

Dipeptidyl Peptidase-4 Inhibitors and Diabetic Kidney Disease: A Narrative Review



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Diabetic kidney disease is one of the most frequent complications in patients with diabetes mellitus and affects morbidity and mortality. The recent therapies include oral hypoglycemic drugs that, in addition to optimizing glycemic control and reducing the risk of hypoglycemia, may affect the development and progression of diabetic kidney disease; these novel therapies include inhibitors of the enzyme dipeptidyl peptidase 4 (DPP-4), a group of oral hypoglycemic therapeutic agents that act at the level of the incretin system. DPP-4 inhibitors show additional pleiotropic effects in in vitro models, reducing inflammation, fibrosis, and oxidative damage, further suggesting potential kidney protective effects. Although existing trials suggest a possible benefit in the progression of diabetic kidney disease, further studies are needed to demonstrate kidney-specific benefits of DPP-4 inhibitors.

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INTRODUCTION

Type 2 diabetes is common and an important risk factor for cardiovascular disease, chronic kidney disease (CKD), and mortality. Poor glycemic control in individuals with type 2 diabetes increases the risk of these complications, including the risk of the development and progression of diabetic kidney disease (DKD). DKD, defined by albuminuria of >300 mg/d in the setting of diabetes, is common in individuals with type 2 diabetes and, in most parts of the world, is the leading cause of kidney failure. Around 30% to 50% of patients with type 2 diabetes develop DKD and can have rapid progression, leading to kidney replacement therapy.^{1,2}

Until the year 2008, the choice of oral hypoglycemic medication for the management of type 2 diabetes was based solely on achieving adequate glycemic control; however, the high incidence of cardiovascular complications and additional treatment options have led to a change in the paradigm of the treatment of diabetes. Nowadays, the choice of oral hypoglycemic agent should be individualized according to the risk profile of each patient, including their comorbid conditions and risk of hypoglycemia. However, achieving adequate metabolic control with oral hypoglycemic agents in patients with type 2 diabetes and CKD is challenging, with uncertainty regarding metformin use, particularly because of very low glomerular filtration rate and safety concerns with several sulfonylureas; thus, achieving adequate metabolic control without increasing the risk of hypoglycemia in this group of patients has been a therapeutic challenge in the last decade. For example, metformin appears associated with the risk of lactic acidosis, glibenclamide is associated with hypoglycemia, thiazolidinediones cause fluid retention, and insulin carries high risk of hypoglycemia in patients with advanced CKD.³

In recent years, new oral hypoglycemic agents have been introduced; currently, we have therapeutic choices with effectiveness to control the serum glucose concentration and an adequate safety profile in patients with CKD. Several clinical trials label sodium/glucose transport protein 2 inhibitors and glucagon-like peptide 1 (GLP-1) agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors as medications that are safe and effective for patients with diabetic and nondiabetic CKD. Of the previously mentioned group of medications, DPP-4 inhibitors stand out in the treatment of advanced CKD.

DPP-4 inhibitors comprise a group of molecules that are safe and effective in the general population. Known as incretin analogues, these agents act as hormones that regulate the homeostasis of glucose by stimulating the release of insulin.⁴ Medications in this class have a low risk of causing hypoglycemia and neutral effect on body weight, which gives them a strong safety profile. Notably, some DPP-4 inhibitors require dose adjustment depending on the glomerular filtration rate, although none are contraindicated in people with CKD.⁵ In a recent systematic review, the efficacy and safety profiles of DPP-4 inhibitors were similar to those of other oral hypoglycemic medications used in a broad population of individuals with type 2 diabetes,⁶ including individuals with CKD. This review discusses DPP-4 inhibitors, including their physiologic effect on the incretin system, mechanism of action in the kidney, and effects on glucose control, kidney disease, and cardiovascular disease.

