Accepted Manuscript

Title: Exploring the effects of DPP-4 inhibitors on the kidney from the bench to clinical trials

Authors: Giuseppe Coppolino, Christian Leporini, Laura Rivoli, Francesco Ursini, Eugenio Donato di Paola, Valeria Cernaro, Franco Arturi, Davide Bolignano, Emilio Russo, Giovambattista De Sarro, Michele Andreucci

Please cite this article as: Coppolino Giuseppe, Leporini Christian, Rivoli Laura, Ursini Francesco, di Paola Eugenio Donato, Cernaro Valeria, Arturi Franco, Bolignano Davide, Russo Emilio, De Sarro Giovambattista, Andreucci Michele.Exploring the effects of DPP-4 inhibitors on the kidney from the bench to clinical trials.*Pharmacological Research* https://doi.org/10.1016/j.phrs.2017.12.001

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Exploring the effects of DPP-4 inhibitors on the kidney from the bench to clinical trials.

Giuseppe Coppolino[1,#], Christian Leporini[5,#], Laura Rivoli[2], Francesco Ursini[5], Eugenio Donato di Paola[5], Valeria Cernaro[4], Franco Arturi[6], Davide Bolignano[3], Emilio Russo[5], Giovambattista De Sarro[5,], Michele Andreucci[2]*

[1]Nephrology and Dialysis Unit, "Pugliese-Ciaccio" Hospital of Catanzaro, Italy.

[2]Renal Unit, Department of Health Sciences, Magna Graecia University, Catanzaro, Italy.

[3]CNR-Institute of Clinical Physiology, Reggio Calabria, Italy.

[4]Nephrology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

[5]Pharmacology Unit, Department of Health Sciences, Magna Graecia University, Catanzaro, Italy.

[6]Internal Medicine Unit, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy.

[#]These two Authors equally contributed to the present work

[*]**Corresponding Author**

Prof. Giovambattista De Sarro,

Clinical Pharmacology Unit,

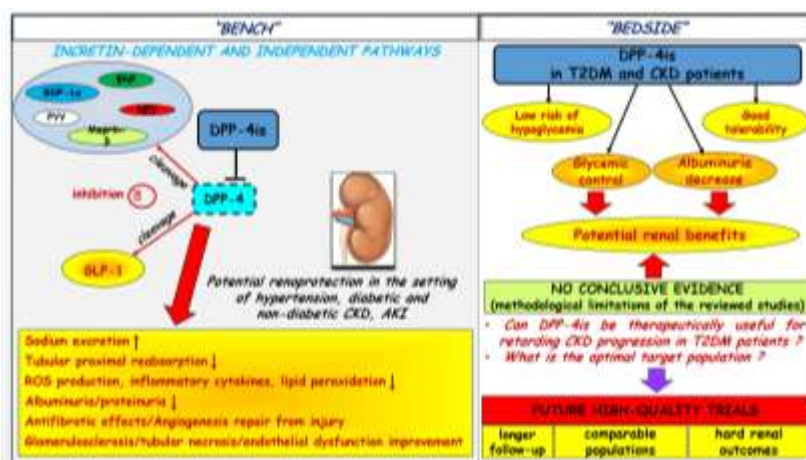Department Science of Health, School of Medicine and Surgery,

University of Catanzaro;

Viale Europa - Germaneto 88100 Catanzaro, ITALY.

Phone +39 0961 3694191/Fax: +39 0961 3694192

e-mail: desarro@unicz.it

1

Graphical abstract

ABSTRACT

Dipeptidyl-peptidase-4 (DPP-4) inhibitors are a relatively new class of non-insulin glucose-lowering agents, belonging to the incretin family, which are able to improve glycemic control with a favorable safety profile, since they are associated with a low risk of hypoglycemia, no weight gain, and good tolerability in patients with chronic renal failure. Some experimental and clinical studies suggest that these drugs may exert significant pleiotropic effects, in particular on chronic kidney disease (CKD) progression, but data from clinical trials are still controversial. In an effort to clarify the effects of DPP-4 inhibitors (DPP-4is) on diabetes-related renal damage, we performed a narrative review of available clinical trials and other experimental studies focusing on renal effects of DPP-4is. Currently, there is no conclusive evidence proving the usefulness of this drug class for improving diabetes-related renal damage. However, our literature review suggests that DPP-4is are safe and well tolerated in type 2 diabetes mellitus (T2DM) patients with CKD. More importantly, results from the reviewed studies indicate that DPP-4 inhibitor therapy may improve two major risk factors for diabetic nephropathy, such as hyperglycemia and albuminuria, resulting in potential renal benefits beyond glycemic control. Despite several limitations, the conclusions of our review

corroborate previous evidence on the potential renal benefits of DPP-4is, highlighting the urgent need of future trials adequately powered and designed on hard renal outcomes to ascertain (or contradict) the therapeutic benefit of DPP-4is in T2DM and CKD patients.

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; CKD; chronic kidney disease; DKD, diabetic kidney disease; DM, diabetes mellitus; DN, diabetic nephropathy; DPP-4, dipeptidyl-peptidase-4; DPP-4is, dipeptidyl-peptidase-4 inhibitors; ECs, endothelial cells; EVs, extracellular vesicles; GLP-1, glucagon-like peptide-1; GLP-1R; glucagon-like peptide-1 receptor; GLP-1RA, glucagon-like peptide-1 receptor agonist; NO, nitric oxide; RAS, renin-angiotensin system; ROS, reactive oxygen species; T2DM, type 2 diabetes mellitus.

ABBREVIATIONs:
AEs: adverse experiences
AKI: acute kidney injury
BMI: Body max index
BW: body weight
CAD: Acute myocardial infarction/myocardial infarction
CI: Confidence Interval
CKD: Chronic kidney disease
CrCl: creatinine clearance
CVD: cardiovascular diseases
DPP-4: Dipeptidyl peptidase-4 inhibitor
DS: standard deviation
FPG: Free Plasmatic glucose
GFR: Glomerular filtration rate
GLP-1: Glucagon-like peptide-1
HbA1c: glycosilated haemoglobin
HR: Hazard Ratio
IGC: inadequate glycaemic contro
IMA: Acute myocardial infarction
LD: liver diseases
MEN2: multiple endocrine neoplasia syndrome type 2.
MRF: Multiple risk factors "To meet the criteria for the multiple risk factors, patients had to be at least 55 years of age (men) or 60 years of age (women) with at least one of the following additional risk factors: dyslipidemia, hypertension, o active smoking."
OAD: oral antihyperglycemic agents
OHdG: Urinary 8-hydroxy-2'-deoxy guanosine
RT: renal transplant
SAE: severe adverse experiences
SMBG: self-monitored blood glucose

SDF-1α: Stromal cell-derived factor-1α
SU: sulfonylurea
T2DM: Type 2 diabetes mellitus
T1DM: Type 1 diabetes mellitus
TDZs: Thiazolidinediones
TIA: transient ischemic attack

Keywords: DPP-4 inhibitors, kidney function, renal benefits, proteinuria, renal detriments, adverse events.

1. Introduction

Diabetes mellitus (DM) is a multifactorial disease [1] associated with serious comorbidities. This condition has recently reached epidemic proportions, as its occurrence has exponentially increased in the general population. Over 400 million people worldwide were estimated to have DM and total mortality increased by 32.1% from 2005 to 2015. Diabetes caused 5 million deaths in 2015, representing the seventh leading cause of death in the United States [2, 3]. Moreover, the risk of both microvascular and macrovascular complications has significantly increased, including diabetic kidney disease (DKD), an independent risk factor for coronary artery and peripheral vascular disease. Hyperglycemia triggers many mechanisms resulting in alteration of kidney architecture, oxidative and inflammatory stress, and eventually progressive loss of renal function [4, 5].

Strict glucose control through lifestyle changes (i.e., diet, physical exercise, and weight loss) is crucial for slowing DKD progression. However, most type 2 diabetic patients need also medications such as oral hypoglycemic agents and insulin to achieve sustained control of hyperglycemia [6]. Other pharmacological treatments have a positive effect on renal function, retarding the evolution to end-stage renal disease (ESRD) [7]. For instance, renin–angiotensin system (RAS) inhibitors [8] as well as the use of antioxidant agents [9]

have demonstrated significant renoprotection, particularly related to their anti-proteinuric activity. Interestingly, the anti-inflammatory and hemorrheologic drug pentoxifylline may also afford renoprotective effects, even though there is still no conclusive evidence supporting its widespread use for improving renal outcomes in subjects with chronic kidney disease (CKD) of various etiology [10]. Some drugs specifically used to treat diabetes, like incretin-based therapies, represent a relatively new tool against the global epidemic of DM. Incretin-based drugs include glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) and inhibitors of dipeptidyl-peptidase-4 (DPP-4). They basically promote a significant decrease in serum glucose that is accompanied by low risk of hypoglycemia and weight loss (with GLP-1RAs) or weight neutrality (with DPP-4 inhibitors) when compared to conventional therapies (metformin monotherapy or combination therapy) [11, 12]. However, conflicting results have been obtained with these drugs: some clinical studies, in fact, have shown positive pleiotropic effects in retarding DKD [13-16], whereas others pointed out the possible accumulation of these agents in patients with impaired renal function, thereby exposing them to adverse events [17-22].

In the first part of this review, we describe the incretin system, explaining its main physiological and pathophysiological characteristics and discussing the pleiotropic effects of DPP-4 inhibitor therapy, particularly with regard to renal protection. We then report on pre-clinical results in animal models, followed by evidence on the progression or regression of renal damage following DPP-4 inhibitor therapy obtained by an analysis of clinical studies.

2. Main pharmacologic features of DPP-4 Inhibitors: an overview

Drugs that inhibit DPP-4 activity, commonly referred to as *gliptins*, represent a relatively new class of non-insulin glucose-lowering agents endowed with great ability to

improve glycemic control, with a favorable tolerability and safety profile [23, 24]. DPP-4 belongs to a family of proteolytic enzymes that are ubiquitously expressed in several tissues where they exert different functions. In particular, the DPP-4 enzyme exists in two forms, a soluble form circulating in the blood and a membrane-bound one present in several cell types [25]. In the kidney, DPP-4 is localized on glomerular visceral epithelial cells, the proximal tubule brush border and on endothelial cells [26] where it usually acts by preferentially cleaving peptide hormones containing a position two alanine or proline at the NH_2-terminus [27]. The incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are the best-studied substrates for the DPP-4 enzyme. These peptide hormones are secreted respectively by L (in the lower gut) and K cells (in the upper gut), in response to food intake. Notably, GLP-1 is mainly involved in post-prandial glucose homeostasis through the stimulation of pancreatic GLP-1 receptor (GLP-1R), thus facilitating insulin secretion from β-cells and inhibiting glucagon secretion from α-cells in a glucose-dependent manner [28, 29]. Upon GLP-1 secretion, DPP-4 rapidly breaks down this hormone, inactivating it [30]. Furthermore, the incretin hormones are quickly removed from the bloodstream by the circulating DPP-4 and renal filtration [31, 32]. Taking into account the pancreatic effects of GLP-1 and its fast degradation, DPP-4 represents a relevant pharmacological target to manage diabetes. In this setting, DPP-4 inhibitors (DPP-4is) prevent GLP-1 inactivation resulting in the potentiation of pancreatic GLP-1R signaling, which enhances glucose consumption and reduces hepatic glucose production [28, 29].

DPP-4is show two relevant benefits in the clinical management of type 2 diabetic patients: negligible risk of severe hypoglycemia, particularly when compared with sulphonylureas [33, 34], and weight neutrality, in contrast with the weight gain generally observed with insulin therapy, sulfonylureas, glinides, and thiazolidinediones [11, 33]. Indeed, since the insulinotropic effects of DPP-4is are glucose-dependent, these agents do not

affect the glucagon compensatory response to hypoglycemia, leading to low incidence of hypoglycemic episodes [24].

Currently, five DPP-4is are available for use in clinical practice: sitagliptin, vildagliptin, saxagliptin, linagliptin, and alogliptin [24]. The main pharmacokinetic and pharmacodynamic features of DPP-4is available on the European market are summarized in **Table 1**.

All these agents are rapidly absorbed orally, irrespective of concomitant administration with food, and their peak plasma concentrations (t_{max}) occur between 1 and 3 hours after administration [35]. Their bioavailability is ≥63% except for linagliptin (~30%) [36], whose gastrointestinal absorption is inhibited by P-glycoprotein [37].

Both lipophilicity and protein binding strongly affect the distribution of DPP-4is. Compared to other gliptins, linagliptin exhibits higher volume distribution (Vd) (more than 1000 L) and protein binding (≥ 75%), showing extensive distribution into tissues [35, 38]. Metabolism of DPP-4is is widely variable. Both vildagliptin and saxagliptin are largely metabolized in the liver: vildagliptin produces several inactive metabolites through pathways that are not mediated by the cytochrome P450 (CYP) system, while saxagliptin is mainly metabolized by CYP 3A4/5 isoforms to 5-hydroxy saxagliptin, a major metabolite that is two-fold less potent than its parent molecule [39]. On the other hand, metabolism represents a minor elimination pathway for sitagliptin [40]. No DPP-4 inhibitor has been shown to induce or inhibit CYP isoforms: hence, a low risk of clinically significant drug-drug interactions is associated with these agents. However, a potential higher risk of drug-drug interactions with saxagliptin exists when this agent is co-administered with drugs that are strong inhibitors (e.g. ketoconazole) or inducers (e.g. rifampicin) of CYP3A4/5 isoforms. Dose adjustment is required in these cases [35, 39].

All gliptins are predominantly excreted in the urine, with 60–85% of each dose eliminated as unchanged parent compound. In contrast, linagliptin undergoes enterohepatic cycling and it is mainly excreted in the feces (~90%). Accordingly, the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) guidelines advocate dosing-adjustment for sitagliptin, vildagliptin, saxagliptin, and alogliptin in patients with moderate or severe renal impairment whereas no restrictions have been posed for linagliptin [18, 42].

3. Pleiotropic effects of DPP-4 Inhibitors beyond glycemic control

Beyond the pancreas, GLP-1R and DPP-4 are expressed in a wide variety of organs and tissues, such as the central and peripheral nervous system, heart, lung, gastrointestinal tract, eye and kidney, thereby explaining the pleiotropic effects of the incretin system [43-45]. Some of these extra-pancreatic effects might be exploited to prevent or treat diabetes-related complications, independently of the achievement of glycemic control. Accordingly, GLP-1 has been shown to prevent atherosclerosis-related diseases (i.e., cerebrovascular, coronary artery and peripheral artery disease), through direct actions on the brain [46-49], heart [50-53] and vascular endothelial cells (ECs) [54-59]. Particularly, GLP-1 has been reported to inhibit macrophage-driven atherosclerosis in healthy and diabetic apolipoprotein E-deficient mice [61, 62]. Furthermore, GLP-1-mediated suppression of inflammatory cytokines has been shown in diabetic patients, resulting in improved endothelial dysfunction [63-65]. In addition, *in vitro* studies showed that GLP-1 was able to increase endothelial nitric oxide (NO) production and promote both proliferation and differentiation of cultured endothelial progenitor cells by upregulating vascular endothelial growth factor [56, 57]. These effects respectively translated into increased microvascular blood flow and improved endothelial dysfunction in preclinical models [56, 58]. Inhibition of both nuclear factor (NF)-kB pathway and apoptosis of human umbilical vein ECs appear to be other GLP-1-mediated

anti-atherogenic mechanisms [59, 66]. Consistent with the above anti-atherosclerotic effects, sitagliptin [67], alogliptin [67, 68], and vildagliptin [69, 70] inhibited the production of inflammatory cytokines and the NF-kB pathway while increasing endothelial NO production in experimental animal models. Interestingly, such vasoprotective effects were also observed in type 2 diabetic patients treated with sitagliptin [71, 72]. It is noteworthy that the increase in NO production might explain the ability of GLP-1 to counteract hypertension by exerting an arteriolar vasodilatory action, as consistently shown in several clinical trials [73, 74]. Moreover, it has been reported that sitagliptin attenuates blood pressure in both hypertensive rats [75, 76] and humans [77, 78].

GLP-1 also showed cardioprotective effects (i.e., infarct size reduction and ejection fraction improvement) in experimental models of myocardial ischemia-reperfusion injury by suppressing caspase-3 activation and preventing apoptosis of cardiomyocytes [50, 51]. Of note, such a cardioprotection was previously reported to be mediated by both GLP-1R-dependent and GLP-1R-independent mechanisms [79]. More importantly, GLP-1 has been reported to improve ejection fraction of left ventricle and to prevent its ischemic dysfunction in patients with acute myocardial infarction [80] and coronary artery disease (CAD) [53], respectively. Besides its beneficial effects in CAD, GLP-1 might improve heart failure by increasing glucose uptake and, therefore, left ventricular function, as suggested by both animal [81] and human [82, 83] studies. DPP-4 inhibition resulted in similar cardioprotective effects in preclinical models [84, 85].

Regarding cerebrovascular function, GLP-1 attenuated cerebral oxidative stress and neuronal cell death by reducing reactive oxygen species (ROS) production and exerting anti-apoptotic effects in both non-diabetic and diabetic animals after cerebral ischemia [46-48]. In accordance, linagliptin afforded neuroprotection in a diabetic mouse model of ischemic brain damage. It is interesting to note that sulfonylurea glimepiride was not able to show similar

neuroprotective effects in the same study, suggesting that neuroprotection was independent of lowering glucose levels [49].

The incretin system also indirectly contributes to improved macrovascular function by regulating lipid metabolism [60]. Dyslipidemia amelioration has been associated with GLP-1 infusion in both experimental animals and humans through the down-regulation of intestinal lipid absorption [60, 86, 87]. GLP-1 has been also reported to modulate hepatic lipid metabolism by suppressing fatty acid synthesis and promoting fatty acid oxidation [88, 89]. Based on these mechanisms, vildagliptin and sitagliptin have been shown to suppress postprandial elevation of triglycerides in type 2 diabetic patients, suggesting their potential role in the prevention of macrovascular complications [90, 91].

