATHY

GLP-1 exerts its action mainly through its high-affinity receptor GLP-1 R. It is present in the pancreas and also in extrapancreatic tissues, such as the kidneys, vascular tissues, the central nervous system and the lungs. Animal studies have shown some functional relevance of its presence in the kidney. GLP-1R has been demonstrated at the mRNA level in porcine PTCs (proximal tubular cells) [23] and in human PTCs (U. Panchapakesan, A. Mather, S. Saad and C. Pollock, unpublished work). There is evidence to suggest that long-term treatment with the GLP-1 R agonist exendin-4 ameliorates diabetic nephropathy in both Type 1 and Type 2 DM animal models, most probably through its action on the glomerular endothelial and infiltrating inflammatory cells [24,25]. GLP-1 can also directly act on mesangial cells via the GLP-1R and works as an anti-inflammatory agent against AGEs by reducing RAGE (receptor for AGEs) expression via activation of cAMP pathway [26]. Mechanistically, exendin-4 and recombinant GLP-1 have also been shown to attenuate the actions of AngII [27], resulting in an antihypertensive effect in salt-sensitive mice and a reduction in proteinuria, and renal and cardiovascular pathology [28]. This has also been shown with the exanetide analogue AC3174 in Dahl salt-sensitive rats [29], where it attenuated hypertension, insulin resistance and renal dysfunction. Other effects on the kidney include modulation of sodium homeostasis in the kidney via its action on proximal tubular NHE3 [30,31], and this has been shown with intravenous infusions of GLP-1 which enhanced sodium excretion, reduced H+ secretion and reduced glomerular hyperfiltration in obese men, supporting its action at the level of the proximal renal tubule [32]. Although the main action of DPP-4 inhibitors is to augment endogenous GLP-1 levels, they are known to exert non-GLP-1 effects, as DPP-4 cleaves a range of peptides that have a proline/alanine residue in the penultimate position at the N-terminal end. Hence, mechanistically, DPP-4 inhibitors have effects that are independent of GLP-1 and this will be discussed below.

DPP-4 INHIBITION AND THE KIDNEY

There are two studies that have looked at the effect of DPP-4 inhibition on the diabetic animal kidney. Liu et al. [33] assessed the effect of vildagliptin in a Type 1 DM rat model [STZ (streptozotocin)-induced diabetes]. Using a Type 1 DM model minimizes the effect of DPP-4 inhibition on insulin release as STZ destroys the islet cells in the pancreas, so the glucose-lowering effect of the incretin system is thought to be abolished. In that study [33], the authors reported that vildagliptin was renoprotective, with a reduction in albuminuria and improvement in the histological changes in the kidney, which were associated with reduced DPP-4 activity and increased GLP-1 levels. The authors concluded that these changes were probably not attributable to the hypoglycaemic effect of vildagliptin. However, the HbA1c (glycated haemoglobin) in the diabetic group was 12.1% (compared with 4.7% in the control group) and the diabetic + vildagliptin (8 mg/kg of body weight per day) group was 10.4%, which was significantly lower than the diabetic group. We know from the UKPDS (UK Prospective Diabetes Study) that even small changes in HbA1c levels can lead to significant differences in the development of diabetic microvascular complications [34].

The proteolytic functions of DPP-4 in the kidney have been described using LC (liquid chromatography)-MS-based peptidomics, where kidney tissue from DPP-4+/+ (wild-type) and DPP-4−/− (knockout) mice were compared, and this revealed ten peptides regulated by DPP-4 in vivo [39]. Further studies with brush border membranes showed that aminopeptidase activity is required to generate DPP-4 substrates [2]. This suggests that DPP-4 is involved in the extracellular catabolism of proteins in the kidney, specifically the degradation/catabolism of proline-containing peptides [40]. As DPP-4 is present on the brush border.

GLP-1-DEPENDENT EFFECTS OF DPP-4 INHIBITORS

The GLP-1-independent effects of DPP-4 inhibitors relate to the direct effects of DPP-4 inhibition irrespective of changes in systemic GLP-1 levels. As stated previously, the membrane-bound form of DPP-4 is a type II transmembrane glycoprotein, which is expressed on the surface of many cell types, including kidney tubular cells, endothelial cells and T-cells [2]. It has a high level of expression and activity in the kidney, is found on the apical/brush border surface of kidney PTCs [36] and is found in the urine [37]. DPP-4 is a multifunctional protein and has at least five functions: (i) a serine protease, (ii) a receptor, (iii) a co-stimulatory protein, (iv) an adhesion molecule for collagen and fibronectin, and (v) in apoptosis [38]. DPP-4 inhibitors in clinical use are likely to affect peptides other than GLP-1. This is because DPP-4 cleaves a number of other substrates, such as neuropeptides, hormones, cytokines and chemokines, and, in doing so, regulates a number of peptides [38]. There has been a great deal of interest in identifying other endogenous substrates and establishing their physiological relevance in vivo. Hence the therapeutic potential of DPP-4 inhibitors exists above and beyond glucose-lowering.