Physiological Effect on the Incretin System and Its Role in Glycemic Control

The normal physiologic response to an oral glucose load is the release of several hormones in the intestine that affect the production of insulin at the level of the pancreas; these

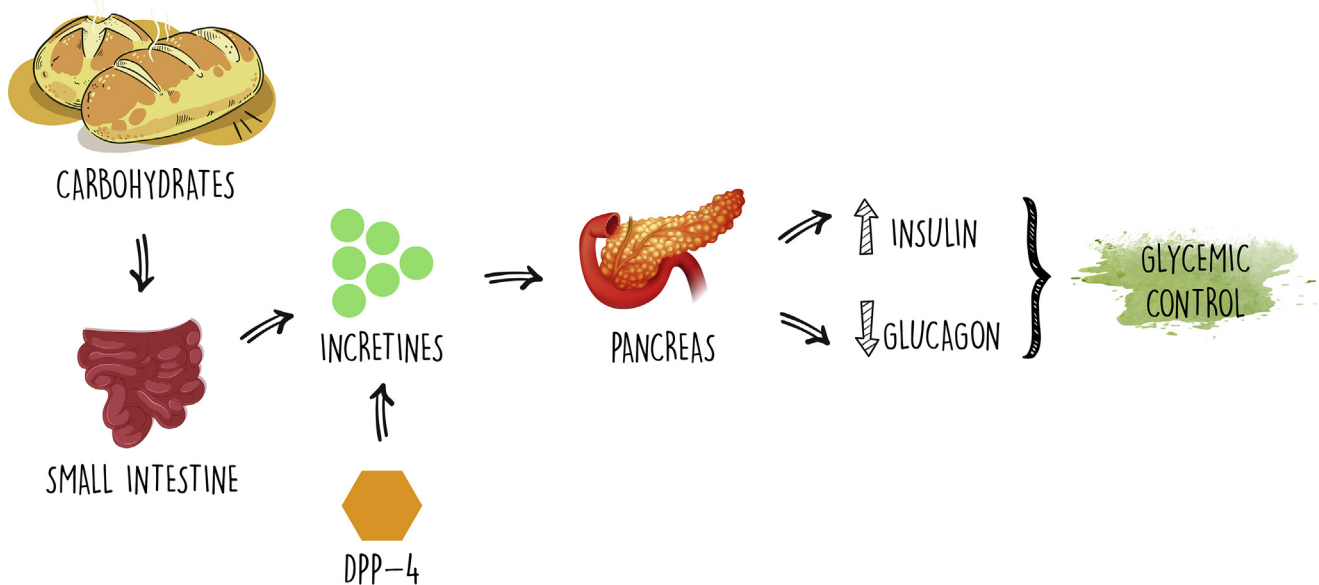


Figure 1. Physiologic effects of the incretin system and its response to an oral glucose load. DPP-4, dipeptidyl peptidase 4.

are GLP-1 and glucose-dependent insulinotropic polypeptide. These molecules comprise the incretin system, a series of hormones with insulinotropic effects produced in intestinal cells as a response to the ingestion of food and increase in the serum glucose concentration.⁷

Glucose-dependent insulinotropic polypeptide is secreted by K intestinal cells, which are located primarily in the duodenum and jejunum, and maximal production occurs between 15 and 30 minutes after the ingestion of calories or lipids, generating a stimulus in β pancreatic cells for the release of insulin. GLP-1 is secreted by L intestinal cells, which are located in the ileum and colon, and its production occurs immediately after the oral ingestion of carbohydrates; GLP-1 stimulates the release of insulin, the inhibition of glucagon secretion, and a delay in the velocity of gastric emptying.⁸ The glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are both responsible for what is known as the incretin effect, an increase in the secretion of insulin after an oral glucose load that is higher than values that are produced after the intravenous administration of glucose.⁹ Additionally, the expression of the members of the incretin system is not limited to the pancreas, and these proteins are widely distributed throughout the body, with GLP-1 receptors expressed in other organs, including the intestine, kidneys, heart, and central nervous system.