Furthermore, some effects of GLP-1 in the peripheral nervous system, eyes, and kidney could be clinically significant in the treatment of diabetes-related microvascular complications [60].

Consistent with its ability to promote neurite outgrowth of the dorsal root ganglion neurons in diabetic mice, GLP-1 might be useful for ameliorating diabetic polyneuropathy, irrespective of glycemic control [92]. Accordingly, the vildagliptin analogue PKF275-055 partially improved the nerve conduction velocity deficit observed in diabetic rats [93]. Moreover, vildagliptin was shown to provide protection against nerve fiber loss in diabetic animals [94]. Taken together, these findings suggest the potential clinical significance of DPP-4is in the treatment of peripheral neuropathy.

Accruing studies on diabetes animal models have also shown beneficial effects of GLP-1 and DPP-4is on the retina [95-98]. In particular, sitagliptin was able to decrease the nitrosative stress, IL-1beta production, and cell apoptosis in diabetic rat retinas, thus protecting the blood-retinal barrier [98]. However, the involvement of GLP-1 in these effects needs to be confirmed.

Last but not least, the kidney function is heavily influenced by GLP-1 and DDP-4is [60] whose effects might be clinically meaningful in the treatment of kidney-related disorders such as diabetic nephropathy (DN), a major cause of kidney failure [99]. Most notably, preclinical studies and meta-analyses of clinical trials have shown that DDP-4is afford direct renoprotective effects that make them potentially effective in acute and chronic renal failure [100].

4. Effects of DPP-4 Inhibitors on Kidney function: physiological settings

GLP-1 signaling mediates important renal functions [101], as suggested by the expression of both DPP-4 and GLP-1R in the kidney of several species, including humans [102]. However, controversial data exists on the specific expression pattern of these proteins, based on the specificity and sensitivity of detection methods [88, 103]. Few studies suggest their presence in the renal blood vessels, glomerular cells and tubular cells [102]. Studies on rodents show that DPP-4 is extensively expressed on the brush border of proximal tubules and glomerular podocytes, as well as in preglomerular vascular smooth cells and mesangial cells [26, 104]. Hence, DPP-4is are expected to have a significant impact on renal physiology.

In addition to the direct stimulation of renal GLP-1Rs, the regulation of atrial natriuretic peptide (ANP) and the RAS represent two possible pathways underlying GLP-1 renal actions. Notably, accumulating evidence supports that incretin system is able to modulate sodium and water homeostasis [101]. The natriuretic effect is probably the best reported one in several studies, both in rodents and in humans. Chronic infusion of GLP-1 increased glomerular filtration rate (GFR), urinary flow and sodium excretion in Dahl salt-sensitive rats [105, 106]. However, no effect on GFR was present in rats with denervated kidneys, showing that renal GLP-1 signaling also depends on functional neurotransmission

[107]. Moreover, exendin-4 increased GFR in non-diabetic mice whereas did not show acute effect in diabetic db/db mice [108]. A significant increase in urinary sodium excretion and GFR decrease have been reported in obese, insulin-resistant men [109], whereas GLP-1 infusion resulted in dose-dependent natriuretic effect without GFR change in healthy subjects [110].

In light of these findings, GLP-1 markedly increases GFR in healthy rodents but shows a limited effect in healthy humans. Conversely, GLP-1 decreases GFR in both rodents and humans that are metabolically challenged (e.g., with hyperglycemia).

The GLP-1-mediated vasodilation of glomerular capillaries increases renal blood flow and therefore GFR in healthy rodents; however, this effect is minimal in humans receiving pharmacologically relevant GLP-1 doses. On the other hand, the GLP-1-mediated decrease in the proximal tubular reabsorption increases the proximal hydrostatic pressure, thereby decreasing GFR due to a decreased glomerular pressure gradient [111].

Natriuresis has been suggested to be due to the reduction of tubular proximal reabsorption that, in turn, is predominantly mediated by the inhibition of the Na^+/H^+ exchanger isoform 3 (NHE3) [101]. Interestingly, GLP-1R activation has been shown to down-regulate NHE3 activity through a protein kinase A (PKA)-dependent mechanism [112]. Furthermore, it has been recently shown that GLP-1R stimulation in the heart atria can indirectly induce natriuretic and vasorelaxant effects by releasing ANP which, in turn, stimulates its own receptor in the kidney. Interestingly, in the same study, liraglutide was able to only reduce blood pressure acutely in hypertensive mouse models (e.g., angiotensin-2 induced or pressure overload) [113]. These findings highlight a gut-heart axis in mice suggesting that ANP release mediates all acute physiological GLP-1-induced renal actions. On the other hand, the existence of a functional gut-heart axis in humans is questionable: GLP-1 infusion substantially increased natriuresis but had no effect on ANP secretion in

healthy males [114]. Rodent and human studies have demonstrated that GLP-1, in a GLP-1R- and PKA-dependent manner, also inhibits angiotensin-2 (ANG-2) actions by downregulating ANG-2 signaling and its plasma concentration [113, 115, 116]: ANG-2 is crucially involved in tubular proximal reabsorption by increasing NHE3 activity.

Taken together, these specific mechanisms of action may largely account for the above reported GLP-1-mediated anti-hypertensive effects.

Furthermore, GLP-1 has also been shown to decrease renal ROS production and inflammation both in *vitro* and *in vivo* by stimulating glomerular GLP-1Rs and contrasting the increase of oxidative stress induced by ANG-2 [116, 117]. In cultured mesangial cells, GLP-1 prevented cell damage by blocking ANG-2-induced superoxide formation, activation of NF-kB, and up-regulation of intercellular adhesion molecule-1 (ICAM-1) and plasminogen activator inhibitor-1: this effect was PKA-mediated [117]. Similarly, GLP-1R stimulation inhibited ANG-2 signaling via PKA-mediated cRaf phosphorylation in glomerular endothelium cells [116]. The pleiotropic properties of incretin-based therapy also include anti-inflammatory effects. In cultured mesangial cells, GLP-1 suppressed monocyte chemoattractant protein-1 (MCP-1) expression by directly stimulating GLP-1R, possibly exerting an anti-inflammatory action [118]. Furthermore, alogliptin has been reported to reduce the Toll-like receptor-4-mediated up-regulation of pro-inflammatory cytokines in mononuclear cells [68].

In summary, long-term GLP-1 treatment may preserve GFR and protect the kidney.

Based on the above background, gliptins may exert natriuretic and diuretic effects as well [112, 119]. In accordance with this, Girardi and co-workers have demonstrated a physical interplay between DPP-4 and the NHE3 exchanger in the brush-border epithelium of the proximal renal tubule, suggesting a functional relationship between them [119-121]. This supports the involvement of DPP-4 enzyme in the NHE3-mediated reabsorption of sodium,

bicarbonate and water. DPP-4 inhibition might enhance natriuresis and diuresis in two ways: 1) by promoting down-regulation of NHE3 activity associated with GLP-1R activation and 2) by directly impairing NHE3 function due to the inhibition of DPP-4. The latter pathway is supported by *in vitro* as well as *in vivo* studies by Girardi et al. [119, 120] clearly demonstrating a correlation between DPP-4 inhibition and decreased NHE3 function. Specifically, DPP-4 inhibition has been reported to decrease NHE3 function in a cultured opossum kidney proximal tubular cell line [120] and in normotensive wild-type Wistar rats [119]. In the latter study, DPP-4 inhibition resulted in a diuretic and natriuretic effect, which was associated with the redistribution of NHE3 and a small fraction of DPP-4 from the apical microvillar membranes to the intermicrovillar microdomain of the brush border. In opossum kidney proximal cells, suppression of NHE3 activity by DPP-4is was not antagonized by a PKA inhibitor [120]. This pre-clinical evidence suggests that the natriuretic and anti-hypertensive effects of gliptins may rely on mechanisms other than renal GLP-1 signaling. However, the inhibition of NHE3 function by exendin-4 (a GLP-1R agonist) [122] supports the first hypothesized pathway, which is the enhancement of GLP-1 physiological action on its own receptors (related to NHE3) through the reduction of GLP-1 degradation. Nevertheless, the possible co-existence of both pathways cannot be ruled-out. Overall, these mechanisms further clarify the aforementioned studies showing the sitagliptin-mediated blood pressure attenuation in spontaneously hypertensive rats (SHRs) and hypertensive diabetic patients [75, 78].

In line with the above results by Girardi and colleagues [120], Rieg et al. [108] have demonstrated that alogliptin induced natriuretic and diuretic effects in non-diabetic mice independently of GLP-1R or changes in NHE3. Accordingly, in contrast to exendin-4, the alogliptin-induced diuresis and natriuresis were preserved in GLP-1R knockout mice. On the other hand, in contrast to exendin-4, the GLP-1R-independent natriuretic effect of alogliptin

14

was abolished in a mouse model of obese type 2 diabetes, where the GLP-1R-mediated natriuretic mechanisms were clearly kept. Furthermore, DPP-4 inhibition did not increase GFR in healthy rats, while both GLP-1 and exendin-4 markedly increased creatinine clearance [112]. These findings indicate that, under physiological conditions, the mechanisms mediating the diuretic and natriuretic actions of DPP-4is diverge from both GLP-1 and GLP-1RAs.

In this regard, it should be considered that multiple peptide substrates other than GLP-1 are likely cleaved by DPP-4 [24, 28], thus suggesting that DPP-4 inhibition may affect the kidney physiology by other, non-incretin mediated pathways. For example, DPP-4 may target ANP, brain-derived natriuretic peptide (BNP), neuropeptide Y (NPY), peptide YY (PYY), and stromal-derived factor (SDF)-1α [24]. Similar to ANP, BNP is known for its natriuretic and vasorelaxant effects. NPY promotes vasoconstriction and up-regulation of sympathetic nerve activity whereas PYY mediates vasoconstriction only. SDF-1α plays a crucial role in the protection of ischemically-injured tissues as well as in angiogenesis. DDP-4is may therefore participate in the modulation of natriuresis, blood pressure, vascular function, and tissue repair by augmenting endogenous levels of these peptides [28, 100].

The inhibition of NPY cleavage may also contribute to the effect of gliptins on blood pressure [123]: NPY is an agonist of Y1 receptor mediating peripheral vasoconstriction. Interestingly, blood pressure in adult SHRs was not affected by single dose administration of a specific DPP-4i whereas blood pressure was significantly increased after DPP-4 inhibition in SHRs pre-treated with captopril. This effect was prevented by the administration of a selective Y1 receptor antagonist. On the other hand, the inhibition of DPP-4 did not affect arterial blood pressure when animals were pre-treated with a sympathetic nervous system blocker. Therefore, DPP-4 inhibition increased arterial blood pressure via Y1 receptors when elevated blood pressure had been previously reduced with anti-hypertensive drugs, provided

that the sympathetic nervous system was functional. These results suggest the need to monitor the use of gliptins in hypertensive patients treated with anti-hypertensive drugs such as angiotensin converting enzyme (ACE) inhibitors [123].

Of note, DPP-4is may potentiate the ANG-2-mediated renal vasoconstriction only in SHRs [124]: this effect is mediated by the NPY/Y1 receptor pathway that promotes vasoconstriction only in these animals but not in wild-type rats [125].

Overall, the above reported preclinical evidence suggests that DDP-4is may offer renoprotective (and cardioprotective) effects in the context of hypertension and other disorders of sodium retention via both incretin-dependent and independent mechanisms. Furthermore, it is likely that long-term DDP-4 inhibition may potentially have clinical benefits in patients with diabetic chronic kidney disease (CKD), such as DN, as well as in patients with non-diabetic CKD and acute kidney injury (AKI). Accordingly, DPP-4 expression has been reported to be up-regulated in cultured human glomerular epithelial cells during inflammation [126] and in a rat model of type 2 diabetes mellitus (T2DM) [127]. More importantly, increased DPP-4 renal activity is considered as a biomarker for human glomerular diseases [128, 129].

5. Effects of DPP-4 Inhibitors on Kidney function: pathophysiological settings

5.1. Potential benefits of DPP-4 inhibition in Diabetic Kidney Disease (DKD)

The above preclinical and clinical evidence of gliptin-related renoprotective actions beyond glycemic control might account for the potential ability of DPP-4 inhibition to improve the pathophysiological processes leading to DKD. Although hyperglycemia, increased intra-glomerular pressure, and hyperfiltration are key players in the pathogenesis of DN [101], accruing evidence indicates that alternative mechanisms, including the enhanced production of inflammatory cytokines and ROS, advanced glycation end-products (AGEs),

and the up-regulation of the polyol and the protein kinase C pathways, may offer a significant contribution [130]. Genetic and epidemiologic studies also demonstrated that the immune-related gene B7-1 is critically involved in podocyte injury in type 2 DN [131]. Interestingly, the increased activation of extracellular ATP signaling has been recently reported to play a crucial role in increasing kidney damage and inflammation in DKD [132]. Moreover, Krolewski and colleagues have reported that serum concentrations of uric acid, tumor necrosis factor receptor-1 (TNFR-1) and TNFR-2 strongly contributed in a similar way to renal decline in both normoalbuminuric and microalbuminuric type 1 diabetes patients. Conversely, a potential role for a number of circulating adhesion molecules and chemokines (VCAM, ICAM, IL-6, IL-8, IP-10, and MCP-1) in the etiology of renal decline was excluded in the same study group. Such a congruence supports that early progressive renal decline can be considered the primary clinical disorder of DN leading to impaired kidney function and eventually to ESRD in type 1 diabetes [133, 134]. A positive association between urinary inflammatory markers (IL-6, IL-8, MCP-1) and renal decline was previously demonstrated in microalbuminuric type 1 diabetics [135].

Several observations suggest that the incretin system is crucially involved in the pathophysiology of DN [26, 126, 127, 136-138]. In particular, DDP-4 expression and activity are up-regulated in the kidney of rats treated with a high-fat diet and streptozotocin (STZ) [127]. In contrast, DPP-4 deficiency makes rats more resistant to STZ-induced type 1 diabetes [136]. DPP-4 up-regulation has been also shown in human glomerular epithelial cells during inflammation [126], which frequently contributes to glomerulosclerosis in DN [28]. Overall, these findings suggest a role for DPP-4 in the development of both T2DM and DN. This concept seems to be supported by a positive correlation between DPP-4 activity and HbA1c levels [139] (and thus hyperglycemia [137]) in type 2 diabetic patients. Therefore, DPP-4is might be clinically useful for retarding the progression of DN.

Interestingly, hyperglycemia decreased the expression of renal GLP-1Rs in STZ-induced diabetic rats whereas DPP-4is up-regulated their expression [138]. In this light, one might speculate that renal benefits of DPP-4is in DN are mediated by renal GLP-1Rs and also linked to an improvement of hyperglycemia.

Moreover, the urinary level of microvesicle-associated DPP-4 is significantly higher in type 2 diabetic subjects compared with non-diabetic healthy controls, and is positively correlated with the worsening of albuminuria in diabetic patients [26]. Of note, since albuminuria generally predicts the progression of renal disease, especially in DN [101], urinary microvesicle-bound DPP-4 could be exploited as a specific biomarker for the onset of DKD and for staging its severity [26]. Accordingly, an increasing body of evidence indicates that extracellular vesicles (EVs), mainly composed by exosomes and microvesicles, play a relevant role in the kidney pathophysiology by mediating cell-to-cell communication, transferring their content (proteins, lipids and nucleic acids), and activating signaling pathways in target cells. In particular, most of renal cells along the nephron and the urogenital tract have been shown to actively secrete urinary EVs in order to communicate with downstream urinary tract cells, thereby affecting the function of recipient cells. EV-mediated renal communication appears to be a physiological system of cell signaling essential for kidney homeostasis. It involves several roles of EVs, including elimination of cellular waste, proximal-to-distal signaling, developmental roles, control of ion transport, regulation of inflammation and immune response. In parallel, recent findings also support the crucial involvement of these microparticles in renal regenerative processes and kidney diseases, such as cancer, inflammatory and genetic diseases, glomerular and tubular damage, and other pathologies. Specifically, EVs have been involved in the pathogenesis of sepsis and the related AKI. They were also implicated in renal failure associated with hemolytic uremic syndrome induced by infection of enterohemorrhagic Escherichia Coli. In addition, EVs

released by nephron cells can transfer pro-inflammatory or profibrotic signals from tubular epithelial and interstitial cells, mediating harmful pathways leading to renal fibrosis. Taken together, the above evidence suggests that EVs mediate opposing renal actions as a consequence of their cellular origin and their target cell. On the other hand, EVs derived from progenitor and stem cells showed protective and regenerative properties in renal pathological processes, by modulating fibrosis, tubular and glomerular damage, and angiogenesis [140-144]. Interestingly, Jiang and colleagues have recently suggested that EVs secreted by human urine-derived stem cells may prevent renal injury in a rat model of streptozotocin-induced diabetes by promoting vascular regeneration and preventing podocyte apoptosis [145]. All these pre-clinical findings open, therefore, the perspective to therapeutic application of EVs in nephrology.

Moreover, any variation in number, origin or content of EVs isolated from urine may reflect an alteration in the pathophysiological state of the kidneys [146]. Hence, EVs secreted by renal cells conveying in urine represent a great source of information about the kidney state of health as well as a promising non-invasive diagnostic tool for renal disease. Indeed, urinary EVs can be easily isolated from patients providing a suitable resource for biomarkers discovery. This could allow to improve diagnosis, prognosis, and clinical monitoring of renal diseases [140]. Consistent with above findings by Sun and co-workers [26], the number of EVs is elevated in DN [147]. Furthermore, Delic et al. [148] suggested an association between micro-RNA (miRNA) alteration in urinary EVs and early renal impairment in T2DM patients.

