REVIEW

Effects of glucagon-like peptide-1 receptor agonists on renal function

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Abstract

Glucagon-like peptide 1 (GLP-1) receptor agonists result in greater improvements in glycemic control than placebo and promote weight loss with minimal hypoglycemia in patients with type 2 diabetes mellitus. A number of case reports show an association of GLP-1 receptor agonists, mainly exenatide, with the development of acute kidney injury. The present review aims to present the available data regarding the effects of GLP-1 receptor agonists on renal function, their use in subjects with chronic renal failure and their possible association with acute kidney injury. Based on the current evidence, exenatide is eliminated by renal mechanisms and should not be given in patients with severe renal impairment or end stage renal disease. Liraglutide is not eliminated by renal or hepatic mechanisms, but it should be used with caution since there are only limited data in patients with renal or hepatic impairment. There is evidence from animal studies that GLP-1 receptor agonists exert protective role in diabetic nephropathy with mechanisms that seem to be independent of their glucose-lowering effect. Additionally, there is evidence that GLP-1 receptor agonists influence water and electrolyte balance. These effects may represent new ways to improve or even prevent diabetic nephropathy.

Core tip: Glucagon-like peptide 1 (GLP-1) receptor agonists improve glycemic control in patients with type 2 diabetes mellitus. A number of case reports show an association of GLP-1 receptor agonists, mainly exenatide, with the development of acute kidney injury. Exenatide is eliminated by renal mechanisms, but liraglutide is not eliminated by renal or hepatic mechanisms. GLP-1 receptor agonists exert protective role in animal models of diabetic nephropathy. The effects of these drugs may represent new ways to improve or even prevent diabetic nephropathy, but their exact mechanism of action need to be elucidated.

INTRODUCTION

Increased glucose states are associated with many cardiovascular and renal complications[1-5]. Furthermore, the incidence of type 2 diabetes mellitus (T2DM) is increasing dramatically and is associated with high morbidity and mortality rates[6,7]. Various drug therapies are used in the treatment of T2DM and its complications[8,9]. Recent evidence has demonstrated the beneficial effects of glucagon-like peptide-1 (GLP-1)-associated drugs in the treatment of T2DM[10].

  GLP-1 is an incretin hormone secreted by the small intestine in response to nutrient ingestion and degraded

by the enzyme dipeptidyl peptidase-IV (DPP-IV). GLP-1 acts through the GLP-1 receptor, which is a G-coupled protein receptor expressed in the gastrointestinal tract, but also in the nervous system, heart, vascular smooth muscles, proximal tubules and glomerulus of the kidney[11-13]. GLP-1 increases insulin secretion from pancreatic β-cells and reduces glucagon release from α-cells through induction of adenylate cyclase and cyclic adenosine monophosphate (cAMP) production[14,15]. GLP-1 also decreases gastric motility and emptying and increases the feeling of satiety[16,17]. GLP-1 has been associated with modulation of cardiovascular risk factors and atherosclerosis-related mechanisms, as well as with cardiomyocyte and neuronal cell protection[14,18,19].

GLP-1 receptor agonists extend the effects of endogenous GLP-1 by resisting enzymatic degradation[20]. The GLP-1 receptor agonist exendin-4 is a 39-amino acid peptide that was originally isolated from the salivary secretions of the Gila monster lizard[21]. It shares approximately 53% homology with the mammalian GLP-1, binds to the mammalian receptor and activates it for synthesis of GLP-1. A synthetic version of exendin-4, exenatide, is currently used for the treatment of T2DM. The extended activity of liraglutide, the second GLP-1 receptor agonist used for the treatment of T2DM, is due to structural modifications of the human GLP-1 peptide aiming to increase its circulating time[20].

The administration of GLP-1 receptor agonists results in greater improvements in glycemic control than placebo when administered as monotherapy or in combination with one or two oral antidiabetic drugs in patients with T2DM. Moreover, these drugs promote weight loss with minimal hypoglycemia and seem to exert a number of other pleiotropic effects on cardiovascular complications of T2DM and diabetic nephropathy[22-25]. However, there are concerns regarding the long-term consequences of incretin-associated therapies, which are focused on the lack of evidence on long-term cardiovascular effects and issues raised regarding possible side effects, such as the development of acute pancreatitis, chronic pancreatitis, pancreatic cancer and thyroid cancer[26-30]. Furthermore, there are a number of reports associating the use of these drugs with the development of acute kidney injury[31,32].

The present review aims to present the available data regarding the effects of GLP-1 receptor agonists on renal function, their use in subjects with chronic renal failure and their possible association with acute kidney injury.