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of the kidney PTCs, inhibition of membrane DPP-4 is likely to alter the degradation/regulation of peptides in the lumen and thus influence the kidney tubulointerstitium in patients with DM.

DPP-4 SUBSTRATES

Recent interest in DPP-4 research has focused on the identification of new substrates of DPP-4 that are physiologically relevant. Some identified substrates include RANTES (regulated upon activation, normal T-cell expressed and secreted) [41], neuropeptide Y and substance P [42]. Once identified, it is important to ascertain the physiological relevance of DPP-4 substrates in vivo. Many substrates have been identified as being pharmacological substrates (cleaved by recombinant DPP-4 in vitro), but are not cleaved in vivo. An example of the physiological relevance of these non-GLP-1 substrates is highlighted by the commonly seen adverse effects of DPP-4 inhibitors, such as rhinitis and sinus congestion. This is thought to occur because the loss of DPP-4 activity contributes to the neurogenic inflammation induced by substance P in the nasal mucosa [43].

DPP-4 SUBSTRATES RELEVANT TO DIABETIC NEPHROPATHY: MEPРIN AND HMGB1 (HIGH-MOBILITY GROUP BOX 1 PROTEIN)

Although certain DPP-4 substrates in the kidney have been identified in DPP-4 −/− animal models, as well as in animal models treated with DPP-4 inhibitors, the functional relevance of these substrates in diabetic nephropathy has not been determined and remains highly speculative. Below, we discuss two substrates that have been identified as being cleaved by DPP-4 and how they may relate to diabetic nephropathy.

Meprin β

MS-based global peptide profiling is a useful tool for studying peptide metabolism in vivo. Tagore et al. [39] used this technique to compare kidney tissue from DPP-4 +/+ and DPP-4 −/− mice, as well as with mice treated with vildagliptin, a DPP-4 inhibitor [39]. In both the knockout and inhibitor experiments, meprin β-(21–41) was identified as a DPP-4 substrate [meprin β-(25–41) was elevated in DPP-4 +/+ animals]. The role of DPP-4 inhibition on Meprin A or B in diabetic nephropathy is not known and has not been investigated previously.

Meprins are metalloendopeptidases located in the brush border membrane of the kidney PTCs [44]. They are able to proteolytically degrade extracellular matrix proteins, as well as process bioactive proteins. Structurally, they are composed of two subunits (α and β). The terminology is confusing and is clarified as follows: the meprin protein is composed of various combinations of α and β subunits and as long as there is an α subunit the protein is known as Meprin A. Conversely, Meprin B is composed of only β subunits. The β subunit has a hydrophobic transmembrane portion and is anchored to the membrane, whereas the α subunits are not anchored and can be found in the urine [45]. Meprin β gene polymorphisms were found to be associated with susceptibility to nephropathy in Pima Indians (a group with a high incidence of Type 2 DM and an accelerated rate of renal failure) [46]. The level of protein expression and localization of Meprin β has also been associated with several types of renal pathology, such as renal ischaemia/reperfusion injury [47], acute renal failure [48] and in diabetic kidneys of db/db mice [45]. The physiological relevance of Meprin B (homodimers of β subunits) has been further investigated by Herzog et al. [49], where purified recombinant Meprin β was able to process the IL (interleukin)-β precursor to a biologically active form. This suggests that Meprin B has a role in activation of this pro-inflammatory cytokine. Inhibition of Meprin either at a gene or protein level afforded renal protection in various settings. For example, wild-type mice were markedly more susceptible to renal injury after ischaemia/reperfusion compared with Meprin β-knockout mice with higher levels of TNF (tumour necrosis factor)-α, TGFβ, iNOS (inducible NO synthase) and hsp27 (heat-shock protein 27) [50], which have been previously to be up-regulated in tubular cells exposed to high glucose [51]. In keeping with this, studies using actinomin (a meprin inhibitor) showed that Meprin inhibition was protective in renal hypoxic injury in vitro and in vivo [52]. Apart from the transcription, expression and localization of meprin as described above, meprin activity was found to be increased in STZ-induced diabetic rats [53]. The functional relevance of DPP-4 cleaving Meprin β and what effect it has on the activity is not known, but, based on the evidence above, Meprin may be a useful therapeutic target and the role of DPP-4 inhibition in promoting this needs to be elucidated.