Other experimental studies in animal models of both type 1 and type 2 DN have demonstrated renoprotective effects of DPP-4is, such as reduction in urinary albumin excretion and in proteinuria and improvement in vascular, glomerular, tubular and interstitial histopathology. These protective effects could be partly explained by the reduction of

oxidative stress damage to DNA, inflammation, apoptosis, and lipid peroxidation [138, 153, 154]. In particular, linagliptin significantly decreased albuminuria when combined with an angiotensin-2 receptor blocker in STZ-induced diabetic endothelial nitric oxide synthase knockout mice. The reduction in albuminuria associated with linagliptin may reflect the ability of DPP-4 inhibition to attenuate podocyte injury which anticipates the development of glomerulosclerosis leading to proteinuria [153, 155]. Moreover, these results suggest that incretin-based therapy might exert a complementary effect with the RAS blockade in DN treatment. Vildagliptin treatment reduced albuminuria and histological damage while improving GFR in STZ-induced diabetic rats. A significant attenuation of DNA oxidation and apoptosis accounted for these findings [138]. Similar protective effects of DPP-4is (sitagliptin) were also observed in Zucker diabetic fatty rats, a model of type 2 diabetes [154]. A few clinical studies confirm the above pre-clinical evidence about the beneficial effects of DPP-4 inhibition [13, 15, 156].

Nevertheless, whether such benefits are fully independent from the improvement of glycemic control still remains an open question.

5.2. Potential benefits of DPP-4 inhibition in Non-Diabetic Chronic Kidney Disease (CKD)

Experimental studies in models of non-diabetic CKD support the possibility that DDP-4 inhibition may exert direct renoprotective effects also in other renal diseases. Sitagliptin treatment was shown to attenuate kidney injury, renal dysfunction and structural damage in non-diabetic rats with hypertensive nephropathy [157] or subtotal nephrectomy [158]. Specifically, renoprotection in the hypertensive nephropathy rat model was mediated by the increase in serum GLP-1 levels and the up-regulation of GLP-1Rs which resulted in decreased lipid peroxidation and increased antioxidant defense mechanisms. This observation, which is in line with experimental findings in diabetic rats [138], suggests that

DKD and non-diabetic CKD could share some of the renoprotective pathways mediated by DPP-4is.

In the subtotal nephrectomy model of renal damage, the improvement in kidney function and structural damage was associated with anti-apoptotic and anti-inflammatory effects and with an increase in total anti-oxidants [158]. However, in contrast with the hypertensive nephropathy rat model, linagliptin attenuated oxidative stress without affecting blood pressure levels in rats with renovascular hypertension [159].

Interestingly, DPP-4 might also play a pivotal role in the pathogenesis of immune complex-mediated glomerulonephritis [28, 160]. In fact, a monoclonal antibody targeting DPP-4 completely suppressed proteinuria and mesangial proliferation in a rat strain with experimental nephritis, whereas these protective actions were not observed in another rat model with a deletion of the DPP-4 gene. In particular, the protective effect of the anti-DPP-4 antibody was attributed to the suppression of the complement cascade, as confirmed by *in vitro* analysis [160]. These conclusions suggest that DPP-4 targeting may exert a protective role against complement-dependent tissue injury and, therefore, might be clinically useful in the treatment of immune-mediated glomerulopathies.

5.3. Potential benefits of DPP-4 inhibition in Acute Kidney Injury (AKI)

The potential benefits of DPP-4is in the setting of AKI are supported by some preclinical studies showing the effects of these agents in ischemic AKI [161, 162]. Consistently, DPP-4is exhibited protective actions in experimental models of ischemia-reperfusion injury in the heart and lung [163-166].

Particularly, administration of sitagliptin to streptozotocin-nicotinamide-induced diabetic rats prior to induction of ischemic renal injury led to a significant decrease in serum creatinine, blood urea nitrogen and markers of tissue injury [161]. In the same animals, the

drug also induced a significant increase in anti-oxidant enzymes (i.e. glutathione, glutathione peroxidase, superoxide dismutase, and catalase) and a decrease in DNA fragmentation and apoptosis [161, 167]. Interestingly, such renoprotective effects of sitagliptin were associated with a reduction in blood glucose to levels observed in non-diabetic control rats, suggesting a possible close link between protective effects of DPP-4 inhibition and improved glycemic control. In another model of ischemia-reperfusion injury, pre-treatment of non-diabetic rats with vildagliptin similarly improved serum creatinine levels and reduced tubular necrosis, apoptosis, lipid peroxidation and the expression of pro-inflammatory markers [162]. Post-treatment with sitagliptin conveyed similar benefits than pre-administration in terms of kidney recovery after acute ischemia-reperfusion injury [168]: renal protection was associated with anti-oxidant and anti-inflammatory effects which were probably mediated by the up-regulation of GLP-1 and GLP-1Rs [169].

The relevance of GLP-1 in attenuating renal damage after ischemic injury was recently shown in a study by Yang et al. [170] reporting that pre-treatment with exendin-4, a GLP-1RA, significantly protected against ischemia-reperfusion injury in rats through GLP-1R activation. This resulted in up-regulation of the protective gene heme oxygenase-1 (HO-1), an observation consistent with the anti-oxidant actions exhibited by DPP-4is in rat models of renal ischemia-reperfusion injury [161, 162, 168]. In addition, GLP-1 was shown to inhibit ANG-2-induced oxidative stress [117]. Finally, GLP-1R activation associated with DPP-4 inhibition might also reduce the severity of renal ischemic insult via down-regulation of NHE3, thereby limiting energy consumption in the proximal tubule and protecting the kidney [171, 172]. As alluded to before, SDF-1α is another important DPP-4 substrate potentially mediating the protective effects of DPP-4is in AKI induced by ischemic injury. This hypothesis is supported by the up-regulation of mRNA expression of both SDF-1α and its receptor, C-X-C chemokine receptor type 4 (CXCR4), found in the kidney after such

experimentally-induced damage [173]. Specifically, the SDF-1α/CXCR4 axis has been shown to provide functional and morphological protection of ischemically-injured kidney [174]. Therefore, the increase in SDF-1α levels by DPP-4is might represent another mechanism for their renoprotective effects. On the other hand, DPP-4is might also contribute to the pathogenesis of renal injury after ischemia-reperfusion by inhibiting the cleavage of meprin-β, a member of a metalloproteinase family that is highly expressed in mouse kidney proximal tubules: the redistribution of meprin proteases in response to ischemia-reperfusion was proposed to cause damage to kidney proteins eventually resulting in cellular injury and inflammation [175].

The protective effects of DPP-4is were also observed in an AKI model of cisplatin toxicity. In such a model, alogliptin reduced renal injury by attenuating apoptosis [176]. Interestingly, alogliptin increased serum GLP-1 levels, without affecting the levels of other DPP-4 substrates, such as SDF-1α. In addition, the renoprotective effects of alogliptin were prevented by the suppression of renal GLP-1R expression *in vivo* by small interfering RNAs [176]. These findings corroborate the hypothesis that benefits of DPP-4is in AKI mostly rely on the protective capacity of endogenous GLP-1.

In light of such promising preclinical data, clinical studies are eagerly awaited in order to test a possible applicability of these agents for preventing AKI in patients at high risk of this complication.

6. Clinical evidence of renal benefits or detriments of DPP-4 inhibitors from randomized controlled clinical trials

The clinical impact of DPP-4is on renal outcomes represents a timely and controversial issue, as findings from various clinical studies are somewhat conflicting. In order to catch the most relevant evidence on this topic, we approached the existing literature

by using predefined search criteria (see below) in order to find the most relevant randomized controlled trials (RCTs) and meta-analyses dealing with the effects of these agents on renal outcomes in individuals with evidence of renal impairment. Main characteristics and findings from the studies retrieved (summarized in **Table 2**) were analyzed and discussed in a pragmatic way.

6.1. Literature search strategy

Ovid-MEDLINE, PubMed and CENTRAL databases were searched for English-language articles without time restriction up to April 30, 2017. References from relevant studies were screened for supplementary articles. The search was designed and performed by combining the following medical subject heading (MeSH) terms: "renal disease" or "chronic kidney disease" or "renal failure" or "albuminuria" or "serum creatinine" or "acute kidney injury" with the terms "DPP-4 inhibitor", "gliptin" and each of the generic names "sitagliptin", "vildagliptin", "saxagliptin", "alogliptin", "linagliptin". We included in the analysis any randomized controlled trial (RCT), quasi-RCT (trials in which allocation to treatment was made by alternation, use of alternate medical records, date of birth or other expected methods), prospective or retrospective studies including diabetic patients with any degree of renal function impairment (CKD stage 1 to 5, not including end-stage kidney disease [ESKD] patients on dialysis) treated with DPP-4is alone or in combination with other hypoglycemic agents versus placebo or no treatment or lifestyle interventions or any other hypoglycemic agents. The presence of CKD was defined according to the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF KDOQI) guidelines by a reduced glomerular filtration rate (GFR) < 90 mL/min/1.73 m^2 or by the persistence of urinary abnormalities such as albuminuria, proteinuria or hematuria in subjects with GFR ≥ 90 mL/min/1.73 m^2. GFR was estimated using Cockcroft–Gault formula [177] or MDRD equation [178]. DPP-4i administration was considered independently from dosage, mode or

duration. Renal outcomes considered for analysis were: 1) CKD progression or changes in GFR or in creatinine; 2) doubling of serum creatinine; 3) changes in urine albumin/creatinine ratio (UACR); 3) need for renal replacement therapy; 4) renal and urinary disorders; 5) acute kidney injury (AKI) onset.

6.2. Discussion of clinical evidence

The analysis of published clinical evidence aimed at evaluating effects of DPP-4is, in particular their benefits or detrimental aspects in patients affected by CKD and results on specific renal outcomes. We focused our attention on glycemic control, renal safety and adverse events, and, finally, on a specific renal outcome such as the proteinuria. We performed a narrative review, a scientific article design that is now extensively being used in current literature.

Despite the inclusion of clinical trials focusing on renal effects of DPP-4is, our review shows certain limitations. First of all, enrolling criteria in single studies are not homogeneous, then populations are often non-comparable because trials are not specifically designed to focus on renal outcome. Furthermore, the follow-up period is too short to assess a hard renal outcome. For these reasons, we prefer to define the present paper as a narrative review.

6.2.1. DPP-4 inhibitors and glycemic control

Almost all the studies included in our analysis considered the glycated hemoglobin (HbA1c %) decline as first end-point. Secondary efficacy outcomes also included the change in fasting plasma glucose (FPG) level. Unfortunately, this point may represent a considerable limit in the assessment of the antidiabetic agent efficacy in CKD populations. Indeed, in a renal failure setting, especially in the late stages and in renal replacement therapy, a huge

number of confounding factors may affect the legitimacy of the HbA1c dosage. Generally, when compared to placebo, DPP-4is have been shown to reduce HbA1c % in all the included studies. However, only two trials compared DPP-4is with sulfonylureas. In particular, the study of Chan et al. [179] analyzed the difference between sitagliptin and placebo or glipizide, resulting in favor of DPP-4is. On the other hand, Dobs et al. [190] valued the efficacy and safety of sitagliptin as add-on therapy to metformin and rosiglitazone, concluding with an improved glycemic control compared with only administration of metformin and rosiglitazone. The recent meta-analysis performed by Howse et al. [192] supports these data; the authors carried out a pooled analysis of 11 RCTs demonstrating that HbA1c level significantly decreased from baseline in the incretin-based group versus placebo group, while the change in HbA1c level was not statistically significant when DPP-4is were compared with sulfonylureas. In addition, different papers reported the difference in HbA1c % stratified for kidney impairment. Kothny et al. [180] documented a slightly different decrease in HbA1c after one year of treatment with vildagliptin (50 mg/day) in patients with moderate CKD compared to subjects with severe renal impairment. Barnett et al. [191] found similar results, in an elderly population. On the contrary, in the pooled analysis of 3 RCTs carried out by Groop et al. [156], no inter-group difference emerged in terms of glycemic control efficacy among normal, mild and moderate renal impairment (p = 0.74). No differences were also reported by Nowicki et al. [184] and Lukashevic et al. [183].

6.2.2. Renal safety of DPP-4 inhibitors

While the US FDA in 2008 established as a rule that new antidiabetic drugs should demonstrate their cardiovascular safety prior to drug approval, the renal safety is not yet required, even though renal failure is a major consequence of diabetes. Summarizing, in clinical studies, all DPP-4is were well tolerated in patients with CKD, with no dose adjustment needed in patients with mild CKD. However, dose adjustments are needed in

patients with moderate or severe renal impairment for all DPP-4is, except for linagliptin because this agent is primarily cleared by non-renal mechanisms [42].

Almost all included RCTs evaluated the safety profile of DPP-4is, showing them to be without risk and well tolerated also in patients with moderate and severe kidney diseases. McGill et al. [181], using linagliptin that does not require dose adjustment, observed, after one year, only a tiny eGFR decrease in both experimental and placebo groups. No renal failure related to linagliptin was reported. Similar results were found in the DelPrato [186], Owens [188], Taskinen [189] and Barnett trials, with no clinically significant changes in renal function detected over the study period. Exclusively for linagliptin, Cooper et al. [193] concluded a pooled analysis of 13-RCTs including 5,000 diabetics. The analysis ascertained that linagliptin treatment was not associated with an increase in kidney injury. Otherwise, linagliptin administration significantly decreased the risk and slowed down the progression of kidney disease by 16% compared with placebo (HR, 0.84; 95% CI, 0.72-0.97; P = 0.02). In studies carried out by saxagliptin administration (SAVOR-TIMI [13] and Nowicki [184]), the overall outcome was that this agent was well tolerated also in moderate and severe kidney disease, even though the dosage was always adjusted for GFR < 50 ml/min at 2.5 mg once daily. Notably, in the SAVOR-TIMI trial [13] the renal outcome was a composite of doubling of creatinine level, initiation of dialysis, renal transplantation or creatinine > 6.0 mg/dl. The incidence of the renal end-point was similar in the saxagliptin (2.2%) and placebo groups (2.0%). On the other hand, in the trial performed by the Nowicki group [184], at the end of the study, patients had not statistically significant worsening of renal parameters but 4 patients belonging equally to saxagliptin and control groups shifted to severe renal impairment. Conversely, 10 patients had a better renal function after 12 weeks. For vildagliptin, Lukashevic et al. [183] and Kothny et al. [180] already demonstrated a safe profile in moderate and severe CKD diabetic patients testing this drug at a 50-mg dosage

compared with placebo. During the 24-week observation period, no meaningful changes in renal function from baseline were observed in groups arranged for renal impairment. Accordingly, in the GALIANT study [185], vildagliptin was administered at the dose of 100 mg once daily and was retrospectively compared with a thiazolidinedione as an add-on therapy to metformin in normal and mild nephropathic diabetic subjects. As shown in **Table 2**, Blood Urea Nitrogen > 9.99 had been reported in a slight, but not statistically significant, percentage of patients in the control group. Alogliptin has been tested only by White et al. [182], in the EXAMINE trial which selected a specific diabetic population with history of acute coronary syndromes, including acute myocardial infarction and unstable angina. A dose of 12.5 mg of alogliptin was administered in patients with moderately impaired renal function (eGFR $\geq$ 30 and < 60 mL/min) whereas a dose of 6.25 mg was given to subjects with severely impaired renal function or ESRD (eGFR < 30 mL/min). Incidences of hypoglycemia, cancer, pancreatitis, and initiation of dialysis were similar with alogliptin and placebo. Passing on sitagliptin in all trials the dosage has been modified based on eGFR (50 or 25 mg according to eGFR). Chan et al. [179] in 91 T2DM subjects with moderate or severe renal insufficiency, also including patients with ESRD and/or on dialysis, compared sitagliptin with placebo/glipizide (5-10 mg/day). In patients with moderate renal insufficiency, a small mean increase of serum creatinine was observed after 12 weeks followed by a little decrease after 54 weeks. Moreover, sitagliptin has been evaluated in ESRD by Dobs et al. [190], who enrolled patients with on renal replacement therapy, compared with glipizide 5-10 mg/day. Similarly, renal outcomes or adverse events were not reported.

6.2.3. Adverse events

Overall, DPP-4is did not significantly increase the risk of hypoglycemia compared with placebo. Similar results were found when the active comparator was a sulfonylurea. As for

glycemic control, few studies differentiated adverse events incidence for CKD stages. Among them, Kothny et al. [180] showed that a similar proportion of patients experienced an adverse event (84 vs. 85%), and a serious adverse event (21 vs. 19%), with vildagliptin and placebo, respectively in both severe and moderate CKD. Lukashevic et al. [183] and the GALIANT trials [185] confirmed these findings for vildagliptin. In the Groop et al. [156] analysis using linagliptin, the incidence of hypoglycemia, the overall adverse event and serious adverse event rates were comparable to placebo in all renal failure categories. Of note, Cooper et al. [193] specifically focused on renal adverse events, also reporting the incidence of additional adverse events of special interest for CKD individuals such as hyperkalemia and hypotension. They did not find any difference between linagliptin and control group. Importantly, the question of cardiovascular safety of DPP-4is in the renal setting remains still unclear. Indeed, findings regarding all-cause mortality and cardiovascular events are limited, due to the lack of events, short follow-up of included studies, and lack of formal adjudication of cardiovascular events within all studies. The SAVOR-TIMI [13] study alone used a composite outcome of cardiovascular death, myocardial infarction, or ischemic stroke as primary endpoint in the assessment of saxagliptin cardiovascular safety. Notably, the trial did not show any difference in cardiovascular events, but disclosed a major incidence of hospitalization for cardiovascular failure in the experimental arm. Therefore, results were not specifically stratified for kidney disease stages.