A PubMed/Scopus search was performed up to June 2013 using combinations of "glucagon-like peptide-1 receptor agonists" with the following keywords: exendin-4, exenatide, liraglutide, glucagon-like peptide-1, renal function, renal impairment, acute kidney injury, diabetic nephropathy, electrolytes, sodium, potassium, adverse effects. Randomised controlled trials, original papers, review articles and case reports are included in the present review. References of these articles were scrutinised for relevant articles.

EXENATIDE

Effects of renal impairment on the metabolism of exenatide

Exenatide is eliminated primarily *via* the kidneys[33]. Studies in pigs have shown that exenatide is cleared by glomerular filtration[34].

In an open-label study, 31 subjects (one with T2DM) were given exenatide 5 or 10 μg subcutaneously and divided in normal renal function group (Cockcroft-Gault creatinine clearance > 80 mL/min, n = 8), mild renal impairment group (51-80 mL/min, n = 8), moderate renal impairment group (31-50 mL/min, n = 7) or end-stage renal disease (ESRD) requiring hemodialysis group (n = 8)[35]. Mean exenatide clearance was substantially reduced in subjects with ESRD (0.9 L/h) compared with the control group (3.4 L/h). Mean half-life of exenatide was 1.5 h in subjects with normal renal function, 2.1 h in patients with mild renal impairment, 3.2 h in patients with moderate renal impairment and 6 h in ESRD patients. The most common treatment-emergent adverse events were vomiting, nausea and headache. Although exenatide clearance was decreased by 13% in the mild renal impairment group compared with subjects with normal renal function, the tolerability of exenatide 10 μg was acceptable and, consequently, this reduction in clearance did not seem clinically relevant. Exenatide clearance was decreased by 36% in patients with moderate renal impairment, but these patients also tolerated well both exenatide doses of 5 and 10 μg. Patients with ESRD had significantly reduced clearance of exenatide by 84% and did not tolerate well the 5 μg exenatide dose. Hence, no dosage adjustment of exenatide is required for patients with mild to moderate renal impairment, but the recommended starting dosage of 5 μg exenatide may not be suitable for patients with ESRD or severe renal impairment (creatinine clearance < 30 mL/min)[35].

Interestingly, a placebo-controlled, crossover study randomized elderly patients (≥ 75 years, n = 15) or controls (≥ 45 to ≤ 65 years, n = 15) with T2DM to single subcutaneous doses of exenatide 5 μg, exenatide 10 μg or placebo before a standardized breakfast over three consecutive days[36]. Although the dose-normalized plasma maximum concentration and exposure of exenatide were greater in elderly patients, no statistically significant between-age group differences were observed. These results imply that exenatide dose adjustments should be based on renal function rather than age in elderly T2DM patients[36] (Table 1).

Exenatide-induced acute kidney injury

There are a number of case reports associating exenatide with the development of acute kidney injury[37-39]. The United States Food and Drug Administration (FDA) reported that between April 2005 and October 2008 there were 78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency) with exenatide[32]. Also, there was incomplete recovery of kidney function in many patients. Some of these cases