GLP-1 increase minutes after the ingestion of carbohydrates, but the physiologic response is very short, given the rapid endogenous degradation by the enzyme DPP-4, a serine-type exopeptidase responsible for the cleavage of the N-terminus of GLP-1, annulling its biological action (Fig 1).¹⁰ DPP-4 has 2 isoforms: a circulating soluble form in the plasma that is responsible for the cleavage of GLP-1 and a form that is found in the membrane of several cell types, including endothelial cells, T cells, and kidney

tubular cells (located in the membrane brush border of the proximal convoluted tubule in podocytes); the GLP-1 isoform is of great interest in terms of the pleiotropic action of DPP-4 inhibitors.¹¹ Given its transmembrane location, DPP-4 is likely responsible for the cleavage of other peptides, such as pronatriuretic brain peptide, Y-neuropeptide, and stromal derived factor-1 alpha.¹²

Conversely, DPP-4 is involved in multiple protein-to-protein interactions, including in association with adenosine deaminase in most tissues and as a receptor by facilitating entrance to cells in some viral infections; an example would be glycoprotein 120 in the capsid of HIV (human immunodeficiency virus), which facilitates its entrance into T lymphocytes.¹³ The other known sites of interaction include the chemokine receptor 4, tyrosine phosphatase, sodium-hydrogen exchanger 3, fibronectin, collagen, caveolin-1, and mannose-6-phosphate or insulin-like growth factor II.¹³⁻¹⁵ Through these interactions, DPP-4 participates in several biological processes, such as modulation of the immune system (including costimulation of T cells), activation of intracellular signaling pathways, natriuresis, cellular interactions with the extracellular matrix, and as a receptor for the entry of several viruses, such as HIV and Middle East respiratory syndrome coronavirus.^{15,16}

In the kidney, DPP-4 has been found to participate in the catabolism levels of extracellular proteins that contain proline.¹¹ An analysis in rats demonstrated that inhibition of DPP-4 influenced the metabolism of collagen, leading to depletion of collagen-derived peptides, which suggests that extracellular collagen can be a substrate in vivo for DPP-4. In this context, one can consider that remodeling of the extracellular matrix during the pathogenesis of diabetic nephropathy can be modulated by DPP-4 inhibitors.¹⁷

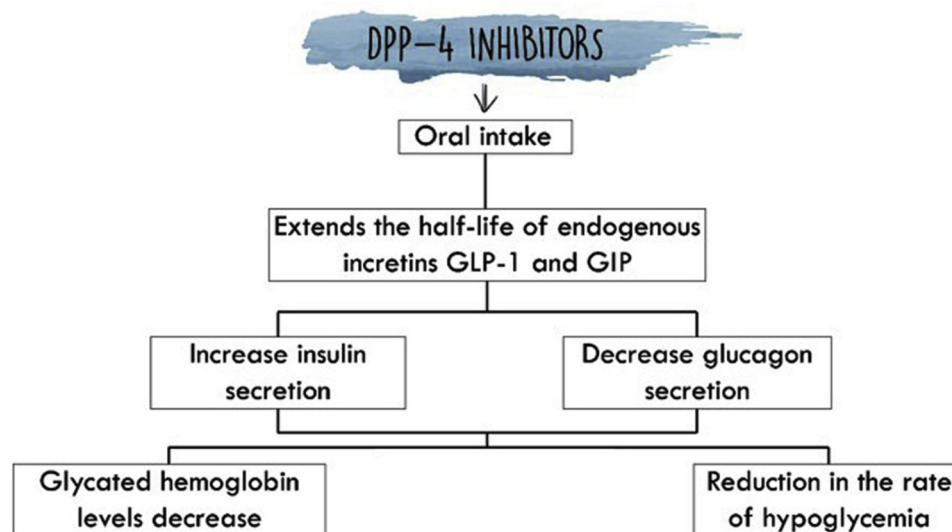


Figure 2. Mechanisms of the action of DPP-4 inhibitors and their effects in treating diabetes mellitus. DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; GPI, glucose-dependent insulinotropic peptide.

DPP-4 Inhibitors and Their Role in the Management of Type 2 Diabetes

The pathophysiologic characteristics of diabetes mellitus, specifically the mechanisms that yield systemic disease that affects multiple organs and compounds the effects of obesity and hypertension on cardiovascular risk, require an integrated therapeutic approach. In addition to optimizing glycemic control and reducing the risk of hypoglycemia, this approach should also reduce the risk of microvascular and macrovascular complications that are attributed to endothelial damage caused by chronic inflammation and persistent hyperglycemia. Given the latter, in recent years, most clinical trials have focused on oral hypoglycemic agents that decrease the incidence and progression of DKD because it is the microvascular complication of diabetes that has the highest effect on mortality and, perhaps, the quality of life. It is here that medications, such as DPP-4 inhibitors, which act at the level of the incretin system, play an important role in adequate glycemic control with a safe security profile, either as monotherapy or dual therapy with other oral hypoglycemic agents.¹⁸