6.2.4. Effect on the proteinuria

Microalbuminuria and proteinuria are the primary intervention targets in the prevention of CKD and ESRD in diabetic patients. Moreover, albuminuria is a key predictor of cardiovascular complications both in diabetic and non-diabetic CKD populations. According to guidelines, the first-step approach is the administration of RAS inhibitors acting drugs. However, the demonstration of a synergic antiproteinuric effect carried out by an antidiabetic

drug may be of special interest [8]. The underlying mechanisms have been already described and are mostly related to the oxidative stress and inflammation reduction and improvement of endothelial dysfunction [9]. Evidence exists not only in DKD, but also in models of non-diabetic CKD. In clinical settings, the first observation of a positive effect of DPP-4is on albuminuria has been made in a small trial by Hattori et al. [194] in 37 non-CKD diabetic patients in which sitagliptin administered at a 50-mg dose was able to reduce albumin-to-creatinine ratio (ACR) compared to placebo [194]. Similarly, Mori et al. [195] obtained a noteworthy albuminuria reduction in T2DM patients after six months of treatment with sitagliptin compared with other antidiabetic agents [195]. In the SAVOR-TIMI-53 trial [13], even in normoalbuminuric patients, the treatment with saxagliptin improved ACR, without any adverse effect on kidney function. Indeed, the favorable action of saxagliptin on albuminuria was not related to the improvement of glycemia. Anyway, despite lowering albumin excretion, no difference was found in ESRD incidence or in the progression of renal injury between saxagliptin and placebo. More specifically, Kawasaki et al. [196] in 2015 investigated the action of sitagliptin on albuminuria in 247 T2DM patients in an observational trial. They found that the ACR reduction was associated with the antihypertensive effect of sitagliptin. Therefore, authors concluded that sitagliptin exerts an antiproteinuric effect through impacting on both blood pressure and eGFR [196]. On the other hand, Fujita et al. [15] confirmed the observations made in preclinical models in a crossover study. In their small cohort, DPP-4is treatment lessened urinary levels of albumin and abated oxidative stress markers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), increasing urinary cAMP levels. On top of that about antiproteinuric power, more evidences exist for linagliptin. In 2013, Groop et al. [156] published a comprehensive analysis of RCTs involving 217 subjects with albuminuria (UACR: 30–3000mg/g creatinine) receiving stable treatment with RAS inhibitors. In this 24-week study linagliptin decreased ACR by 32%

versus 6% in the placebo group. Afterwards, the metanalysis from Cooper et al. [193] demonstrated that linagliptin (5 mg/daily) reduced the risk of new onset of moderate elevation of albuminuria by 18%, promoting renal protection. Lastly, a more recent observational cohort study was conducted by Kim et al.. Authors retrospectively collected albuminuria and kidney function data from patients on DPP-4is therapy in their center with a total of 414 patients enrolled and with a long term follow up of four years. In this analysis, DPP-4is appeared more beneficial in macroalbuminuric diabetic patients ameliorating eGFR reduction over time [197]. From all these pieces of evidence, it is suggested that emerging data should be systematically used to plan new RCTs directly focusing on a possible renal class-effect of DPP-4is. Two ongoing trials, the MARLINA-T2D™ (Efficacy, Safety & Modification of Albuminuria in Type 2 Diabetes Subjects with Renal Disease with LINAgliptin) trial (**ClinicalTrials.gov Identifier: NCT01792518**) and the CARMELINA® (CArdiovascular Safety & Renal Microvascular outcomE study with LINAgliptin) trial (**NCT01897532**) have also started enrolling patients [198].

7. Conclusions.

DPP-4is are among the most used and effective oral antidiabetic agents. They have many advantages, including high glucose-lowering potency, low risk of hypoglycemia, no association with weight gain, and tolerability by chronic renal failure patients. However, their efficacy for preventing diabetic complications, especially DN, is not well established.

In summary, diabetes management is complex, multi-dimensional and potentially expensive in patients with T2DM and renal insufficiency. Our literature review suggests that DPP-4is have the potential to improve and simplify glycemic control in this setting without exposing patients to hypoglycemia or other important adverse events. The renoprotective

potential of DPP-4is remains unproven, but it is a subject of ongoing investigations in clinical trials. However, findings from the reviewed studies indicate that the glucose-lowering efficacy of DPP-4is may provide additional renal benefits in patients with kidney failure, since improved glycemic control has been shown to reduce the risk of DN and ESRD. More importantly, beyond glycemic control, accruing evidence (especially for linagliptin) has demonstrated that this drug class may also reduce albuminuria, another risk factor for DN, especially in macroalbuminuric diabetic patients. Such an improvement in albuminuria suggests that DPP-4is may potentially provide renal benefits beyond their glucose-lowering effects. Therefore, early detection and treatment of DN risk factors, such as hyperglycemia and albuminuria, with DPP-4is may possibly prevent this clinical condition or slow its progression. Notwithstanding, the aforementioned poor methodological quality of the studies included in this review prevents definite conclusions to be drawn, also hampering the identification of the specific subpopulation of T2DM and CKD patients who would benefit most from DDP-4 inhibitor therapy. Future studies with longer follow-up, comparable populations, and specifically designed on hard renal outcomes are needed for ascertaining whether DPP-4is may offer a promising therapeutic option for retarding CKD progression in T2DM patients as well as for establishing the optimal target population.

Given the high financial burden and reduced quality of life of patients with T2DM and renal insufficiency, further economic and quality of life analyses are also warranted.

Conflict of interest

The Authors declare no conflict of interest related to the present work

Chemical compounds studied in this article

Glucagon-like peptide-1 (PubChem CID: 16135499); Sitagliptin (PubChem CID: 4369359);

Vildagliptin (PubChem CID: 6918537); Saxagliptin (PubChem CID: 11243969); Linagliptin

(PubChem CID: 10096344); Alogliptin (PubChem CID: 11450633)

References

[1] C.R. Pullinger, I.D. Goldfine, S. Tanyolac, I. Movsesyan, M. Faynboym, V. Durlach, E. Chiefari, D.P. Foti, P.H. Frost, M.J. Malloy, A. Brunetti, J.P. Kane, Evidence that an HMGA1 gene variant associates with type 2 diabetes, body mass index, and high-density lipoprotein cholesterol in a Hispanic-American population, Metab Syndr Relat Disord 12(1) (2014) 25-30.

[2] International Diabetes Federation. Diabetes Atlas 7th ed., 2015.

[3] G.B.D. Mortality, C. Causes of Death, Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015, Lancet 388(10053) (2016) 1459-1544.

[4] V. Usuelli, E. La Rocca, Novel therapeutic approaches for diabetic nephropathy and retinopathy, Pharmacol Res 98 (2015) 39-44.

[5] S.K. Goru, A. Kadakol, A.B. Gaikwad, Hidden targets of ubiquitin proteasome system: To prevent diabetic nephropathy, Pharmacol Res 120 (2017) 170-179.

[6] C. Leporini, R. Piro, F. Ursini, F. Maida, C. Palleria, F. Arturi, M. Pavia, G. De Sarro, E. Russo, Monitoring safety and use of old and new treatment options for type 2 diabetic patients: a two-year (2013-2016) analysis, Expert opinion on drug safety 15(sup2) (2016) 17-34.

[7] V. Lacava, V. Pellicano, C. Ferrajolo, V. Cernaro, L. Visconti, G. Conti, M. Buemi, D. Santoro, Novel avenues for treating diabetic nephropathy: new investigational drugs, Expert opinion on investigational drugs 26(4) (2017) 445-462.

[8] D. Bolignano, A. Pisano, G. Coppolino, The Dark Side of Blocking RAS in Diabetic Patients with Incipient or Manifested Nephropathy, Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association 124(6) (2016) 350-60.

[9] D. Bolignano, V. Cernaro, G. Gembillo, R. Baggetta, M. Buemi, G. D'Arrigo, Antioxidant agents for delaying diabetic kidney disease progression: A systematic review and meta-analysis, PloS one 12(6) (2017) e0178699.

[10] C. Leporini, A. Pisano, E. Russo, G. D'Arrigo, G. de Sarro, G. Coppolino, D. Bolignano, Effect of pentoxifylline on renal outcomes in chronic kidney disease patients: A systematic review and meta-analysis, Pharmacol Res 107 (2016) 315-32.

[11] T. Karagiannis, P. Paschos, K. Paletas, D.R. Matthews, A. Tsapas, Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis, Bmj 344 (2012) e1369.

[12] M. Monami, I. Iacomelli, N. Marchionni, E. Mannucci, Dipeptydil peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomized clinical trials, Nutrition, metabolism, and cardiovascular diseases : NMCD 20(4) (2010) 224-35.

[13] B.M. Scirica, D.L. Bhatt, E. Braunwald, P.G. Steg, J. Davidson, B. Hirshberg, P. Ohman, R. Frederich, S.D. Wiviott, E.B. Hoffman, M.A. Cavender, J.A. Udell, N.R. Desai, O. Mosenzon, D.K. McGuire, K.K. Ray, L.A. Leiter, I. Raz, S.-T.S. Committee, Investigators, Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus, The New England journal of medicine 369(14) (2013) 1317-26.

[14] H. Zhang, X. Zhang, C. Hu, W. Lu, Exenatide reduces urinary transforming growth factor-beta1 and type IV collagen excretion in patients with type 2 diabetes and microalbuminuria, Kidney & blood pressure research 35(6) (2012) 483-8.

[15] H. Fujita, H. Taniai, H. Murayama, H. Ohshiro, H. Hayashi, S. Sato, N. Kikuchi, T. Komatsu, K. Komatsu, K. Komatsu, T. Narita, Y. Yamada, DPP-4 inhibition with alogliptin on top of angiotensin II type 1 receptor blockade ameliorates albuminuria via up-regulation of SDF-1alpha in type 2 diabetic patients with incipient nephropathy, Endocrine journal 61(2) (2014) 159-66.

[16] S. Imamura, K. Hirai, A. Hirai, The glucagon-like peptide-1 receptor agonist, liraglutide, attenuates the progression of overt diabetic nephropathy in type 2 diabetic patients, Tohoku J Exp Med 231(1) (2013) 57-61.

[17] H. Linnebjerg, P.A. Kothare, S. Park, K. Mace, S. Reddy, M. Mitchell, R. Lins, Effect of renal impairment on the pharmacokinetics of exenatide, Br J Clin Pharmacol 64(3) (2007) 317-27.

[18] B. Gallwitz, Safety and efficacy of linagliptin in type 2 diabetes patients with common renal and cardiovascular risk factors, Therapeutic advances in endocrinology and metabolism 4(3) (2013) 95-105.

[19] A.J. Scheen, Pharmacokinetics of dipeptidylpeptidase-4 inhibitors, Diabetes Obes Metab 12(8) (2010) 648-58.

[20] W.J. Weise, M.S. Sivanandy, C.A. Block, R.J. Comi, Exenatide-associated ischemic renal failure, Diabetes care 32(2) (2009) e22-3.

[21] Y. Kaakeh, S. Kanjee, K. Boone, J. Sutton, Liraglutide-induced acute kidney injury, Pharmacotherapy 32(1) (2012) e7-11.

[22] T.D. Filippatos, M.S. Elisaf, Effects of glucagon-like peptide-1 receptor agonists on renal function, World J Diabetes 4(5) (2013) 190-201.

[23] A.J. Scheen, Cardiovascular effects of gliptins, Nature reviews. Cardiology 10(2) (2013) 73-84.

[24] G. Schernthaner, C.E. Mogensen, G.H. Schernthaner, The effects of GLP-1 analogues, DPP-4 inhibitors and SGLT2 inhibitors on the renal system, Diabetes & vascular disease research 11(5) (2014) 306-23.

[25] A.M. Lambeir, C. Durinx, S. Scharpe, I. De Meester, Dipeptidyl-peptidase IV from bench to bedside: an update on structural properties, functions, and clinical aspects of the enzyme DPP IV, Critical reviews in clinical laboratory sciences 40(3) (2003) 209-94.

[26] A.L. Sun, J.T. Deng, G.J. Guan, S.H. Chen, Y.T. Liu, J. Cheng, Z.W. Li, X.H. Zhuang, F.D. Sun, H.P. Deng, Dipeptidyl peptidase-IV is a potential molecular biomarker in diabetic kidney disease, Diabetes & vascular disease research 9(4) (2012) 301-8.

[27] D.J. Drucker, Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes: preclinical biology and mechanisms of action, Diabetes care 30(6) (2007) 1335-43.

[28] T. Tanaka, Y. Higashijima, T. Wada, M. Nangaku, The potential for renoprotection with incretin-based drugs, Kidney international 86(4) (2014) 701-11.

[29] M.A. Nauck, N. Kleine, C. Orskov, J.J. Holst, B. Willms, W. Creutzfeldt, Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients, Diabetologia 36(8) (1993) 741-4.

[30] T. Vilsboll, F.K. Knop, T. Krarup, A. Johansen, S. Madsbad, S. Larsen, T. Hansen, O. Pedersen, J.J. Holst, The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype, The Journal of clinical endocrinology and metabolism 88(10) (2003) 4897-903.

[31] T. Vilsboll, T. Krarup, C.F. Deacon, S. Madsbad, J.J. Holst, Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients, Diabetes 50(3) (2001) 609-13.

[32] C.F. Deacon, M.A. Nauck, M. Toft-Nielsen, L. Pridal, B. Willms, J.J. Holst, Both subcutaneously and intravenously administered glucagon-like peptide I are rapidly degraded from the NH2-terminus in type II diabetic patients and in healthy subjects, Diabetes 44(9) (1995) 1126-31.

[33] S.C. Liu, Y.K. Tu, M.N. Chien, K.L. Chien, Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis, Diabetes, obesity & metabolism 14(9) (2012) 810-20.

[34] S.A. Amiel, T. Dixon, R. Mann, K. Jameson, Hypoglycaemia in Type 2 diabetes, Diabetic medicine : a journal of the British Diabetic Association 25(3) (2008) 245-54.

[35] L.K. Golightly, C.C. Drayna, M.T. McDermott, Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors, Clin Pharmacokinet 51(8) (2012) 501-14.

[36] S. Retlich, V. Duval, A. Ring, A. Staab, S. Huttner, A. Jungnik, U. Jaehde, K.A. Dugi, U. Graefe-Mody, Pharmacokinetics and pharmacodynamics of single rising intravenous doses (0.5 mg-10 mg) and determination of absolute bioavailability of the dipeptidyl peptidase-4 inhibitor linagliptin (BI 1356) in healthy male subjects, Clin Pharmacokinet 49(12) (2010) 829-40.

[37] C.Y. Wu, L.Z. Benet, Predicting drug disposition via application of BCS: transport/absorption/ elimination interplay and development of a biopharmaceutics drug disposition classification system, Pharm Res 22(1) (2005) 11-23.

[38] T.M. Davis, Dipeptidyl peptidase-4 inhibitors: pharmacokinetics, efficacy, tolerability and safety in renal impairment, Diabetes, obesity & metabolism 16(10) (2014) 891-9.

[39] A. Capuano, L. Sportiello, M.I. Maiorino, F. Rossi, D. Giugliano, K. Esposito, Dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapy--focus on alogliptin, Drug Des Devel Ther 7 (2013) 989-1001.

[40] G.A. Herman, C. Stevens, K. Van Dyck, A. Bergman, B. Yi, M. De Smet, K. Snyder, D. Hilliard, M. Tanen, W. Tanaka, A.Q. Wang, W. Zeng, D. Musson, G. Winchell, M.J. Davies, S. Ramael, K.M. Gottesdiener, J.A. Wagner, Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses, Clinical pharmacology and therapeutics 78(6) (2005) 675-88.

[41] S. Arulmozhiraja, N. Matsuo, E. Ishitsubo, S. Okazaki, H. Shimano, H. Tokiwa, Comparative Binding Analysis of Dipeptidyl Peptidase IV (DPP-4) with Antidiabetic Drugs - An Ab Initio Fragment Molecular Orbital Study, PloS one 11(11) (2016) e0166275.

[42] J. Thrasher, Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies, The American journal of medicine 130(6S) (2017) S4-S17.

[43] R.V. Campos, Y.C. Lee, D.J. Drucker, Divergent tissue-specific and developmental expression of receptors for glucagon and glucagon-like peptide-1 in the mouse, Endocrinology 134(5) (1994) 2156-64.

[44] B.P. Bullock, R.S. Heller, J.F. Habener, Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor, Endocrinology 137(7) (1996) 2968-78.

[45] R.K. Campbell, Clarifying the role of incretin-based therapies in the treatment of type 2 diabetes mellitus, Clinical therapeutics 33(5) (2011) 511-27.

[46] S. Teramoto, N. Miyamoto, K. Yatomi, Y. Tanaka, H. Oishi, H. Arai, N. Hattori, T. Urabe, Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia, J Cereb Blood Flow Metab 31(8) (2011) 1696-705.

[47] C.H. Lee, B. Yan, K.Y. Yoo, J.H. Choi, S.H. Kwon, S. Her, Y. Sohn, I.K. Hwang, J.H. Cho, Y.M. Kim, M.H. Won, Ischemia-induced changes in glucagon-like peptide-1 receptor and neuroprotective effect of its agonist, exendin-4, in experimental transient cerebral ischemia, J Neurosci Res 89(7) (2011) 1103-13.

[48] V. Darsalia, S. Mansouri, H. Ortsater, A. Olverling, N. Nozadze, C. Kappe, K. Iverfeldt, L.M. Tracy, N. Grankvist, A. Sjoholm, C. Patrone, Glucagon-like peptide-1 receptor activation reduces ischaemic brain damage following stroke in Type 2 diabetic rats, Clin Sci (Lond) 122(10) (2012) 473-83.

[49] V. Darsalia, H. Ortsater, A. Olverling, E. Darlof, P. Wolbert, T. Nystrom, T. Klein, A. Sjoholm, C. Patrone, The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride, Diabetes 62(4) (2013) 1289-96.

[50] M.H. Noyan-Ashraf, M.A. Momen, K. Ban, A.M. Sadi, Y.Q. Zhou, A.M. Riazi, L.L. Baggio, R.M. Henkelman, M. Husain, D.J. Drucker, GLP-1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice, Diabetes 58(4) (2009) 975-83.

[51] M. Matsubara, S. Kanemoto, B.G. Leshnower, E.F. Albone, R. Hinmon, T. Plappert, J.H. Gorman, 3rd, R.C. Gorman, Single dose GLP-1-Tf ameliorates myocardial ischemia/reperfusion injury, The Journal of surgical research 165(1) (2011) 38-45.