Table 1 Studies of the effects of exenatide on renal function

Ref.	Study details	Main findings
Li *et al*[57]	Administration of exendin-4 in human mesangial cells.	Exendin-4 decreased mRNA and protein levels of TGF-β1 and connective tissue growth factor. These effects were mainly dependent on the activation of adenylate cyclase[57].
Carraro-Lacroix *et al*[70]	Investigation of the role of exendin-4 in modulating the activity of Na$^+$/H$^+$ exchanger NHE3 in LLC-PK(1) cells.	GLP-1 receptor agonists modulate sodium homeostasis most likely by affecting NHE3 activity.
Liu *et al*[60]	*In vitro* administration of exendin-4 in spontaneously hypertensive rat renal arteries and aortic endothelial cells. Additionally, exendin-4 administration in renal arteries from hypertensive patients.	*In vitro* exendin-4 improved endothelium-dependent relaxation and restored renal blood flow in spontaneously hypertensive rat renal arteries and increased nitric oxide production in spontaneously hypertensive rat aortic endothelial cells[60]. *Ex vivo* exendin-4 administration improved endothelial function of renal arteries from hypertensive patients.
Park *et al*[58]	Administration of exendin-4 for 8 wk in a mouse model of diabetes (male *db/db* mice).	Exendin-4 improved intraperitoneal glucose tolerance test and decreased urinary albumin excretion in a dose-dependent manner. It also reduced glomerular hypertrophy, mesangial matrix expansion, TGF-β1 expression and type Ⅳ collagen accumulation, whereas it increased the renal immunoreactivity of peroxisome proliferator-activated receptor α and GLP-1 receptor-positive cells in the glomeruli of *db/db* mice.
Kodera *et al*[59]	Administration of exendin-4 in a streptozotocin-induced rat model of type 1 diabetes.	Exendin-4 improved albuminuria, glomerular hyperfiltration, glomerular hypertrophy and mesangial matrix expansion, reduced macrophage infiltration and protein levels of intercellular adhesion molecule-1 and type Ⅳ collagen and decreased oxidative stress and nuclear factor-κB activation in kidney tissue of the diabetic rats.
Mima *et al*[61]	Mice overexpressing protein kinase Cβ2 (results in a reduction of GLP-1 receptor expression) in endothelial cells (EC-PKCβ2Tg).	*In vivo* treatment with exendin-4 was partially effective to reduce glomerular pathology of both diabetic wild type and EC-PKCβ2Tg mice.
Hirata *et al*[62]	Exendin-4 for 12 wk in *db/db* mice (they have increased intra-renal angiotensin Ⅱ concentration) and in angiotensin Ⅱ-infused non-diabetic mice.	Exendin-4 inhibited the development of hypertension in *db/db* mice. Exendin-4 attenuated the delay of the urinary sodium excretion and elevation of blood pressure induced by a high-salt load. Exendin-4 prevented hypertension in angiotensin Ⅱ-infused non-diabetic mice.
Liu *et al*[64]	A peptide analogue with exenatide (AC3174) was given for 4 wk via subcutaneous infusion in Dahl salt-sensitive rats.	The combination of AC3174 with captopril produced the most effective improvement in renal morphology (reduction of extensive sclerosis) in high salt diet rats compared with monotherapy. The combination of AC3174 with captopril also reduced the deleterious effects of high salt on posterior wall thickness and left ventricular mass.
Vaghasiya *et al*[66]	Exenatide treatment (14 d) in T2DM rats with induced renal ischemia for 30 min followed by reperfusion for 24 h.	Exenatide treatment normalized serum creatinine phosphokinase activity, liver function enzymes and antioxidant enzymes such as glutathione, superoxide dismutase, catalase and glutathione peroxidase (all *P* < 0.01).
Rieg *et al*[72]	Parenteral exendin-4 in wild-type mice and in mice lacking GLP-1 receptor. Additionally, administration of exendin-4 in diabetic *db/db* mice.	Parenteral exendin-4 in wild-type mice induced diuresis and natriuresis. These effects were associated with renal membrane expression of the Na$^+$/H$^+$ NHE3, a site for cAMP-dependent protein kinase A. These effects were abolished in mice lacking the GLP-1 receptor. The administration of exendin-4 in diabetic *db/db* mice resulted in a reduction of renal fluid and Na$^+$ reabsorption.
Thomson *et al*[73]	Exenatide infusion in hydropenic male Wistar and Wistar-Froemter rats.	Exenatide infusion increased single-nephron glomerular filtration rate, early distal flow rate and urine flow rate and reduced proximal tubular reabsorption. These effects were observed without altering the efficiency of glomerulotubular balance, tubuloglomerular feedback responsiveness or the tonic influence of tubuloglomerular feedback.
Marina *et al*[78]	Exenatide administration in Wistar rats with normal serum concentration of glucose and potassium and in Wistar rats with hyperkalemia produced by intraperitoneal injection of 1.25% KCl solution.	Exenatide increased renal excretion of potassium in Wistar rats with normal serum concentration of glucose and potassium. Exenatide enhanced excretion of potassium in Wistar rats with hyperkalemia.
Simonsen *et al*[34]	Exendin-4 administration in anesthetised pigs (*n* = 9).	Exenatide is solely cleared by glomerular filtration.
Linnebjerg *et al*[35]	Exenatide administration in 31 subjects (one with T2DM).	No dosage adjustment of exenatide is required for patients with mild to moderate renal impairment. In contrast, even the recommended starting dosage of 5 μg may not be suitable for patients with ESRD or severe renal impairment (creatinine clearance < 30 mL/min).
Linnebjerg *et al*[36]	Placebo-controlled, crossover study of elderly patients (≥ 75 yr, *n* = 15) or controls (≥ 45 to ≤ 65 yr, *n* = 15) with T2DM who received single subcutaneous doses of exenatide before a standardized breakfast.	Exenatide dose adjustments should be based on renal function rather than age in elderly T2DM patients.
Zhang *et al*[65]	31 patients with T2DM and microalbuminuria randomly received exenatide (*n* = 13) or glimepiride (*n* = 18) for 16 wk.	Similar reductions of fasting plasma glucose and HbA1c were observed between the two groups. Exenatide reduced body mass index (-5.95%), urinary type Ⅳ collagen and 24-h urinary albumin and urinary TGF-β1 (all *P* < 0.01).