DPP-4 inhibitors were introduced as therapeutic agents for the management of type 2 diabetes mellitus in 2006 along with GLP-1 agonists, both of which act within the incretin system and have an excellent cardiovascular safety profile while providing glycemic control with low hypoglycemia risk. DPP-4 inhibitors are an oral medication, generally with good bioavailability that is not affected by food intake and peak level of action in 2 to 3 hours.¹⁹ The mechanism of action is primarily the inhibition of the enzyme DPP-4 to prolong the half-life of GLP-1, blocking its inactivation and, as a result, promoting an increase in insulin secretion. DPP-4 inhibitors also decrease the concentration of glucagon in a glucose-dependent manner by decreasing the fasting glucose and postprandial glucose

levels (Fig 2). DPP-4 is present in multiple organs in its transmembrane form, and potentially, DPP-4 inhibitors can confer cardiovascular and kidney protection via mechanisms that differ from their action in the incretin system.²⁰

In 2006, sitagliptin was endorsed as the first DPP-4 inhibitor for the treatment of diabetes mellitus, followed by the introduction of vildagliptin, saxagliptin, linagliptin, and alogliptin. Of note, vildagliptin has not been approved by the US Food and Drug Administration but has been approved by the European Medicines Agency for the management of type 2 diabetes. An overview of the characteristics of several of these medications are shown in Table 1. The additional agents in this class include gemigliptin, anagliptin, evogliptin, and teneligliptin, which have been approved in countries such as South Korea, Japan, and Argentina.²¹ All these medications belong to the same class but are heterogeneous among themselves.

Mechanistic Basis for DPP-4 Inhibitor Use in Patients With DKD

The DPP-4 enzyme is present in several tissues in the body; however, its levels vary in different organs and tissues, with the highest level per gram in the kidney.²² Throughout the course of conditions in which an inflammatory state is predominant, such as diabetes mellitus, the levels of circulating and membrane-associated DPP-4 increase. Circulating levels increase due to the proteolysis of membrane-bound DPP-4 by kallikrein-related peptidase 5 in circulating CD4⁺ helper T cell type 17 cells.²³ The increase in the expression and enzymatic activity of DPP-4 has been studied in multiple models to determine its role in the development of DKD.

In murine diabetes models, DPP-4 was found to be present in podocytes and in the proximal tubule, forming a

Table 1. Overview of DPP-4 Inhibitors

| Medicine | Sitagliptin | Vildagliptin | Linagliptin | Saxagliptin | Alogliptin |
|--------------------|--|---|--|--|--|
| Administration | Oral | Oral | Oral | Oral | Oral |
| Metabolism | Low | High, hepatic, independent of cytochrome p450 | Low | High, hepatic, cytochrome dependent (CIP3A4/5) | Low |
| Excretion | Via kidney (80%) | Via kidney (85%) | Via liver (84%) | Via kidney (51%-75%) | Via kidney (71%) |
| Enzyme selectivity | High | Moderate | High | Moderate | High |
| Dose adjustment | GFR > 45 mL/min/1.73 m ² does not require adjustment: 100 mg/d; GFR 15-30 mL/min/1.73 m ² : 50 mg/d; GFR < 15 mL/min/1.73 m ² : 25 mg/d | GFR > 50 mL/min/1.73 m ² : 100 mg/d; GFR < 50 mL/min/1.73 m ² : 50 mg/d | 5 mg/d; does not require dose adjustment, not even in dialysis | GFR > 50 mL/min/1.73 m ² : 5 mg/d; GFR < 50 mL/min/1.73 m ² : 2.5 mg/d | GFR > 45 mL/min/1.73 m ² : 25 mg/d; GFR 15-45 mL/min/1.73 m ² : 12.5 mg/d; GFR < 15 mL/min/1.73 m ² : 6.25 mg/d |
| Adverse effects | Headache, constipation, itching | Nausea, headache, vertigo | Constipation, vertigo | Vertigo, fatigue | Headache, itching, vertigo |