[52] B.B. Dokken, L.R. La Bonte, G. Davis-Gorman, M.K. Teachey, N. Seaver, P.F. McDonagh, Glucagon-like peptide-1 (GLP-1), immediately prior to reperfusion, decreases neutrophil activation and reduces myocardial infarct size in rodents, Horm Metab Res 43(5) (2011) 300-5.

[53] P.A. Read, F.Z. Khan, D.P. Dutka, Cardioprotection against ischaemia induced by dobutamine stress using glucagon-like peptide-1 in patients with coronary artery disease, Heart 98(5) (2012) 408-13.

[54] T. Gaspari, H. Liu, I. Welungoda, Y. Hu, R.E. Widdop, L.B. Knudsen, R.W. Simpson, A.E. Dear, A GLP-1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE-/- mouse model, Diabetes & vascular disease research 8(2) (2011) 117-24.

[55] L. Ding, J. Zhang, Glucagon-like peptide-1 activates endothelial nitric oxide synthase in human umbilical vein endothelial cells, Acta pharmacologica Sinica 33(1) (2012) 75-81.

[56] W. Chai, Z. Dong, N. Wang, W. Wang, L. Tao, W. Cao, Z. Liu, Glucagon-like peptide 1 recruits microvasculature and increases glucose use in muscle via a nitric oxide-dependent mechanism, Diabetes 61(4) (2012) 888-96.

[57] X. Xiao-Yun, M. Zhao-Hui, C. Ke, H. Hong-Hui, X. Yan-Hong, Glucagon-like peptide-1 improves proliferation and differentiation of endothelial progenitor cells via upregulating VEGF generation, Medical science monitor : international medical journal of experimental and clinical research 17(2) (2011) BR35-41.

[58] L. Han, Y. Yu, X. Sun, B. Wang, Exendin-4 directly improves endothelial dysfunction in isolated aortas from obese rats through the cAMP or AMPK-eNOS pathways, Diabetes Res Clin Pract 97(3) (2012) 453-60.

[59] Y. Zhan, H.L. Sun, H. Chen, H. Zhang, J. Sun, Z. Zhang, D.H. Cai, Glucagon-like peptide-1 (GLP-1) protects vascular endothelial cells against advanced glycation end products (AGEs)-induced apoptosis, Medical science monitor : international medical journal of experimental and clinical research 18(7) (2012) BR286-91.

[60] Y. Seino, D. Yabe, Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: Incretin actions beyond the pancreas, Journal of diabetes investigation 4(2) (2013) 108-30.

[61] M. Nagashima, T. Watanabe, M. Terasaki, M. Tomoyasu, K. Nohtomi, J. Kim-Kaneyama, A. Miyazaki, T. Hirano, Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice, Diabetologia 54(10) (2011) 2649-59.

[62] Y. Nogi, M. Nagashima, M. Terasaki, K. Nohtomi, T. Watanabe, T. Hirano, Glucose-dependent insulinotropic polypeptide prevents the progression of macrophage-driven atherosclerosis in diabetic apolipoprotein E-null mice, PloS one 7(4) (2012) e35683.

[63] J.D. Wu, X.H. Xu, J. Zhu, B. Ding, T.X. Du, G. Gao, X.M. Mao, L. Ye, K.O. Lee, J.H. Ma, Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus, Diabetes Technol Ther 13(2) (2011) 143-8.

[64] S.J. Ha, W. Kim, J.S. Woo, J.B. Kim, S.J. Kim, W.S. Kim, M.K. Kim, X.W. Cheng, K.S. Kim, Preventive effects of exenatide on endothelial dysfunction induced by ischemia-reperfusion injury via KATP channels, Arterioscler Thromb Vasc Biol 32(2) (2012) 474-80.

[65] J. Koska, E.A. Schwartz, M.P. Mullin, D.C. Schwenke, P.D. Reaven, Improvement of postprandial endothelial function after a single dose of exenatide in individuals with impaired glucose tolerance and recent-onset type 2 diabetes, Diabetes care 33(5) (2010) 1028-30.

[66] A. Shiraki, J. Oyama, H. Komoda, M. Asaka, A. Komatsu, M. Sakuma, K. Kodama, Y. Sakamoto, N. Kotooka, T. Hirase, K. Node, The glucagon-like peptide 1 analog liraglutide reduces TNF-alpha-induced oxidative stress and inflammation in endothelial cells, Atherosclerosis 221(2) (2012) 375-82.

[67] Z. Shah, T. Kampfrath, J.A. Deiuliis, J. Zhong, C. Pineda, Z. Ying, X. Xu, B. Lu, S. Moffatt-Bruce, R. Durairaj, Q. Sun, G. Mihai, A. Maiseyeu, S. Rajagopalan, Long-term dipeptidyl-peptidase 4 inhibition reduces atherosclerosis and inflammation via effects on monocyte recruitment and chemotaxis, Circulation 124(21) (2011) 2338-49.

[68] N.N. Ta, C.A. Schuyler, Y. Li, M.F. Lopes-Virella, Y. Huang, DPP-4 (CD26) inhibitor alogliptin inhibits atherosclerosis in diabetic apolipoprotein E-deficient mice, J Cardiovasc Pharmacol 58(2) (2011) 157-66.

[69] M. Terasaki, M. Nagashima, T. Watanabe, K. Nohtomi, Y. Mori, A. Miyazaki, T. Hirano, Effects of PKF275-055, a dipeptidyl peptidase-4 inhibitor, on the development of atherosclerotic lesions in apolipoprotein E-null mice, Metabolism 61(7) (2012) 974-7.

[70] S. Maeda, T. Matsui, S. Yamagishi, Vildagliptin inhibits oxidative stress and vascular damage in streptozotocin-induced diabetic rats, Int J Cardiol 158(1) (2012) 171-3.

[71] A. Makdissi, H. Ghanim, M. Vora, K. Green, S. Abuaysheh, A. Chaudhuri, S. Dhindsa, P. Dandona, Sitagliptin exerts an antinflammatory action, The Journal of clinical endocrinology and metabolism 97(9) (2012) 3333-41.

[72] N. Satoh-Asahara, Y. Sasaki, H. Wada, M. Tochiya, A. Iguchi, R. Nakagawachi, S. Odori, S. Kono, K. Hasegawa, A. Shimatsu, A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients, Metabolism 62(3) (2013) 347-51.

[73] J.B. McGill, Liraglutide: effects beyond glycaemic control in diabetes treatment, Int J Clin Pract Suppl (167) (2010) 28-34.

[74] C. Irace, S. De Luca, E. Shehaj, C. Carallo, A. Loprete, F. Scavelli, A. Gnasso, Exenatide improves endothelial function assessed by flow mediated dilation technique in subjects with type 2 diabetes: results from an observational research, Diabetes & vascular disease research 10(1) (2013) 72-7.

[75] B.P. Pacheco, R.O. Crajoinas, G.K. Couto, A.P. Davel, L.M. Lessa, L.V. Rossoni, A.C. Girardi, Dipeptidyl peptidase IV inhibition attenuates blood pressure rising in young spontaneously hypertensive rats, J Hypertens 29(3) (2011) 520-8.

[76] L. Liu, J. Liu, W.T. Wong, X.Y. Tian, C.W. Lau, Y.X. Wang, G. Xu, Y. Pu, Z. Zhu, A. Xu, K.S. Lam, Z.Y. Chen, C.F. Ng, X. Yao, Y. Huang, Dipeptidyl peptidase 4 inhibitor sitagliptin protects endothelial function in hypertension through a glucagon-like peptide 1-dependent mechanism, Hypertension 60(3) (2012) 833-41.

[77] A. Kubota, H. Maeda, A. Kanamori, K. Matoba, Y. Jin, F. Minagawa, M. Obana, K. Iemitsu, S. Ito, H. Amemiya, M. Kaneshiro, M. Takai, H. Kaneshige, K. Hoshino, M. Ishikawa, N. Minami, T. Takuma, N. Sasai, S. Aoyagi, T. Kawata, A. Mokubo, H. Takeda, S. Honda, H. Machimura, T. Motomiya, M. Waseda, Y. Naka, Y. Tanaka, Y. Terauchi, I. Matsuba, Pleiotropic effects of sitagliptin in the treatment of type 2 diabetes mellitus patients, J Clin Med Res 4(5) (2012) 309-13.

[78] S. Ogawa, M. Ishiki, K. Nako, M. Okamura, M. Senda, T. Mori, S. Ito, Sitagliptin, a dipeptidyl peptidase-4 inhibitor, decreases systolic blood pressure in Japanese hypertensive patients with type 2 diabetes, Tohoku J Exp Med 223(2) (2011) 133-5.

[79] K. Ban, M.H. Noyan-Ashraf, J. Hoefer, S.S. Bolz, D.J. Drucker, M. Husain, Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways, Circulation 117(18) (2008) 2340-50.

[80] L.A. Nikolaidis, S. Mankad, G.G. Sokos, G. Miske, A. Shah, D. Elahi, R.P. Shannon, Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion, Circulation 109(8) (2004) 962-5.

[81] L.A. Nikolaidis, D. Elahi, T. Hentosz, A. Doverspike, R. Huerbin, L. Zourelias, C. Stolarski, Y.T. Shen, R.P. Shannon, Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy, Circulation 110(8) (2004) 955-61.

[82] D. Nathanson, B. Ullman, U. Lofstrom, A. Hedman, M. Frick, A. Sjoholm, T. Nystrom, Effects of intravenous exenatide in type 2 diabetic patients with congestive heart failure: a double-blind, randomised controlled clinical trial of efficacy and safety, Diabetologia 55(4) (2012) 926-35.

[83] G.G. Sokos, L.A. Nikolaidis, S. Mankad, D. Elahi, R.P. Shannon, Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure, J Card Fail 12(9) (2006) 694-9.

[84] M. Sauve, K. Ban, M.A. Momen, Y.Q. Zhou, R.M. Henkelman, M. Husain, D.J. Drucker, Genetic deletion or pharmacological inhibition of dipeptidyl peptidase-4 improves cardiovascular outcomes after myocardial infarction in mice, Diabetes 59(4) (2010) 1063-73.

[85] B. Hocher, Y. Sharkovska, M. Mark, T. Klein, T. Pfab, The novel DPP-4 inhibitors linagliptin and BI 14361 reduce infarct size after myocardial ischemia/reperfusion in rats, Int J Cardiol 167(1) (2013) 87-93.

[86] X. Qin, H. Shen, M. Liu, Q. Yang, S. Zheng, M. Sabo, D.A. D'Alessio, P. Tso, GLP-1 reduces intestinal lymph flow, triglyceride absorption, and apolipoprotein production in rats, Am J Physiol Gastrointest Liver Physiol 288(5) (2005) G943-9.

[87] J. Hsieh, C. Longuet, C.L. Baker, B. Qin, L.M. Federico, D.J. Drucker, K. Adeli, The glucagon-like peptide 1 receptor is essential for postprandial lipoprotein synthesis and secretion in hamsters and mice, Diabetologia 53(3) (2010) 552-61.

[88] N. Panjwani, E.E. Mulvihill, C. Longuet, B. Yusta, J.E. Campbell, T.J. Brown, C. Streutker, D. Holland, X. Cao, L.L. Baggio, D.J. Drucker, GLP-1 receptor activation indirectly reduces hepatic lipid accumulation but does not attenuate development of atherosclerosis in diabetic male ApoE(-/-) mice, Endocrinology 154(1) (2013) 127-39.

[89] J.E. Mells, P.P. Fu, S. Sharma, D. Olson, L. Cheng, J.A. Handy, N.K. Saxena, D. Sorescu, F.A. Anania, Glp-1 analog, liraglutide, ameliorates hepatic steatosis and cardiac hypertrophy in C57BL/6J mice fed a Western diet, Am J Physiol Gastrointest Liver Physiol 302(2) (2012) G225-35.

[90] N. Matikainen, S. Manttari, A. Schweizer, A. Ulvestad, D. Mills, B.E. Dunning, J.E. Foley, M.R. Taskinen, Vildagliptin therapy reduces postprandial intestinal triglyceride-rich lipoprotein particles in patients with type 2 diabetes, Diabetologia 49(9) (2006) 2049-57.

[91] A.J. Tremblay, B. Lamarche, C.F. Deacon, S.J. Weisnagel, P. Couture, Effect of sitagliptin therapy on postprandial lipoprotein levels in patients with type 2 diabetes, Diabetes, obesity & metabolism 13(4) (2011) 366-73.

[92] W.J. Liu, H.Y. Jin, K.A. Lee, S.H. Xie, H.S. Baek, T.S. Park, Neuroprotective effect of the glucagon-like peptide-1 receptor agonist, synthetic exendin-4, in streptozotocin-induced diabetic rats, Br J Pharmacol 164(5) (2011) 1410-20.

[93] R. Bianchi, I. Cervellini, C. Porretta-Serapiglia, N. Oggioni, B. Burkey, P. Ghezzi, G. Cavaletti, G. Lauria, Beneficial effects of PKF275-055, a novel, selective, orally bioavailable, long-acting dipeptidyl peptidase IV inhibitor in streptozotocin-induced diabetic peripheral neuropathy, J Pharmacol Exp Ther 340(1) (2012) 64-72.

[94] H.Y. Jin, W.J. Liu, J.H. Park, H.S. Baek, T.S. Park, Effect of dipeptidyl peptidase-IV (DPP-IV) inhibitor (Vildagliptin) on peripheral nerves in streptozotocin-induced diabetic rats, Arch Med Res 40(7) (2009) 536-44.

[95] Y. Zhang, Q. Wang, J. Zhang, X. Lei, G.T. Xu, W. Ye, Protection of exendin-4 analogue in early experimental diabetic retinopathy, Graefes Arch Clin Exp Ophthalmol 247(5) (2009) 699-706.

[96] Y. Zhang, J. Zhang, Q. Wang, X. Lei, Q. Chu, G.T. Xu, W. Ye, Intravitreal injection of exendin-4 analogue protects retinal cells in early diabetic rats, Invest Ophthalmol Vis Sci 52(1) (2011) 278-85.

[97] Z. Fu, H.Y. Kuang, M. Hao, X.Y. Gao, Y. Liu, N. Shao, Protection of exenatide for retinal ganglion cells with different glucose concentrations, Peptides 37(1) (2012) 25-31.

[98] A. Goncalves, E. Leal, A. Paiva, E. Teixeira Lemos, F. Teixeira, C.F. Ribeiro, F. Reis, A.F. Ambrosio, R. Fernandes, Protective effects of the dipeptidyl peptidase IV inhibitor sitagliptin in the blood-retinal barrier in a type 2 diabetes animal model, Diabetes, obesity & metabolism 14(5) (2012) 454-63.

[99] D. Koya, S. Araki, M. Haneda, Therapeutic management of diabetic kidney disease, Journal of diabetes investigation 2(4) (2011) 248-54.

[100] B. Hocher, C. Reichetzeder, M.L. Alter, Renal and cardiac effects of DPP4 inhibitors--from preclinical development to clinical research, Kidney & blood pressure research 36(1) (2012) 65-84.

[101] J. Skov, Effects of GLP-1 in the kidney, Reviews in endocrine & metabolic disorders 15(3) (2014) 197-207.

[102] K. von Websky, C. Reichetzeder, B. Hocher, Physiology and pathophysiology of incretins in the kidney, Curr Opin Nephrol Hypertens 23(1) (2014) 54-60.

[103] C.J. Hutchings, M. Koglin, F.H. Marshall, Therapeutic antibodies directed at G protein-coupled receptors, MAbs 2(6) (2010) 594-606.

[104] E.K. Jackson, S.J. Kochanek, D.G. Gillespie, Dipeptidyl peptidase IV regulates proliferation of preglomerular vascular smooth muscle and mesangial cells, Hypertension 60(3) (2012) 757-64.

[105] M. Yu, C. Moreno, K.M. Hoagland, A. Dahly, K. Ditter, M. Mistry, R.J. Roman, Antihypertensive effect of glucagon-like peptide 1 in Dahl salt-sensitive rats, J Hypertens 21(6) (2003) 1125-35.

[106] D. Bolignano, G. Coppolino, M. Criseo, S. Campo, A. Romeo, M. Buemi, Aquaretic agents: what's beyond the treatment of hyponatremia?, Current pharmaceutical design 13(8) (2007) 865-71.

[107] C. Moreno, M. Mistry, R.J. Roman, Renal effects of glucagon-like peptide in rats, European journal of pharmacology 434(3) (2002) 163-7.

[108] T. Rieg, M. Gerasimova, F. Murray, T. Masuda, T. Tang, M. Rose, D.J. Drucker, V. Vallon, Natriuretic effect by exendin-4, but not the DPP-4 inhibitor alogliptin, is mediated via the GLP-1 receptor and preserved in obese type 2 diabetic mice, American journal of physiology. Renal physiology 303(7) (2012) F963-71.

[109] J.P. Gutzwiller, S. Tschopp, A. Bock, C.E. Zehnder, A.R. Huber, M. Kreyenbuehl, H. Gutmann, J. Drewe, C. Henzen, B. Goeke, C. Beglinger, Glucagon-like peptide 1 induces natriuresis in healthy subjects and in insulin-resistant obese men, The Journal of clinical endocrinology and metabolism 89(6) (2004) 3055-61.

[110] J.P. Gutzwiller, P. Hruz, A.R. Huber, C. Hamel, C. Zehnder, J. Drewe, H. Gutmann, Z. Stanga, D. Vogel, C. Beglinger, Glucagon-like peptide-1 is involved in sodium and water homeostasis in humans, Digestion 73(2-3) (2006) 142-50.

[111] P. Persson, P. Hansell, F. Palm, Tubular reabsorption and diabetes-induced glomerular hyperfiltration, Acta physiologica 200(1) (2010) 3-10.

[112] R.O. Crajoinas, F.T. Oricchio, T.D. Pessoa, B.P. Pacheco, L.M. Lessa, G. Malnic, A.C. Girardi, Mechanisms mediating the diuretic and natriuretic actions of the incretin hormone glucagon-like peptide-1, American journal of physiology. Renal physiology 301(2) (2011) F355-63.