HMGB1

HMGB1 is a highly conserved nuclear protein that binds to DNA and regulates transcription [54]. It is passively released during cell damage or secreted by cells in response to injury via non-traditional pathways (i.e. not through the endoplasmic reticulum or Golgi apparatus). Extracellular HMGB1 incites inflammation, and HMGB1 has been well described to have a pathogenic role in the development of diabetic nephropathy [55–57] and kidney ischaemia/reperfusion injury [58]. HMGB1 is a known ligand of RAGE, as well as TLR (Toll-like receptor) 2 and TLR4 [59], both of which are central to the development of diabetic nephropathy. Through ligand binding, TLR2 and TLR4 are involved in the inflammatory process of diabetic nephropathy [60–64] and, on activation, both of these pathways converge at NF-κB (nuclear factor κB), which leads to cytokine release [65] and initiates an inflammatory response. Interestingly, DPP-4 was found to cleave recombinant HMGB1 in in vitro studies and this cleavage affected its angiogenic activity in murine vascular cells, suggesting that HMGB1 is a substrate of DPP-4 [66] in these cells. Although renal HMGB1 has not been identified as a substrate of DPP-4, HMGB1 is secreted by the kidney PTCs and is present in the urine [67], making it possible to interact with PTC brush border DPP-4. HMGB1 is released extracellularly and is readily accessible to modification by DPP-4 on the extracellular cell membrane. Alogliptin has been shown to have an anti-inflammatory effect in an LPS (lipopolysaccharide)-stimulated in vitro model...
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DPP4

？Cleaves HMGB1

\[ \text{DPP4} \rightarrow \text{HMGB1 cleavage} \]

\( \nabla \text{TLR} \)

Mediates NF-κB activation and downstream inflammation

Figure 2 Effect of DPP on HMGB1 cleavage

HMGB1 is a known ligand of TLR2 and 4 and on binding activates the NF-κB pathway. DPP-4 has been shown to cleave HMGB1 in vitro. DPP-4 may also interact with TLR2 and TLR4 to influence the NF-κB pathway.

Cardiovascular Effects of GLP-1R Agonists and DPP-4 Inhibition

The main cause of mortality and morbidity in DM remains cardiovascular in origin. It would be highly attractive for physicians and patients if novel diabetic agents have additional renal- and cardiovascular-protective effects. There have been recent concerns about the disconnection between the glucose-lowering effect and cardiovascular safety of certain diabetic agents. For example, the thiazolidinedione rosiglitazone has been associated with a significant increase in the risk of myocardial infarction and with a marginal increase in the risk of death from cardiovascular causes [70], despite significant glucose-lowering effects and short-term studies suggesting renoprotection [71,72]. This highlights the need for novel diabetic agents to be assessed for solid cardiovascular outcomes and, in fact, regulatory agencies now mandate that new diabetic agents undergo cardiovascular assessment prior to marketing. Similarly, the treatment and prevention of cardiovascular disease has not responded to glucose-lowering therapies in the same way as microvascular disease [76,77].

Outcomes seen with GLP-1 or GLP-1 analogues have been found to be independent of their achievement of euglycaemia [75]. In both an isolated perfused rat heart and whole-animal models of ischaemia/reperfusion, treatment with GLP-1 before ischaemia is able to significantly reduce infarct size [76], and some of these beneficial effects have been associated with the modulation of molecular mechanisms related to apoptosis and oxidative stress [77]. In human studies, infusion of GLP-1 in patients with ischaemia [78] and LV (left ventricular) dysfunction [79] or LV dysfunction alone [80] showed improvement in myocardial salvage or LV wall motion. The effects of GLP-1 or its analogues on cardiovascular outcomes relate to a direct effect on cardiomyocytes mediated both by GLP-1-increased myocardial insulin sensitivity and subsequent glucose uptake [81], and by GLP-1 binding with GLP-1R to modulate the apoptotic control of the survival of these cells [76,77].

However, cardiovascular outcomes are also closely related to endothelial function, and emerging lines of evidence show a beneficial effect of GLP-1 on the endothelium. In addition to cardiomyocytes, GLP-1R expression has been demonstrated on endothelial cells and VSMCs (vascular smooth muscle cells) [82]. Animal studies have shown that GLP-1 can induce an endothelium-dependent relaxation of pulmonary artery rings that occurs, which is dependent on NO (nitric oxide) production (a well-known vasodilatory endothelium-derived factor) [83,84], whereas other studies have observed vasodilation independent of NO [85] via a direct action on VSMCs through GLP-1R. These experiments have been expanded further to explore the molecular basis behind these developments, with coronary flow improvements appearing to occur via the GLP-1 metabolite GLP-1-(9–36) and, at least in part, via a GLP-1R-independent effect [86]. From a vascular cell growth perspective, in vivo studies using a vascular injury model have shown that continuous infusion of exendin4, a GLP-1 analogue, reduced neointimal formation independent of metabolic effects, by suppressing PDGF (platelet-derived growth factor)-induced proliferation of VSMCs [87]. Furthermore, exendin-4 stimulates the proliferation of human coronary artery endothelial cells via eNOS (endothelial NO synthase)-, PKA (protein kinase A)- and PI3K (phosphoinositide 3-kinase)/Akt-dependent pathways [88], and the proliferation of the vasculoprotective endothelial progenitor cells via an action on VEGF (vascular endothelial growth factor) [89].