Abbreviations: CIP3A4/5, cytochrome P450 3A4/5; DPP-4, dipeptidyl peptidase 4; GFR, glomerular filtration rate.

complex with sodium-hydrogen exchanger 3 in the membrane brush border, where it acted by modulating the exchange of Na⁺ and H⁺ by the exchanger, to reduce natriuresis.^{24,25} Contrastingly, the activity of DPP-4 exopeptidase, which is in the proximal tubule, permits the reabsorption of oligopeptides that contain proline,²⁶ and in rat models fed with a diet rich in fatty acids or treated with streptozocin to induce diabetes, DPP-4 was overexpressed in tubular cells, whereas deficiency of DPP-4 protected the kidneys from acute ischemic reperfusion injury.²⁷ In human models, the overexpression and elevated enzymatic activity of DPP-4 was found only in diseased glomeruli, mainly at the level of podocytes. Additionally, the exposure of endothelial cells of the glomeruli to high concentrations of glucose in vitro increased the mRNA level and enzymatic activity of DPP-4.²⁸ The hyperglycemic milieu also has a direct effect of the production and secretion of extracellular matrix proteins, leading to overexpression of molecules such as glucose transporters GLUT-1 and GLUT-4.²⁹ On the other hand, it has been demonstrated that the activity of urinary DPP-4 is significantly higher in patients with type 2 diabetes and albuminuria than in patients with diabetes and no albuminuria or healthy individuals.³⁰ An analysis of the relationship between the stage of CKD and the serum levels of 10 proteases demonstrated that only angiotensin-converting enzyme level and DPP-4 activity correlate significantly with estimated glomerular filtration rate (eGFR). In both the cases, the relationship was inverted such that patients with higher DPP-4 activity and angiotensin-converting enzyme level exhibited the lowest eGFR.³¹ Other clinical studies established the theory that increased DPP-4 activity plays a pathologic role in DKD.^{30,32,33} Consequently, there has been a substantial interest in the effects of DPP-4 on the pathogenesis and progression of DKD.

Among DPP-4 inhibitors, the effects of linagliptin on the kidneys are particularly interesting because based on its pharmacokinetic characteristics, it is the only agent that is not cleared by the kidneys and, therefore, does not require dose adjustment in patients with CKD.^{34,35} Additionally, it is the only DPP-4 inhibitor that has been evaluated in a randomized clinical trial designed to explore both cardiovascular and kidney outcomes, the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin.³⁶ The effects of linagliptin on the kidneys appear to be pleiotropic, with diverse mechanisms. First, there appears to be an antifibrotic effect, which is notable because kidney fibrosis is the final structural manifestation of progressive kidney diseases, including DKD.³⁷ In animal models, linagliptin reduced tubulointerstitial and glomerular fibroses as well as decreased albuminuria without altering the serum glucose levels.³⁸ These changes occurred secondary to inhibition of endothelial-to-mesenchymal transition within the kidney. This process is believed to be an important source of fibroblasts, given that in this transition, there is detachment of the cells of the endothelium, which then acquire a myofibroblastic pattern that invades the interstitial space. This leads to the expression of a high quantity of a protein that is responsible for fibrosis, such as actin and type I collagen.³⁹ Furthermore, linagliptin inhibited the endothelial-to-mesenchymal transition induced by transforming growth factor β2 (TGF-β2) in animal models, a transcription factor that plays an essential role in the process of fibrosis in cultivated human dermic microvascular endothelial cells, reducing the phosphorylation of TGF-β2-induced Smad3.³⁸ Additionally, in the same murine model, another profibrotic mechanism was identified that comprises an interaction between DPP-4 and beta-1 integrin in endothelial cells that modulates the signaling of TGF-β2 to induce endothelial-to-mesenchymal transition via the phosphorylation of the