[113] M. Kim, M.J. Platt, T. Shibasaki, S.E. Quaggin, P.H. Backx, S. Seino, J.A. Simpson, D.J. Drucker, GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure, Nature medicine 19(5) (2013) 567-75.

[114] J. Skov, J.J. Holst, J.P. Gotze, J. Frokiaer, J.S. Christiansen, Glucagon-like peptide-1: effect on pro-atrial natriuretic peptide in healthy males, Endocrine connections 3(1) (2014) 11-6.

[115] J. Skov, A. Dejgaard, J. Frokiaer, J.J. Holst, T. Jonassen, S. Rittig, J.S. Christiansen, Glucagon-like peptide-1 (GLP-1): effect on kidney hemodynamics and renin-angiotensin-aldosterone system in healthy men, The Journal of clinical endocrinology and metabolism 98(4) (2013) E664-71.

[116] A. Mima, J. Hiraoka-Yamomoto, Q. Li, M. Kitada, C. Li, P. Geraldes, M. Matsumoto, K. Mizutani, K. Park, C. Cahill, S. Nishikawa, C. Rask-Madsen, G.L. King, Protective effects of GLP-1 on glomerular endothelium and its inhibition by PKCbeta activation in diabetes, Diabetes 61(11) (2012) 2967-79.

[117] Y. Ishibashi, T. Matsui, A. Ojima, Y. Nishino, S. Nakashima, S. Maeda, S. Yamagishi, Glucagon-like peptide-1 inhibits angiotensin II-induced mesangial cell damage via protein kinase A, Microvascular research 84(3) (2012) 395-8.

[118] Y. Ishibashi, Y. Nishino, T. Matsui, M. Takeuchi, S. Yamagishi, Glucagon-like peptide-1 suppresses advanced glycation end product-induced monocyte chemoattractant protein-1 expression in mesangial cells by reducing advanced glycation end product receptor level, Metabolism 60(9) (2011) 1271-7.

40

[119] A.C. Girardi, L.E. Fukuda, L.V. Rossoni, G. Malnic, N.A. Reboucas, Dipeptidyl peptidase IV inhibition downregulates Na+ - H+ exchanger NHE3 in rat renal proximal tubule, American journal of physiology. Renal physiology 294(2) (2008) F414-22.

[120] A.C. Girardi, F. Knauf, H.U. Demuth, P.S. Aronson, Role of dipeptidyl peptidase IV in regulating activity of Na+/H+ exchanger isoform NHE3 in proximal tubule cells, American journal of physiology. Cell physiology 287(5) (2004) C1238-45.

[121] A.C. Girardi, B.C. Degray, T. Nagy, D. Biemesderfer, P.S. Aronson, Association of Na(+)-H(+) exchanger isoform NHE3 and dipeptidyl peptidase IV in the renal proximal tubule, The Journal of biological chemistry 276(49) (2001) 46671-7.

[122] L.R. Carraro-Lacroix, G. Malnic, A.C. Girardi, Regulation of Na+/H+ exchanger NHE3 by glucagon-like peptide 1 receptor agonist exendin-4 in renal proximal tubule cells, American journal of physiology. Renal physiology 297(6) (2009) F1647-55.

[123] E.K. Jackson, J.H. Dubinion, Z. Mi, Effects of dipeptidyl peptidase iv inhibition on arterial blood pressure, Clinical and experimental pharmacology & physiology 35(1) (2008) 29-34.

[124] E.K. Jackson, Z. Mi, Sitagliptin augments sympathetic enhancement of the renovascular effects of angiotensin II in genetic hypertension, Hypertension 51(6) (2008) 1637-42.

[125] D.S. Tofovic, V.P. Bilan, E.K. Jackson, Sitagliptin augments angiotensin II-induced renal vasoconstriction in kidneys from rats with metabolic syndrome, Clinical and experimental pharmacology & physiology 37(7) (2010) 689-91.

[126] V. Stefanovic, N. Ardaillou, P. Vlahovic, S. Placier, P. Ronco, R. Ardaillou, Interferon-gamma induces dipeptidylpeptidase IV expression in human glomerular epithelial cells, Immunology 80(3) (1993) 465-70.

[127] J. Yang, J. Campitelli, G. Hu, Y. Lin, J. Luo, C. Xue, Increase in DPP-IV in the intestine, liver and kidney of the rat treated with high fat diet and streptozotocin, Life sciences 81(4) (2007) 272-9.

[128] Y.S. Kanwar, J. Wada, L. Sun, P. Xie, E.I. Wallner, S. Chen, S. Chugh, F.R. Danesh, Diabetic nephropathy: mechanisms of renal disease progression, Exp Biol Med (Maywood) 233(1) (2008) 4-11.

[129] B. Mitic, G. Lazarevic, P. Vlahovic, M. Rajic, V. Stefanovic, Diagnostic value of the aminopeptidase N, N-acetyl-beta-D-glucosaminidase and dipeptidylpeptidase IV in evaluating tubular dysfunction in patients with glomerulopathies, Ren Fail 30(9) (2008) 896-903.

[130] M. Kitada, Z. Zhang, A. Mima, G.L. King, Molecular mechanisms of diabetic vascular complications, Journal of diabetes investigation 1(3) (2010) 77-89.

[131] P. Fiorina, A. Vergani, R. Bassi, M.A. Niewczas, M.M. Altintas, M.G. Pezzolesi, F. D'Addio, M. Chin, S. Tezza, M. Ben Nasr, D. Mattinzoli, M. Ikehata, D. Corradi, V. Schumacher, L. Buvall, C.C. Yu, J.M. Chang, S. La Rosa, G. Finzi, A. Solini, F. Vincenti, M.P. Rastaldi, J. Reiser, A.S. Krolewski, P.H. Mundel, M.H. Sayegh, Role of podocyte B7-1 in diabetic nephropathy, Journal of the American Society of Nephrology : JASN 25(7) (2014) 1415-29.

[132] A. Solini, V. Usuelli, P. Fiorina, The dark side of extracellular ATP in kidney diseases, Journal of the American Society of Nephrology : JASN 26(5) (2015) 1007-16.

[133] A.S. Krolewski, M.A. Niewczas, J. Skupien, T. Gohda, A. Smiles, J.H. Eckfeldt, A. Doria, J.H. Warram, Early progressive renal decline precedes the onset of microalbuminuria and its progression to macroalbuminuria, Diabetes care 37(1) (2014) 226-34.

[134] M.A. Niewczas, L.H. Ficociello, A.C. Johnson, W. Walker, E.T. Rosolowsky, B. Roshan, J.H. Warram, A.S. Krolewski, Serum concentrations of markers of TNFalpha and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes, Clin J Am Soc Nephrol 4(1) (2009) 62-70.

[135] P.P. Wolkow, M.A. Niewczas, B. Perkins, L.H. Ficociello, B. Lipinski, J.H. Warram, A.S. Krolewski, Association of urinary inflammatory markers and renal decline in microalbuminuric type 1 diabetics, Journal of the American Society of Nephrology : JASN 19(4) (2008) 789-97.

[136] Y. Kirino, Y. Sato, T. Kamimoto, K. Kawazoe, K. Minakuchi, Y. Nakahori, Interrelationship of dipeptidyl peptidase IV (DPP4) with the development of diabetes, dyslipidaemia and nephropathy: a streptozotocin-induced model using wild-type and DPP4-deficient rats, The Journal of endocrinology 200(1) (2009) 53-61.

[137] E. Mannucci, L. Pala, S. Ciani, G. Bardini, A. Pezzatini, I. Sposato, F. Cremasco, A. Ognibene, C.M. Rotella, Hyperglycaemia increases dipeptidyl peptidase IV activity in diabetes mellitus, Diabetologia 48(6) (2005) 1168-72.

[138] W.J. Liu, S.H. Xie, Y.N. Liu, W. Kim, H.Y. Jin, S.K. Park, Y.M. Shao, T.S. Park, Dipeptidyl peptidase IV inhibitor attenuates kidney injury in streptozotocin-induced diabetic rats, J Pharmacol Exp Ther 340(2) (2012) 248-55.

[139] J. Ryskjaer, C.F. Deacon, R.D. Carr, T. Krarup, S. Madsbad, J. Holst, T. Vilsboll, Plasma dipeptidyl peptidase-IV activity in patients with type-2 diabetes mellitus correlates positively with HbAlc levels, but is not acutely affected by food intake, European journal of endocrinology / European Federation of Endocrine Societies 155(3) (2006) 485-93.

[140] M.A.C. Pomatto, C. Gai, B. Bussolati, G. Camussi, Extracellular Vesicles in Renal Pathophysiology, Front Mol Biosci 4 (2017) 37.

[141] C. Tetta, E. Ghigo, L. Silengo, M.C. Deregibus, G. Camussi, Extracellular vesicles as an emerging mechanism of cell-to-cell communication, Endocrine 44(1) (2013) 11-9.

[142] G. Camussi, V. Cantaluppi, M.C. Deregibus, E. Gatti, C. Tetta, Role of microvesicles in acute kidney injury, Contrib Nephrol 174 (2011) 191-9.

[143] G. Camussi, M.C. Deregibus, S. Bruno, V. Cantaluppi, L. Biancone, Exosomes/microvesicles as a mechanism of cell-to-cell communication, Kidney international 78(9) (2010) 838-48.

[144] G. Coppolino, P. Presta, L. Saturno, G. Fuiano, Acute kidney injury in patients undergoing cardiac surgery, Journal of nephrology 26(1) (2013) 32-40.

[145] Z.Z. Jiang, Y.M. Liu, X. Niu, J.Y. Yin, B. Hu, S.C. Guo, Y. Fan, Y. Wang, N.S. Wang, Exosomes secreted by human urine-derived stem cells could prevent kidney complications from type I diabetes in rats, Stem Cell Res Ther 7 (2016) 24.

[146] A. Ranghino, V. Dimuccio, E. Papadimitriou, B. Bussolati, Extracellular vesicles in the urine: markers and mediators of tissue damage and regeneration, Clin Kidney J 8(1) (2015) 23-30.

[147] F. Sabatier, P. Darmon, B. Hugel, V. Combes, M. Sanmarco, J.G. Velut, D. Arnoux, P. Charpiot, J.M. Freyssinet, C. Oliver, J. Sampol, F. Dignat-George, Type 1 and type 2 diabetic patients display different patterns of cellular microparticles, Diabetes 51(9) (2002) 2840-5.

[148] D. Delic, C. Eisele, R. Schmid, P. Baum, F. Wiech, M. Gerl, H. Zimdahl, S.S. Pullen, R. Urquhart, Urinary Exosomal miRNA Signature in Type II Diabetic Nephropathy Patients, PloS one 11(3) (2016) e0150154.

[149] S. Eissa, M. Matboli, R. Aboushahba, M.M. Bekhet, Y. Soliman, Urinary exosomal microRNA panel unravels novel biomarkers for diagnosis of type 2 diabetic kidney disease, J Diabetes Complications 30(8) (2016) 1585-1592.

[150] Y. Jia, M. Guan, Z. Zheng, Q. Zhang, C. Tang, W. Xu, Z. Xiao, L. Wang, Y. Xue, miRNAs in Urine Extracellular Vesicles as Predictors of Early-Stage Diabetic Nephropathy, J Diabetes Res 2016 (2016) 7932765.

[151] A. Mohan, R.S. Singh, M. Kumari, D. Garg, A. Upadhyay, C.M. Ecelbarger, S. Tripathy, S. Tiwari, Urinary Exosomal microRNA-451-5p Is a Potential Early Biomarker of Diabetic Nephropathy in Rats, PloS one 11(4) (2016) e0154055.

[152] F. Barutta, M. Tricarico, A. Corbelli, L. Annaratone, S. Pinach, S. Grimaldi, G. Bruno, D. Cimino, D. Taverna, M.C. Deregibus, M.P. Rastaldi, P.C. Perin, G. Gruden, Urinary exosomal microRNAs in incipient diabetic nephropathy, PloS one 8(11) (2013) e73798.

[153] M.L. Alter, I.M. Ott, K. von Websky, O. Tsuprykov, Y. Sharkovska, K. Krause-Relle, J. Raila, A. Henze, T. Klein, B. Hocher, DPP-4 inhibition on top of angiotensin receptor blockade offers a new therapeutic approach for diabetic nephropathy, Kidney & blood pressure research 36(1) (2012) 119-30.

[154] C. Mega, E.T. de Lemos, H. Vala, R. Fernandes, J. Oliveira, F. Mascarenhas-Melo, F. Teixeira, F. Reis, Diabetic nephropathy amelioration by a low-dose sitagliptin in an animal model of type 2 diabetes (Zucker diabetic fatty rat), Experimental diabetes research 2011 (2011) 162092.

[155] Y. Sharkovska, C. Reichetzeder, M. Alter, O. Tsuprykov, S. Bachmann, T. Secher, T. Klein, B. Hocher, Blood pressure and glucose independent renoprotective effects of dipeptidyl peptidase-4 inhibition in a mouse model of type-2 diabetic nephropathy, J Hypertens 32(11) (2014) 2211-23; discussion 2223.

[156] P.H. Groop, M.E. Cooper, V. Perkovic, A. Emser, H.J. Woerle, M. von Eynatten, Linagliptin lowers albuminuria on top of recommended standard treatment in patients with type 2 diabetes and renal dysfunction, Diabetes care 36(11) (2013) 3460-8.

[157] D.M. Abd El Motteleb, S.M. Elshazly, Renoprotective effect of sitagliptin against hypertensive nephropathy induced by chronic administration of L-NAME in rats: role of GLP-1 and GLP-1 receptor, European journal of pharmacology 720(1-3) (2013) 158-65.

[158] K.W. Joo, S. Kim, S.Y. Ahn, H.J. Chin, D.W. Chae, J. Lee, J.S. Han, K.Y. Na, Dipeptidyl peptidase IV inhibitor attenuates kidney injury in rat remnant kidney, BMC nephrology 14 (2013) 98.

[159] L. Chaykovska, M.L. Alter, K. von Websky, M. Hohmann, O. Tsuprykov, C. Reichetzeder, B. Kutil, R. Kraft, T. Klein, B. Hocher, Effects of telmisartan and linagliptin when used in combination on blood pressure and oxidative stress in rats with 2-kidney-1-clip hypertension, J Hypertens 31(11) (2013) 2290-8; discussion 2299.

[160] T. Shinosaki, T. Kobayashi, K. Kimura, H. Kurihara, Involvement of dipeptidyl peptidase IV in immune complex-mediated glomerulonephritis, Laboratory investigation; a journal of technical methods and pathology 82(4) (2002) 505-13.

[161] J. Vaghasiya, N. Sheth, Y. Bhalodia, R. Manek, Sitagliptin protects renal ischemia reperfusion induced renal damage in diabetes, Regulatory peptides 166(1-3) (2011) 48-54.

[162] L.L. Glorie, A. Verhulst, V. Matheeussen, L. Baerts, J. Magielse, N. Hermans, P.C. D'Haese, I. De Meester, A. De Beuf, DPP4 inhibition improves functional outcome after renal ischemia-reperfusion injury, American journal of physiology. Renal physiology 303(5) (2012) F681-8.

[163] B. Huisamen, A. Genis, E. Marais, A. Lochner, Pre-treatment with a DPP-4 inhibitor is infarct sparing in hearts from obese, pre-diabetic rats, Cardiovascular drugs and therapy / sponsored by the International Society of Cardiovascular Pharmacotherapy 25(1) (2011) 13-20.

[164] Y. Ye, K.T. Keyes, C. Zhang, J.R. Perez-Polo, Y. Lin, Y. Birnbaum, The myocardial infarct size-limiting effect of sitagliptin is PKA-dependent, whereas the protective effect of pioglitazone is partially dependent on PKA, American journal of physiology. Heart and circulatory physiology 298(5) (2010) H1454-65.

[165] W. Jungraithmayr, I. De Meester, V. Matheeussen, L. Baerts, S. Arni, W. Weder, CD26/DPP-4 inhibition recruits regenerative stem cells via stromal cell-derived factor-1 and beneficially influences ischaemia-reperfusion injury in mouse lung transplantation, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 41(5) (2012) 1166-73.

[166] W. Zhai, M. Cardell, I. De Meester, K. Augustyns, S. Hillinger, I. Inci, S. Arni, W. Jungraithmayr, S. Scharpe, W. Weder, S. Korom, Ischemia/reperfusion injury: The role of CD26/dipeptidyl-peptidase-IV-inhibition in lung transplantation, Transplantation proceedings 38(10) (2006) 3369-71.

[167] M. Buemi, F. Floccari, C. Costa, C. Caccamo, N. Belghity, S. Campo, F. Pernice, G. Bonvissuto, G. Coppolino, A. Barilla, M. Criseo, E. Crasci, L. Nostro, A. Arena, Dialysis-related genotoxicity: sister chromatid exchanges and DNA lesions in T and B lymphocytes of uremic patients. Genomic damage in patients on hemodiafiltration, Blood purification 24(5-6) (2006) 569-74.

[168] Y.T. Chen, T.H. Tsai, C.C. Yang, C.K. Sun, L.T. Chang, H.H. Chen, C.L. Chang, P.H. Sung, Y.Y. Zhen, S. Leu, H.W. Chang, Y.L. Chen, H.K. Yip, Exendin-4 and sitagliptin protect kidney

from ischemia-reperfusion injury through suppressing oxidative stress and inflammatory reaction, Journal of translational medicine 11 (2013) 270.

[169] M.W. Chang, C.H. Chen, Y.C. Chen, Y.C. Wu, Y.Y. Zhen, S. Leu, T.H. Tsai, S.F. Ko, P.H. Sung, C.C. Yang, H.J. Chiang, H.W. Chang, Y.T. Chen, H.K. Yip, Sitagliptin protects rat kidneys from acute ischemia-reperfusion injury via upregulation of GLP-1 and GLP-1 receptors, Acta pharmacologica Sinica 36(1) (2015) 119-30.