Finally, the production of pro-inflammatory markers by endothelial cells have been altered by treatment with GLP-1 analogues. Exenatide has been associated with a non-significant reduction of NF-κB production and a significant attenuation of the mRNA expression of TNF-α and MCP-1 (monocyte chemoattractant protein-1) [82], all of which have been associated with the development of atherosclerosis. GLP-1 and GLP-1 analogues have therefore been demonstrated to alter vascular cell growth and function and have been linked to alterations in the inflammatory milieu of a number of cell types. The cardiovascular effects of GLP-1 are summarized in Figure 3.

Ongoing cardiovascular outcome trials include EXSCEL (Exenatide Study of Cardiovascular Event Lowering Trial) and also the LEADER (Liraglutide Effect and Action in Diabetes) trial (http://www.clinicaltrials.gov).
**DPP-4 inhibitors**

The DPP-4 class of drugs has offered some promise with pre-clinical studies and post-hoc analyses of clinical trials, suggesting a positive cardiovascular risk profile. Large multicentre clinical trials addressing this very question are in progress (http://www.clintrials.gov), for example TECOS (Tial Evaluating Cardiovascular Outcomes with Sitagliptin) and CAROLINA (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes).

Mechanistically, it is possible that DPP-4 inhibitors provide vascular protection by increasing GLP-1 bioavailability and signalling. However, DPP-4 inhibitors are likely to have pleiotropic effects independent of their effects on GLP-1, as outlined above. Mimicking the clinical experiments using GLP-1 infusions in patients with LV dysfunction, patients with ischaemic heart disease and LVF (LV failure) were treated with sitagliptin and LV function improved. However, this experiment was not designed to distinguish between GLP-1-dependent and -independent effects [90]. There is evidence to suggest that endothelial cell DPP-4 expression and activity is influenced by hypoxia, glucose and a variety of inflammatory markers [91–93], but its expression and activity on VSMCs is unknown. DPP-4 inhibition, both pharmacological and genetic, has been shown to increase endothelial cell growth *in vitro* [94]. Pre-contracted aortic segments are shown to be relaxed by the DPP-4 inhibitor alogliptin, an action that is at least in part dependent on NO release and independent of its action on GLP-1R [95].

The immunomodulatory effects of DPP-4 inhibitors in other disease states are starting to be elucidated, but effects in relation to the inflammatory nature of vascular disease remain poorly studied. Sitagliptin has been shown to reduce MCP-1 [96] and the effect of DPP-4 inhibition on the production of SDF-1α (stromal-cell-derived factor-1α; a chemokine responsible for stimulating the mobilization of endothelial progenitor cells) has been partially addressed [97]. However, the role of DPP-4 inhibitors in the production and mediation of pro-inflammatory cytokines in diabetic vascular disease remains largely unexplored.

Although DPP-4 inhibitors hold promise for the treatment of cardiovascular disease, their significant pleiotropic effects beyond the promotion of GLP-1 mean they cannot be assumed to be the same class as GLP-1R agonists. To date, mechanistic investigation of their effects on large-vessel diabetic vascular disease is lacking.

**DPP-4 AS A BIOMARKER OF KIDNEY DISEASE**

There are conflicting reports on the level of DPP 4 activity in the serum of patients with Type 2 DM [98–101] and it has been reported to correlate positively with HbA1c levels [99]. The utility of DPP-4 as a biomarker of diabetic kidney disease was studied by Sun et al. [102], who found that urinary microvesicle the DPP-4 level was higher in patients with DM compared with controls and that it positively correlated with the urinary albumin/creatinine ratio in patients with Type 2 DM. The role of DPP-4 inhibition in this area of research requires further investigation.

**SUMMARY**

Novel therapies for patients with Type 2 DM that have additional renoprotective and cardiovascular advantages above and beyond glucose-lowering would be highly attractive to both the clinician and the patient. Pre-clinical studies suggest that GLP-1R agonists and DPP-4 inhibitors offer promise in this regard. Large-scale clinical trials with cardiovascular end points are underway. Although there are studies evaluating the safety and tolerability of DPP-4 inhibitors in patients with renal impairment, studies with renal end points are currently lacking.

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