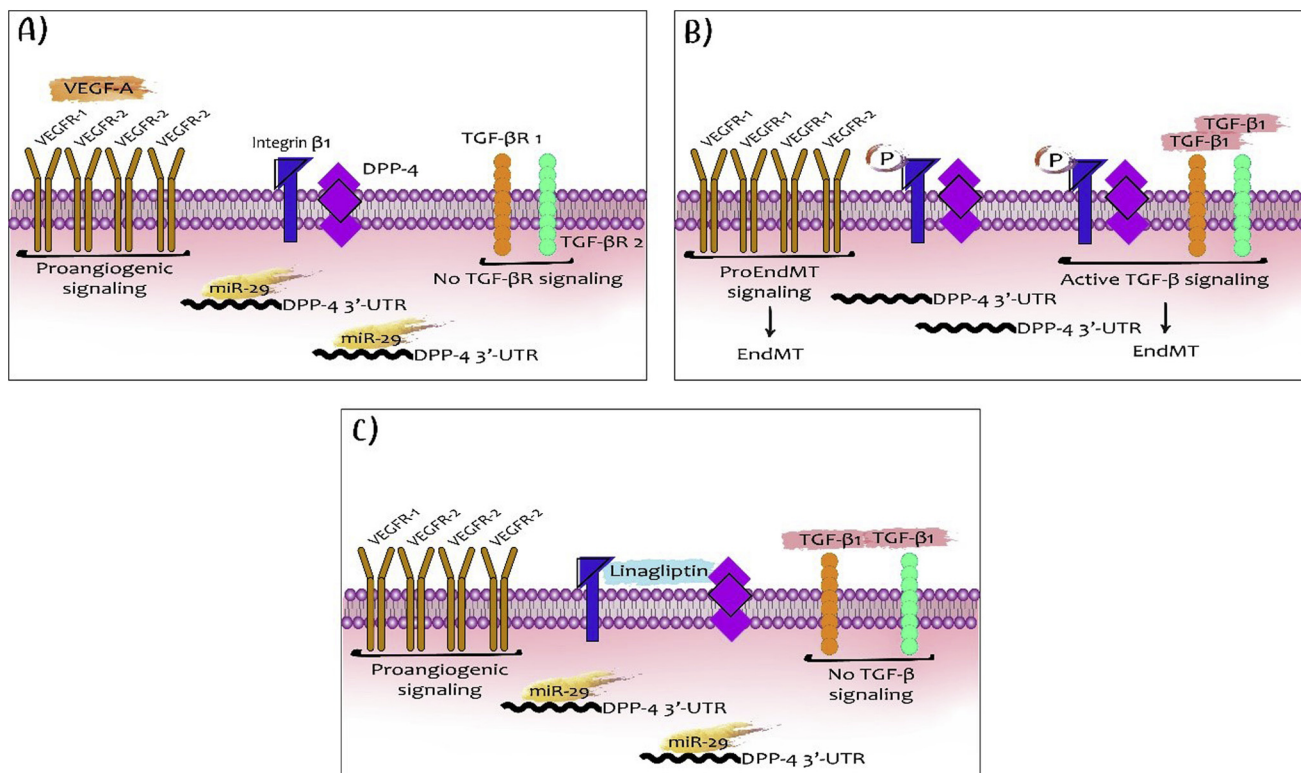


Figure 3. DPP-4 variation in the kidney and its interaction with receptors depending on the glycemic state and in the presence of linagliptin. (A) Euglycemia: Regulation by miR-29 leads to a decrease DPP-4 level because of poor interaction between DPP-4 and $\beta 1$ integrin. The TGF- β receptors are inactive, and VEGFR-2 is more abundant, favoring angiogenesis. (B) Hyperglycemia: The miR-29 level is depleted, so DPP-4 accumulates and interacts with $\beta 1$ integrin, inducing the formation of receptor complexes of TGF- β type I and type II, which allows pro-EndMT signaling in response to TGF- β . (C) Effect of linagliptin and hyperglycemia. Linagliptin restores the levels of miR-29, inhibiting the interaction between DPP-4 and $\beta 1$ integrin, consequently inhibiting the formation of the receptor complexes of TGF- β type I and type II, which limits pro-EndMT signaling.³⁷ The effect of linagliptin re-establishes the density of the VEGFR-2 receptor, favoring angiogenic signaling. DPP-4, dipeptidyl peptidase 4; EndMT, endothelial-to-mesenchymal transition; miR, microRNA; TGF- β , tumor growth factor β ; UTR, untranslated region; VEGFR, vascular endothelial growth factor receptor.