[170] H. Yang, H. Li, Z. Wang, Y. Shi, G. Jiang, F. Zeng, Exendin-4 ameliorates renal ischemia-reperfusion injury in the rat, The Journal of surgical research 185(2) (2013) 825-32.

[171] F. Di Sole, M.C. Hu, J. Zhang, V. Babich, I.A. Bobulescu, M. Shi, P. McLeroy, T.E. Rogers, O.W. Moe, The reduction of Na/H exchanger-3 protein and transcript expression in acute ischemia-reperfusion injury is mediated by extractable tissue factor(s), Kidney international 80(8) (2011) 822-31.

[172] M. Hropot, H.P. Juretschke, K.H. Langer, J.R. Schwark, S3226, a novel NHE3 inhibitor, attenuates ischemia-induced acute renal failure in rats, Kidney international 60(6) (2001) 2283-9.

[173] F. Togel, J. Isaac, Z. Hu, K. Weiss, C. Westenfelder, Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury, Kidney international 67(5) (2005) 1772-84.

[174] G. Stokman, I. Stroo, N. Claessen, G.J. Teske, S. Florquin, J.C. Leemans, SDF-1 provides morphological and functional protection against renal ischaemia/reperfusion injury, Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 25(12) (2010) 3852-9.

[175] J. Bylander, Q. Li, G. Ramesh, B. Zhang, W.B. Reeves, J.S. Bond, Targeted disruption of the meprin metalloproteinase beta gene protects against renal ischemia-reperfusion injury in mice, American journal of physiology. Renal physiology 294(3) (2008) F480-90.

[176] D. Katagiri, Y. Hamasaki, K. Doi, K. Okamoto, K. Negishi, M. Nangaku, E. Noiri, Protection of glucagon-like peptide-1 in cisplatin-induced renal injury elucidates gut-kidney connection, Journal of the American Society of Nephrology : JASN 24(12) (2013) 2034-43.

[177] D.W. Cockcroft, M.H. Gault, Prediction of creatinine clearance from serum creatinine, Nephron 16(1) (1976) 31-41.

[178] A.S. Levey, J.P. Bosch, J.B. Lewis, T. Greene, N. Rogers, D. Roth, A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group, Annals of internal medicine 130(6) (1999) 461-70.

[179] J.C. Chan, R. Scott, J.C. Arjona Ferreira, D. Sheng, E. Gonzalez, M.J. Davies, P.P. Stein, K.D. Kaufman, J.M. Amatruda, D. Williams-Herman, Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency, Diabetes, obesity & metabolism 10(7) (2008) 545-55.

[180] W. Kothny, Q. Shao, P.H. Groop, V. Lukashevich, One-year safety, tolerability and efficacy of vildagliptin in patients with type 2 diabetes and moderate or severe renal impairment, Diabetes, obesity & metabolism 14(11) (2012) 1032-9.

[181] J.B. McGill, L. Sloan, J. Newman, S. Patel, C. Sauce, M. von Eynatten, H.J. Woerle, Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: a 1-year, randomized, double-blind, placebo-controlled study, Diabetes care 36(2) (2013) 237-44.

[182] W.B. White, C.P. Cannon, S.R. Heller, S.E. Nissen, R.M. Bergenstal, G.L. Bakris, A.T. Perez, P.R. Fleck, C.R. Mehta, S. Kupfer, C. Wilson, W.C. Cushman, F. Zannad, E. Investigators, Alogliptin after acute coronary syndrome in patients with type 2 diabetes, The New England journal of medicine 369(14) (2013) 1327-35.

[183] V. Lukashevich, A. Schweizer, J.E. Foley, S. Dickinson, P.H. Groop, W. Kothny, Efficacy of vildagliptin in combination with insulin in patients with type 2 diabetes and severe renal impairment, Vascular health and risk management 9 (2013) 21-8.

[184] M. Nowicki, I. Rychlik, H. Haller, M. Warren, L. Suchower, I. Gause-Nilsson, K.M. Schutzer, Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study, International journal of clinical practice 65(12) (2011) 1230-9.

[185] M.A. Banerji, D. Purkayastha, B.H. Francis, Safety and tolerability of vildagliptin vs. thiazolidinedione as add-on to metformin in type 2 diabetic patients with and without mild renal impairment: a retrospective analysis of the GALIANT study, Diabetes Res Clin Pract 90(2) (2010) 182-90.

[186] S. Del Prato, A.H. Barnett, H. Huisman, D. Neubacher, H.J. Woerle, K.A. Dugi, Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial, Diabetes, obesity & metabolism 13(3) (2011) 258-67.

[187] R. Gomis, R.M. Espadero, R. Jones, H.J. Woerle, K.A. Dugi, Efficacy and safety of initial combination therapy with linagliptin and pioglitazone in patients with inadequately controlled type 2 diabetes: a randomized, double-blind, placebo-controlled study, Diabetes, obesity & metabolism 13(7) (2011) 653-61.

[188] D.R. Owens, R. Swallow, K.A. Dugi, H.J. Woerle, Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study, Diabetic medicine : a journal of the British Diabetic Association 28(11) (2011) 1352-61.

[189] M.R. Taskinen, J. Rosenstock, I. Tamminen, R. Kubiak, S. Patel, K.A. Dugi, H.J. Woerle, Safety and efficacy of linagliptin as add-on therapy to metformin in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled study, Diabetes, obesity & metabolism 13(1) (2011) 65-74.

[190] A.S. Dobs, B.J. Goldstein, P. Aschner, E.S. Horton, G.E. Umpierrez, L. Duran, J.S. Hill, Y. Chen, G.T. Golm, R.B. Langdon, D.E. Williams-Herman, K.D. Kaufman, J.M. Amatruda, J.C. Ferreira, Efficacy and safety of sitagliptin added to ongoing metformin and rosiglitazone combination therapy in a randomized placebo-controlled 54-week trial in patients with type 2 diabetes, Journal of diabetes 5(1) (2013) 68-79.

[191] A.H. Barnett, H. Huisman, R. Jones, M. von Eynatten, S. Patel, H.J. Woerle, Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: a randomised, double-blind, placebo-controlled trial, Lancet 382(9902) (2013) 1413-23.

[192] P.M. Howse, L.N. Chibrikova, L.K. Twells, B.J. Barrett, J.M. Gamble, Safety and Efficacy of Incretin-Based Therapies in Patients With Type 2 Diabetes Mellitus and CKD: A Systematic Review and Meta-analysis, American journal of kidney diseases : the official journal of the National Kidney Foundation 68(5) (2016) 733-742.

[193] M.E. Cooper, V. Perkovic, J.B. McGill, P.H. Groop, C. Wanner, J. Rosenstock, U. Hehnke, H.J. Woerle, M. von Eynatten, Kidney Disease End Points in a Pooled Analysis of Individual Patient-Level Data From a Large Clinical Trials Program of the Dipeptidyl Peptidase 4 Inhibitor Linagliptin in Type 2 Diabetes, American journal of kidney diseases : the official journal of the National Kidney Foundation 66(3) (2015) 441-9.

[194] S. Hattori, Sitagliptin reduces albuminuria in patients with type 2 diabetes, Endocrine journal 58(1) (2011) 69-73.

[195] H. Mori, Y. Okada, T. Arao, Y. Tanaka, Sitagliptin improves albuminuria in patients with type 2 diabetes mellitus, Journal of diabetes investigation 5(3) (2014) 313-9.

[196] I. Kawasaki, Y. Hiura, A. Tamai, Y. Yoshida, Y. Yakusiji, Y. Ikuno, M. Okada, H. Ueno, N. Tanaka, K. Yamagami, M. Fukumoto, M. Hosoi, Sitagliptin reduces the urine albumin-to-creatinine ratio in type 2 diabetes through decreasing both blood pressure and estimated glomerular filtration rate, Journal of diabetes 7(1) (2015) 41-6.

[197] Y.G. Kim, J. Byun, D. Yoon, J.Y. Jeon, S.J. Han, D.J. Kim, K.W. Lee, R.W. Park, H.J. Kim, Renal Protective Effect of DPP-4 Inhibitors in Type 2 Diabetes Mellitus Patients: A Cohort Study, J Diabetes Res 2016 (2016) 1423191.

[198] P.H. Groop, M.E. Cooper, V. Perkovic, K. Sharma, G. Schernthaner, M. Haneda, B. Hocher, M. Gordat, J. Cescutti, H.J. Woerle, M. von Eynatten, Dipeptidyl peptidase-4 inhibition with linagliptin and effects on hyperglycaemia and albuminuria in patients with type 2 diabetes and renal dysfunction: Rationale and design of the MARLINA-T2D trial, Diabetes & vascular disease research 12(6) (2015) 455-62.

Table 1. Main pharmacokinetic and pharmacodynamic features of DPP-4is available on the European market
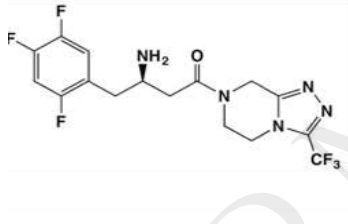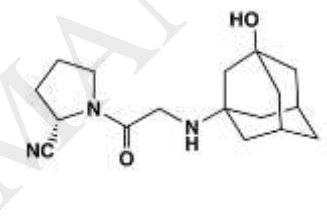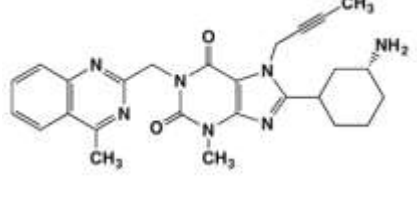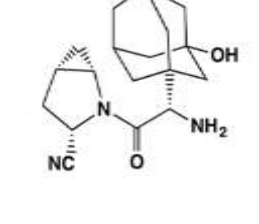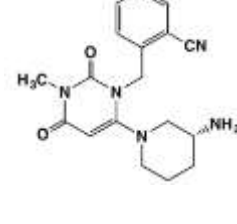
	SITAGLIPTIN[#]	VILDAGLIPTIN[#]	LINAGLIPTIN[#]	SAXAGLIPTIN[#]	ALOGLIPTIN[#]
CHEMICAL STRUCTURE					
PHARMACODYNAMICS					
In vitro DPP-4 inhibition (IC_{50}, nM)	19	62	1	50	24
DPP-4 selectivity (vs DPP-8/-9)	> 2600	< 100	> 10000	> 100	> 14000
PHARMACOKINETICS					
Absorption (T_{max}, h)	1-4	1.7	1.5	2h (4h active metabolite)	1-2
Oral bioavailability (%)	~87	85	~30	> 75	70
Volume distribution (L)	198	71	368-918	151	300
Binding to plasma protein (%)	38	9.3	70	< 10	20
Half-life (h)	8-14	2-3	120–184	2.2-3.8	12.4–21.4
Liver excretion (%)	13	4.5	85	22	13
Kidney excretion (%)	87	85	5	75	76

[#] Modified with permission from Arulmozhiraja S et Al.[41]

Table 2. Main characteristics of the studies included in the literature review.

Study ID	Year Center Country	Study design	-Inclusion criteria -Exclusion Criteria	Population	Intervention	Comparator	Follow-up (week)	Outcomes	Results	Notes
Chan [179]	2008 Multicenter Global	RCT	- age 18–85, T2DM, CKD. Not on OAD. -TDM1, AKI, RT, LD prev. 6 months, CVD, FPG >15 mmol/l or triglycerides >6.8 mmol/l	N= 91 n= 52 GFR>30 <50 ml/min and not on dialysis; n= 39 GFR<30 ml/min and not on dialysis; n= 17 ESRD or dialysis.	N= 65 **Sitagliptin**	N= 26 **Glipizide** 5-10 mg/day or **Placebo + Glipizide**	12 + 42		**Mean change [95%(CI)]**	Double-blind, Parallel-group 2.5:1 randomization Sitagliptin 50 or 25 mg according to GFR
								HbA1c (%) Change at week 12	I: -0.6 (-0.8, -0.4); C: -0.2 (-0.4, - 0.1)	
								HbA1c (%) Change at week 54	I: -0.7 (-0.9, -0.4); C: -1.0 (-1.6, -0.3)	
								FPG(mmol/L) Change at week 12	I: -25.5(-38.2, -12.8); C: -3.0(-15.7,-9.6)	
								FPG(mmol/L) Change at week 54	I: -17.3(-32.3, -2.2); C: -23.6(-46.4, -0.7)	
								AEs Clinical n (N%)	I: 52 (80.0); C: 22 (84.6)	
								Drug-related clinical AEs	I: 8 (12.3); C: 5 (19.2)	
								Serious clinical	I: 20 (30.8); C: 10 (38.5)	

48

								AEs	
								Serious clinical Drug-related AEs	I: 1 (1.5); C: 0
								Death	I: 5 (7.7); C: 1 (3.8)
								Hypoglycemia n (N%)	I: 3 (4.6); C: 6 (23.1) HR: -18.5 (-37.7, -3.9)
								Renal and urinary disorders [n (N%)]	I: 5 (7.7); C: 3 (11.5) HR: -3.8 [(-21.8, 8.0)]
								Increased cCr (N%)	I: (1.6); C: (7.7)
									Mean change ± s.e.
								Mean sCr (mg/dl) Increase after 12 weeks GFR>30<50 ml/min	I: 0.12 ± 0.04; C: 0.07 ± 0.07
								Mean sCr (mg/dl) increase after 54 weeks GFR>30	I: -0.02 ± 0.06 C: 0.69 ± 0.58

49

								<50 ml/min		
								Urine micro albumin/cre atinine ratio, mean increases from baseline after 12 weeks mg/mmol	I: 25425 ±21470 C: 56161 ± 49494	
								Urine micro albumin/cre atinine ratio, mean increases from baseline after 54 weeks mg/mmol	I: -22035 - C: 51641 - 58647	
Kothny [180]	2012 Multicenter Global	RCT	- age 18–85; T2DM, BMI ≤40 kg/m2; Severe CKD	N= 525 -n= 10 GFR >50 ml/min; -n= 294 GFR >30 <50 ml/min; -n= 10GFR <30 ml/min or on dialysis	N= 289 **Vildagliptin** 50 mg	N= 226 **Placebo**	24+ 28		**Mean change ± s.e.**	Double blind placebo controlled 2:1 randomizatio n
								HbA1c (%) moderate CKD	−0.4±0.2 (p=0.005)	
								HbA1c (%) severe CKD	−0.7±0.2 (p<0.0001)	
								FPG(mmol/ L) moderate CKD	-0.9±-0.4	
								FPG(mmol/ L)	1.8±0.54	

								severe CKD	
									Difference between moderate-severe −1.2±0.4 (p=0.008)
									Mean change from baseline
								GFR (ml/min/1.73 m2) decline moderate CKD	I: −1.62; C: −1.80
								GFR (ml/min/1.73 m2) decline severe CKD	I: −1.98; C: −2.44
								Hypoglycemia n(N%) Moderate CKD	I: 32 (26.2); C: 15 (16.9)
								Severe CKD	I: 17 (18.1); C: 11 (17.2)
								Any AEs n(N%) Moderate CKD	I: 103 (84.4); C: 76 (85.4)

								Any AEs Severe CKD	I: 80 (85.1); C: 56 (87.5)	
Mc Gill [181]	2013 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤45 kg/m2;IGC;HbA1c >7.0% <10.0%; OAD,GFR=30mL/min/1.73 m2 - TDZs, GLP-1 analogues, IMA, stroke, or TIA in the previous 6 months; unstable or acute congestive heart failure; AKI; RT; use of any other DPP-4 inhibitor previous 3 months.	N=133 -n=119 GFR> 60 to <30 ml/min; -n= 100 GFR> 15 to <30 ml/min; -n=14 GFR<15 ml/min or on dialysis.	N=68 **Linagliptin** -n= 5 GFR> 30<60ml/min; -n=55 GFR> 15<30ml/min; -n=8 GFR<15 ml/min or on dialysis.	N=65 **Placebo** -n= 5 GFR>30 to <60 ml/min; n=55GFR>15 to <30 ml/min: -n=8GFR<15 ml/min or on dial sis.	52		**Mean change [95%(CI)]**	Double-blind, parallel-group 1:1 randomizatio n
								HbA1c (%) Change at week 12	-0.60% (-0.89 , -0.31; P< 0.0001	
								HbA1c (%) Change at week 52	-0.72 (-1.03, -0.41; P< 0.0001)	
								FPG(mmol/L) Change at week 12	-0.10; (21.35 to 1.16; P= 0.8802)	
								FPG(mmol/L) Change at week 54	-0.82 to -0.97; P = 0.8698	
									Mean changes from baseline	
								GFR (mL/min/1.73 m2)	I: -0.8; C: -2.2	
								AEs related to renal and urinary disorders	Difference between C and I 25.0 vs. 21.5%	