S785 residue of $\beta 1$ integrin.⁴⁰ This study identified that this interaction is interrupted by linagliptin, with linagliptin associated with lower serum levels of cystatin C and with the expression of DPP-4, $\beta 1$ integrin, $\beta 1$ p-integrin, and TGF- β in the endothelial cells of the kidneys of diabetics. Linagliptin also reduces fibrosis, which is dependent on TGF- β , in proximal tubular epithelial cells in the human kidney and high glucose concentrations through a different mechanism. The cation-independent mannose-6-phosphate receptor activates TGF- β in human kidney-2 cells exposed to high glucose levels; linagliptin inhibits the activation of TGF- $\beta 1$ in this cell line through the interruption of protein-to-protein interaction between DPP-4 and the mannose-6-phosphate receptor.^{41–43}

In addition to its antifibrotic properties, linagliptin can protect the kidneys via other pathways; these include the effects on the signaling pathway of advanced glycation end products (AGE) and their receptor, oxidative stress, inflammation, and the endothelial activity of nitric oxide, by increasing the levels of the DPP-4 substrates stromal cell-derived factor 1 and GLP-1. Given that diabetes is associated with increased levels of AGE that contribute to

the development of micro- and macrovascular complications, including DKD, these effects may be meaningful. The binding of AGE to their receptor triggers oxidative stress and inflammation.⁴⁴ In several models, DPP-4, which is soluble in plasma, increased oxidative stress and the expression of the AGE receptor, apparently through binding of the mannose-6-phosphate receptor. These effects were blocked by linagliptin, which also inhibited the increase of the DPP-4 levels induced by AGE.^{45,46} The potential kidney protective mechanisms of linagliptin are summarized in Fig 3.

Two other possible pathways underlying GLP-1 action in the kidney are regulation of atrial natriuretic peptide and effects on the renin-angiotensin system; there is evidence that the incretin system modifies water and sodium homeostasis. In Dahl salt-sensitive rats, infusion of GLP-1 increased the glomerular filtration rate, urinary flow, and sodium excretion. GLP-1 has also been shown to decrease kidney reactive oxygen species production and inflammation in vivo and in vitro by stimulation of the GLP-1 receptor resulting in a lower rise in the levels of reactive oxygen species caused by angiotensin-2.⁴⁷

In cultured mesangial cells, GLP-1 receptor stimulation led to the prevention of cell damage by blocking superoxide formation induced by angiotensin-2, activation of the nuclear factor- κ B pathway, and upregulation of intercellular adhesion molecule-1 and plasminogen activator inhibitor-1. Similarly, in the cultured mesangial cells, pleiotropic anti-inflammatory action by GLP-1 was observed by the suppression of monocyte chemoattractant protein-1. Alogliptin has been shown to reduce the toll-like receptor 4-mediated upregulation of proinflammatory cytokines in mononuclear cells.⁴⁷

In summary, evidence suggests that DPP-4 inhibitors may possess antifibrotic abilities, reducing albuminuria and progression to advanced CKD; linagliptin decreases the expression of the AGE receptor, decreasing oxidative stress and inflammation, which in turn leads to decreased progression toward advanced DKD. Remodeling of the extracellular matrix, as mentioned previously, may be another contributing pathway in the role of DPP-4 inhibitors in DKD.

The antioxidant properties of linagliptin have been studied, and these may not be shared with other DPP-4 inhibitors. In contrast to other agents in this class, linagliptin contains a xanthine backbone and can inhibit xanthine oxidase, an enzyme involved in purine metabolism that generates reactive oxygen species⁴⁸; the antioxidant effects of linagliptin also blocked positive feedback between the degeneration of reactive oxygen species and AGE-AGE receptor signaling in diabetic nephropathy.⁴⁸ Regarding the enzymatic action of linagliptin, the substrates that affect kidney function are stromal cell-derived factor 1 and GLP-1. Stromal cell-derived factor 1 is a chemokine that promotes endothelial repair and has been demonstrated to mediate cell repair during acute ischemic kidney injury,⁴⁹ and linagliptin has been shown to increase the expression of stromal cell-derived factor 1 in the distal tubules in the kidney, with improvement in kidney pathology and a reduction in oxidative stress.⁵⁰ The role of GLP-1 seems to be given by the natriuretic effects mediated by the inhibition of sodium-hydrogen exchanger 3 in the proximal tubule, which affects blood pressure management in a positive manner.⁵¹