Scirica [13] **SAVOR – TIMI53**	2013 Multicenter Global	RCT	-T2DM; HbA1c >6.5% 12.0%; MRF - DPP4inhibitors use; dyalisis, ESRD, RT, sCr> 6.0 mg/dl	N=16492 -n= 336 GFR<30 ml/min -n= 2240 GFR from 30 to ≤50 ml/min -n= 13916 GFR>50 ml/min	N= 8280 **Saxagliptin** -n= 172 GFR<30 ml/min -n= 1122 GFR >30≤50 ml/min -n=6986 GFR>50 ml/min	N= 8212 **Placebo** -n= 164 GFR<30 ml/min -n= 1118 GFR>30≤50 ml/min -n=6930 GFR>50 ml/min	152	Doubling of sCr, initiation of dialysis, RT	I: 194 (2.2); C: 178 (2.0) HR; 1.08 (0.88–1.32) P=0.46	Double-blind, parallel-group 1:1 randomization For GFR <50 Saxagliptin dosage was adjusted at 2,5mg/die
								Renal abnormality	I :483 (5.8); C:418 (5.1)	
								CVD death, IMA, Stroke GFR>50	HR: 1.00 (0.89–1.12) P=0.99	
								CVD Death, IMA, Stroke GFR >30<50	HR: 1.17 (1.00 - 1.37) P=0.0042	
								CVD Death, IMA, Stroke GFR<30	HR:1.53 (1.13 - 2.02) P=0.004	
White [182] **EXAMINE**	2013 Multicenter Global	RCT	- T2DM,OAD combination with HbA1c >6.5% <12.0%; - T1DM; GLP-1 analogues or DPP-4 more than 14 days total or within the 3 months prior to Screening.	N= 5380 -n=157 GFR<30 ml/min -n= 1408 GFR from 30 to ≤60 ml/min -n= 2976 GFR from 60 to ≤90	N=2701 **Alogliptin** -n= 772 GFR ≤60 ml/min -n= 78 GFR<30 ml/min -n= 694 GFR from 30 to ≤60 ml/min -n= 1530 GFR	N= 2679 **Placebo** -n= 793 GFR ≤60 ml/min -n=79 GFR<30 ml/min -n= 714 GFR from 30 to ≤60 ml/min -n= 1446 GFR from 60 to ≤90	144		**Mean change [95%(CI)]**	Double-blind, parallel-group 1:1 randomization
								HbA1c (%)	−0.43 to −0.28 (P<0.001)	
								Composite of death from CV causes, nonfatal	0.96 (≤1.16) P=0.32	

				ml/min -n=839 GFR>90 ml/min	from 60 to ≤90 ml/min -n= 399 GFR>90 ml/min	ml/min -n= 440 GFR>90 ml/min			IMA, or nonfatal stroke		
									Composite of death from CV causes, nonfatal IMA, nonfatal stroke, or urgent revascularization due to unstable angina within 24 hours after hospital admission	0.95 (≤1.14) P= 0.26	
									Death for CVD	0.85 (0.66–1.10) P= 0.21	
									Death for any cause	0.88 (0.71–1.09) P= 0.23	
Groop [156]	2013 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; IGC (HbA1c 7.0–10.0%) - OAD within 10 weeks prior to informed consent, insulin, TDZs, GLP-1 analogues within 3 months. IMA, stroke, TIA within 6 months.	N= 503 -n= 93 GFR > 30 to ≤60 ml/min -n= 838 GFR > 60 to ≤90 ml/min -n= 1212 GFR>90 ml/min	N= 336 **Linagliptin** -n= 68 GFR > 30≤60 ml/min -n= 620 GFR > 60 ≤90 ml/min -n= 870 GFR>90 ml/min	N= 167 **Placebo** -n= 25 GFR > 30 ≤60 ml/min -n= 218 GFR > 60≤90 ml/min -n= 342 GFR>90 ml/min	24			**Mean change [95%(CI)]**	Double-blind, parallel-group 2:1 randomization
									HbA1c (%) GFR >30≤60 ml/min	−0.53 (−0.91, −0.14; p<0.01)	
									HbA1c (%) GFR> 60 ≤90 ml/min	−0.67% (−0.80, −0.54; p<0.0001)	
									HbA1c (%) GFR>90 ml/min	−0.63% (−0.73, −0.53;	

Author	Year/Location	Design	Inclusion/Exclusion	N	Intervention	Comparator	Duration (weeks)	Outcome	Result	Blinding
									p<0.0001)	
								FPG(mmol/L) GFR >30≤60 ml/min	−0.3 (−1.2, 0.6); −5.5 (−22.1, 11.1); p=0.52	
								FPG(mmol/L) GFR>60 ≤90 ml/min	−1.2 (−1.5, −0.9) [−22.0 (−27.8, −16.2); p<0.0001]	
								FPG(mmol/L) GFR>90 ml/min	−0.9 (−1.1, −0.6) [−16.0(−16.0(−1.1, −0.6) [−22.	
								AEs GFR>90 ml/min	I: 58.2 C:58.7	
								AEs GFR>60 ≤90 ml/min	I: 59 C:57	
								AEs GFR>30≤60 ml/min	I: 66.7 C:60	
Lukashevic [183]	2013 Multicenter Global	RCT	- age 18–85; T2DM, BMI ≤42 kg/m2; IGC HbA1c >6.5 <10.0% - TDZs, sulphanilure, GLP-1 analogues, insulin, antiobesity drugs the previous 3 months; IMA, stroke, or TIA in the previous 6 months; unstable or acute congestive heart failure; ESRD.	N= 525 -n= 221 GFR<30 ml/min -n= 294 GFR >30 to ≤50 ml/min -n= 10 GFR>50 ml/min	N= 289 **Vildagliptin** -n= 124 GFR<30 ml/min -n= 165 GFR > 30≤50 ml/min -n= GFR>50 ml/min	N= 226 **Placebo** -n= 97 GFR<30 ml/min -n= 129 GFR > 30≤50 ml/min -n= GFR>50 ml/min	24		**Mean change [95%(CI)]**	Double-blind, parallel-group 1.3:1 randomization
								HbA1c (%) GFR<30 ml/min	−0.9 ± 0.2; −0.6 ± 0.1 (p < 0.0001)	
								HbA1c (%) GFR> 30≤50 ml/min	−0.7 ± 0.1; −0.5 ± 0.1 (p < 0.0001)	
								FPG(mmol/L) GFR<30 ml/min	−0.5 ± 0.4, p = 0.185	

									Outcome	Result	
									FPG(mmol/L) GFR>30≤50 ml/min	−0.5 ± 0.3, p = 0.144	
									AE GFR>30≤50 ml/min	I: 110 (67.5); C: 94 (72.9)	
									AE GFR<30 ml/min	I: 90 (72.6); C: 72 (74.2)	
									Deaths GFR<30 ml/min	I: 3 (2.4); C: 4 (4.1)	
									Deaths GFR>30≤50 ml/min	I: 1 (0.6); C: 1 (0.8)	
Nowicki [184]	2011 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; IGC HbA1c 7.0–11.0% Documented history of GFR <50 ml/min within the 3 months prior to enrollment - T1DM, history of diabetic ketoacidosis or hyposmolar non-ketonic coma DPP-IV inhibitor and/or GLP-1 analogue.	N= 170 -n= 39 GFR<30 ml/min -n= 41 GFR> 30 ≤50 ml/min -n= 90 GFR>50 ml/min	N= 85 **Saxagliptin** -n= 19 GFR<30 ml/min -n= 19 GFR > 30≤50 ml/min -n= 48 GFR>50 ml/min	N= 85 **Placebo** -n= 20 GFR<30 ml/min -n= 23 GFR >30≤50 ml/min -n= 42 GFR>50 ml/min	52		**Mean change [95%(CI)]**		Double-blind, parallel-group 1:1 randomization
									HbA1c (%) GFR<30 ml/min:	I: −0.90 to −0.37; C: −0.33 to 0.22	
									HbA1c (%) GFR >30≤50 ml/min:	C: −0.90 to −0.37; I: −0.33 to 0.22	
									HbA1c (%) ESRD	I: −1.34 to −0.35; C: −1.36 to −0.3	
									FPG(mmol/L) GFR<30 ml/min	I: -2.90 to -0.40; C: -2.16 to 0.04 Difference vs Placebo: -2.26 to 1.07	
									FPG(mmol/L) GFR >30≤50 ml/min	I: -1.75 to 0.16; C:-0.99 to 1.02 Difference vs Placebo: -	

									2.24 to 0.61	
								FPG (mmol/L ESRD	I: -0.47 to -4.81; C: -2.97 to -1.85 Difference vs Placebo: -0.85 to 6.30	
Banerji [185] GALIANT	2010 Multicenter USA	Non-RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; inadequately controlled with metformin 1000mg/die	N= 2627 -n= 1932 Normal renal function GFR >80 ml/min -n= 695 Mild impaired renal function GFR>50 <80 ml/min	N= 1743 **Vildagliptin + metformin** -n= 1279 GFR>80 ml/min -n= 464 GFR<30 ml/min	N= 924 **TDZ + metformin** -n= 693 GFR>80 ml/min -n= 231 GFR<30 ml/min	12	AEs Normal renal function GFR>80 ml/min	I: 89 (7.0); C: 46 (7.2)	Retrospective open label 2:1 randomization
								AEs Mild impaired renal function GFR>50 <80 ml/min	I: 40 (8.6); C: 24 (10.4)	
								Death Normal renal function GFR>80 ml/min	I:0; C:1(0.2)	
								Death Mild impaired renal function GFR>50 <80 ml/min	I:0; C:0	
								Blood Urea Nitrogen >9.99 Normal	I:1/1201 (0.1) C:7/595(1.2)	

Study	Year/Location	Type	Inclusion criteria	Group N	Intervention	Control	Duration (weeks)	Outcome	Results	Design
								renal function GFR>80 ml/min		
								Blood Urea Nitrogen >9.99 Mild impaired renal function GFR>50 <80 ml/min	I:16/447(3.6) C:11/223(4.9)	
Del prato [186]	2011 Multicenter Global	RCT	- age >18; T2DM, (BMI) ≤40 kg/m2;; treatment naïve or OAD not TDZ	N= 503 -n= 18 GFR >30 to ≤60 ml/min -n= 248 GFR >60 to ≤90 ml/min -n= 217 GFR>90 ml/min	N= 336 **Linagliptin** -n= 14 GFR>30 to ≤60 ml/min -n= 165 GFR> 60 to ≤90 ml/min -n= 141 GFR>90 ml/min	N= 167 **Placebo** -n= 4 GFR >30 to ≤60 ml/min -n= 83 GFR> 60 to ≤90 ml/min -n= 76 GFR>90 ml/min	24	**Mean change ± s.e.** HbA1c (%)	I: −0.44 (0.05); C: 0.25 (0.07) Difference vs placebo: −0.85, −0.53−0.69% (p < 0.0001).	Double-blind parallel group 2:1 randomizatio n
								GFR (mL/min/1. 73 m2)	No notable differences in renal function were observed between treatment groups and GFR did not appear to influence tolerability.	
Gomis [187]	2011 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; igc (HbA1c 7.0–11.0%) - IMA, Stroke, TIA,	N= 389 -n= 17 GFR >30 to ≤60 ml/min -n= 52 GFR	N= 249 **Linagliptin+ Pioglitazone** -n= 12 GFR > 30 to ≤60	N= 130 **Placebo+Pioglit azone** -n= 5 GFR >30 to ≤60 ml/min	24	HbA1c (%)	I: −1.06(±0.06); C: −0.56(±0.09) HR: −0.71,	Double-blind parallel group

Study	Year/Location	Type	Inclusion/Exclusion	Total N	Intervention	Control	Duration (weeks)	Outcome	Results	Design
			diabetic GLP-1 analogue, TDZ; pregnancy, nursing or not practicing birth control; FDG>13.3 mmol/l (240 mg/dl) at screening	>60 to ≤90 ml/min -n= 204 GFR>90 ml/min	ml/min -n= 97 GFR > 60 to ≤90 ml/min -n= 140 GFR>90 ml/min	-n= 55 GFR>60 to ≤90 ml/min -n= 64 GFR>90 ml/min			−0.30; (p < 0.0001)	2:1 randomization
								Changes in renal function:	no clinically significant changes in renal function: 93.4 and 95.7% of patients in the linagliptin and placebo groups, respectively, continued to have normal renal function or mild renal impairment at the end of the trial	
								FPG (mmol/l)	I: −1.8; C: −1.0 HR: −0.8 (−1.2, −0.4; p < 0.0001)	
Owens [188]	2011 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; IGC (HbA1c 7.0–10.0%) despite receiving a total metformin - IMA, Stroke, TIA, GLP-1 analogue, TDZ, pregnant, nursing or not practicing birth control; patients with fasting blood glucose >13.3 mmol/l	N= 1055 -n= 53 GFR> 30 to ≤60 ml/min -n= 365 GFR> 60 to ≤90 ml/min -n= 601 GFR>90 ml/min	N= 792 **Linagliptin** -n= 37 GFR >30 to ≤60 ml/min -n= 282 GFR >60 to ≤90 ml/min -n= 37 GFR>90 ml/min	N= 263 **Placebo** -n= 16 GFR >30 to ≤60 ml/min -n= 83 GFR >60 to ≤90 ml/min -n= 158 GFR>90 ml/min	24	HbA1c (%)	HR: -0.73 to -0.50; P < 0.0001	Double-blind parallel group 3:1 randomization
								FPG (mmol/l)	HR: -1.0 to-0.4; P < 0.0001	
								Renal AEs	No reported renal outcomes or adverse events	

			(240 mg/dl)							
Taskinen [189]	2011 Multicenter Global	RCT	- age 18–80; T2DM, (BMI) ≤40 kg/m2; IGC (HbA1c 7.0–10.0%) - IMA, Stroke, TIA; GLP-1 analogue, TDZ, Pregnancy, nursing or not practicing birth control; FDG >13.3 mmol/l (240 mg/dl)	N= 700 -n= 23 GFR from 30 to ≤60 ml/min -n= 238 GFR from 60 to ≤90 ml/min -n= 414 GFR>90 ml/min	N= 523 **Linagliptin** -n= 18 GFR > 30 to ≤60 ml/min -n= 183 GFR> 60 to ≤90 ml/min -n= 201GFR>90 ml/min	N= 177 **Placebo** -n= 5 GFR >30 to ≤60 ml/min -n= 55 GFR > 60 to ≤90 ml/min -n= 112 GFR>90 ml/min	24	HbA1c (%)	HR: −0.78 to −0.50; p < 0.0001	Double-blind parallel group 3:1 randomization
								FPG (mmol/l)	HR: −0.9 to −1.2 p <0.0001	
								Renal AEs	No reported renal outcomes or adverse events	
Dobs [190]	2013 Multicenter Global	RCT	- age>30; T2DM, (BMI) ≤40 kg/m2; IGC (HbA1c 7.0–10.0%) eGFR(MDRD) <50 mL/min/1.73 m2 not on dialysis -taking insulin within 12 weeks of the screening visit IMA, Stroke, TIA, t; GLP-1 analogue, TDZ, FDG >13.3 mmol/l (240 mg/dl)	N=426	N=211 **Sitagliptin**	N=212 **Glipizide**	54	HbA1c (%)	HR: -0.1 (-0.3 to 0.1)	Double-blind parallel group
								FPG (mmol/l)	HR: 7.1 (-1.9 to 16.1)	
								Death	I: 3(1.4) C: 7(3.3)	
								GFR decrease (mL/min/1.73 m2) Normal renal function	I: -3.9 C: -3.3 similar in both groups	
								GFR decrease (mL/min/1.73 m2) Moderate renal insufficiency at baseline	I: 28(18.8); C:17(11) transitioned to severe renal insufficiency	

| Fujita [15] | 2014 Monocentric | RCT | -T2DM, no previously treated with sitagliptin

-Persistent microal-buminuria (incipient DN) was de ned as a urinary albumin-to-creatinine ratio between 30 and 300 mg/g | N=20 | N=20 **Sitagliptin** 50mg/day for 4 weeks (rst period; baseline), (second period), and **Sitagliptin** 50mg/day for 4 weeks (third period). | N=20 **Alogliptin** 25 mg/day for 4 weeks **Sitagliptin** 50mg/day for 4 weeks **Alogliptin** 25 mg/day for 4 weeks | 8 | Urinary albumin/creatinine ratio(mg/g) 8-OHdG cAMP plasma SDF-1α | Urinary levels of albumin were signicantly reduced after the switch from sitagliptin to alogliptin (81.0 ± 52.4 vs. 33.9 ± 23.9 mg/g creatinine) P=0,01 Urinary 8-OHdG levels were signi cantly decreased after the crossover from sitagliptin to alogliptin. Urinary cAMP levels were significantly increased after the change from sitagliptin to alogliptin. SDF-1α levels increase after the switch from sitagliptin to alogliptin | Crossover |
|---|---|---|---|---|---|---|---|---|---|---|

								HbA1c (%)	I: -0.66% (27.25 mmol/mol [95% CI 20.90 to 20.43 (29.82 to 24.69 mmol/mol)]; C: [95% CI 20.90 to 20.43 (29.82 to 24.69 mmol/mol)]; P < 0.0001)	
								FPG (mmol/l)	I: 21.22 mmol/L [222.0 mg/dL]); C: (20.57 mmol/L [210.3 mg/dL]; P = 0.036	
								Body Weight (Kg)	I: -22.41 kg; C:-21.09 P = 0.0052	
								eGFR decrease (mL/min/1.73 m2)	No difference	
								UACR	No difference	
Barnett [191]	2013 Multicenter Global	RCT	-age 70 or older; T2DM; HbA1c 7.0–10.0%); stable diabetes treatment receiving stable doses of metformin,	N=241	N=162 **Linagliptin** 5 mg Normal renal function N=34	N= 79 **Placebo** Normal renal function N= 15	24	HbA1c (%) global	**Mean change [95%(CI)]** –0.81 to –0.48 (p<0.0001)	Parallel double-blind 2:1 randomizatio n

			sulfonylureas, or basal insulin, or combinations of these drugs, for at least 8 weeks - FDG >13.3 mmol/l (240 mg/dl); impaired hepatic function IMA, stroke, TIA (3 months before); bariatric surgery; present or 3 months before treatment with GLP-1 analogues, TDZ, α-glucosidase inhibitor, meglitinide rapid acting or premixed insulin, steroids.		Mild renal impairment N=83 Moderate renal impairment N=41 Severe renal impairment N=2	Mild renal impairment N=42 Moderate renal impairment N=20 Severe renal impairment N=1		Changes in renal function	No relevant changes
							FPG (mmol/l)	−1.68 to −0.62 (p<0.0001)
								Adjusted mean percentage change (SE)
							HbA1c (%) normal renal function	−0.39% (0.19) P=0.0397
							HbA1c (%) mild renal impairment	−0.74% (0.11) P<0.0001
							HbA1c (%) moderate renal impairment	−0.64% (0.17) P< 0.0001
							HbA1c (%) severe renal impairment	- 0.73% (0.74) P=0.3262

63