The DPP-4 levels can be detected in the urine. In 1 small observational study, the levels of microvesicle-bound DPP-4 in the urine were higher in individuals with diabetes, and the levels correlated positively with albuminuria, suggesting that urinary DPP-4 can serve as a biomarker in this population.³⁰ There is also a possibility that urinary DPP-4 can serve as a substitute marker of tubular damage in glomerular diseases such as primary glomerular nephritis and lupus nephritis.⁵²

Clinical Data Supporting DPP-4 Inhibitor Use in Patients With DKD

Despite diverse animal models that have shown potential beneficial effects of linagliptin on the kidney, less evidence is currently available in clinical studies that demonstrate

benefits in clinical care for reducing the progression of DKD in patients. However, DPP-4 inhibitors are effective in glycemic control and well tolerated in patients with diabetes mellitus and kidney disease, including those with concomitant hypertension.⁵³ In a secondary analysis of the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 trial, saxagliptin was associated with significant reductions in albuminuria that were independent of the effects of saxagliptin on glycemic control. However, over 2 years of follow-up there were no significant differences in eGFR or the incidence of hard kidney endpoints, including doubling of the serum concentration of creatinine or kidney failure.⁵⁴ Similarly, in the TECOS (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) study of sitagliptin, there were significant reductions in albuminuria associated with sitagliptin, with no change in eGFR.⁵⁵

The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin trial was a noninferiority, placebo-controlled outcome trial of the DPP-4 inhibitor linagliptin with a secondary composite kidney outcome of a sustained 40% decline in eGFR, end-stage kidney disease, or kidney death. The primary outcome in the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin trial was a cardiovascular disease composite, including cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The Cardiovascular and Renal Microvascular Outcome Study with Linagliptin trial showed a cardiovascular safety profile that was similar to that of a placebo over a mean of 2.2 years of follow-up, with no significant difference in kidney outcomes.³⁶ Notably, patients randomized to receive linagliptin had less progression of albuminuria compared to placebo.³⁶ Critically, additional studies with longer follow-up periods must be conducted to fully evaluate whether these agents have important benefits for delaying DKD progression.

The effects of linagliptin on albuminuria have been seen in other studies. These effects were highlighted in a meta-analysis of 4 small randomized clinical trials that showed that treatment with linagliptin was associated with a reduction of 32% in urine albumin-to-creatinine ratio after 24 weeks of therapy among individuals with albuminuria who were already receiving standard care for DKD (renin-angiotensin-aldosterone system blockers or inhibitors).⁵⁶ In contrast, in the 360 participants in the MARLINA-T2D (Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects With Renal Disease With LINAgliptin) study, which enrolled individuals with a urine albumin-to-creatinine ratio of ≥ 30 mg/g, treatment with linagliptin was associated with improved glycemic control, without a significant effect on the levels of albuminuria.⁵⁷ From a cardiovascular safety standpoint, DPP-4 inhibitors seem well tolerated, although participants treated with saxagliptin in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in

Myocardial Infarction 53 trial were at higher risk of the secondary outcome of hospitalization due to heart failure (which was a component of a composite) in an otherwise negative study.⁵⁸

CONCLUSION

Diabetes mellitus is a disease with high prevalence worldwide. Chronic inflammation and persistent hyperglycemia, which comprise the pathophysiologic base of the disease, result in endothelial damage that leads to macro- and microvascular diabetes complications. DKD is one of these common complications and is extremely impactful, comprising the leading cause of kidney failure in higher-income countries. DPP-4 inhibitors are important therapeutic options that have emerged over the past decade for the treatment of diabetes. DPP-4 inhibitors are oral hypoglycemic agents that have demonstrated efficacy in glycemic control for individuals with type 2 diabetes and DKD, low risk of hypoglycemia, a neutral effect on body weight, and a cardiovascular safety profile that allows its use in patients with CKD. Although several studies in animal models and in people have suggested an antiproteinuric effect, the major clinical trials using DPP-4 inhibitors to date have not shown significant effects on reducing the progression of DKD; moreover, these trials are limited by relatively short durations. Future research is needed to define the role of these agents, specifically evaluating whether they have benefits in treating DKD.

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