Mendis *et al*[74]	Double-blind, randomized, crossover study of a single 10 μg subcutaneous injection of exenatide in healthy male volunteers (*n* = 8).	Exenatide significantly increased after 2 h the urinary sodium/creatinine ratio compared with placebo (*P* < 0.05). Exenatide administration was also associated with a significant increase of heart rate (+ 8.2 beats/min) and cardiac output, whereas a reduction in total peripheral resistance was observed (all *P* < 0.05). No change in blood pressure levels was observed.
US FDA[32]	Case reports of exenatide-induced acute kidney injury.	78 cases of altered kidney function (62 cases of acute renal failure and 16 cases of renal insufficiency) were reported with exenatide between April 2005 and October 2008.
Macconell *et al*[49]	Pooled analysis of 19 randomized, controlled trials of exenatide twice daily (5 μg and 10 μg) with 5594 intent-to-treat patients followed for 12-52 wk.	The incidence of renal impairment-related adverse events, including acute renal failure, was low (1.6 per 100 person-year for both groups) with no significant difference between groups (95%CI: -0.98-0.96). The most frequent adverse event with exenatide was transient, mild-to-moderate nausea (36.9% *vs* 8.3% in the pooled comparator).
Pendergrass *et al*[50]	Retrospective cohort of a large medical and pharmacy claims database including 491539 patients.	The adjusted risk for acute kidney injury among the patients with T2DM was not different between patients who received exenatide compared with patients who received other agents (hazard ratio = 0.77, 95%CI: 0.42-1.41, *P* = 0.40). Kaplan–Meier curves of time to acute kidney injury showed no significant differences between exenatide and other drugs.

TGF-β1: Transforming growth factor beta 1; GLP-1: Glucagon-like peptide 1; T2DM: Type 2 diabetes mellitus; ESRD: End-stage renal disease; FDA: Food and Drug Administration; NHE3: Exchanger isoform 3.

occurred in patients with pre-existing kidney disease. Ninety-five percent of the patients who experienced deterioration of kidney function had at least one risk factor for developing kidney problems, such as use of nephrotoxic medications, cardiac insufficiency or hypertension; these factors could have independently increased the risk for renal dysfunction[32].

In most reports the acute kidney injury seems to be due to exenatide-induced prerenal acute failure. Main side effects of exenatide administration are nausea and vomiting, which result in decreased fluid intake and a significant loss of fluids[40]. The resulting volume contraction may lead to acute renal failure. Effects of GLP-1 such as natriuresis and a possible decrease in renal perfusion may also play a role in the loss of fluids and impairment of renal function[41,42]. The exenatide-induced volume contraction is mainly seen in patients who receive drugs that inhibit the renin-angiotensin system and aldosterone formation, an important homeostatic mechanism in states associated with volume depletion[43]. Furthermore, uremia per se is associated with nausea and may lead to a vicious circle of renal function deterioration[44]. In agreement with the above mechanisms, Weise *et al*[45] reported that four patients with nausea and vomiting experienced deterioration of kidney function following treatment with exenatide. There was incomplete recovery of kidney function in three patients. A kidney biopsy, which was performed in one patient, revealed ischemic glomeruli with moderate to severe interstitial fibrosis and early diabetic nephropathy[45].

It should also be mentioned that other mechanisms of exenatide-induced acute kidney injury have been reported. For example, a 58-year-old man with poorly controlled T2DM was prescribed exenatide 5 μg twice daily as an alternative to treatment with insulin and experienced a deterioration in his kidney function[46]. Treatment with exenatide was initially associated with significant loss of weight (from 83 kg to 77 kg). However,

after 2 mo an increase in serum creatinine concentration [from 1.36 mg/dL (120 μmol/L) to 1.91 mg/dL (169 μmol/L)] was observed, despite the fact that the patient was systemically well, euvolemic and normotensive. He did not take any non-steroidal anti-inflammatory drugs or other non-prescribed medications. One month later, the serum creatinine concentration had increased to 2.36 mg/dL (209 μmol/L) and exenatide was stopped. There was further deterioration in his kidney function over the next month [(creatinine concentration 4.19 mg/dL (370 μmol/)] and treatment with indapamide, candesartan and amlodipine was stopped. His urine contained red and white blood cells. An ultrasound examination revealed two normal kidneys. There was no evidence of a skin rash and the full blood count was normal. A kidney biopsy revealed active, moderately severe diffuse tubulointerstitial nephritis. The inflammatory infiltrate included many eosinophils, implying a drug-induced reaction. There was active tubular damage with desquamation of epithelium. He was treated with prednisolone 50 mg daily and an improvement in kidney function was observed within a few days. Prednisolone was gradually reduced over the next few weeks to a daily dose of 10 mg with a further improvement in kidney function [creatinine concentration 1.98 mg/dL (175 μmol/L)][46].

Similarly, in 2010, Bhatti *et al*[47] reported that two patients had experienced deterioration in kidney function following treatment with exenatide. One patient had no clinical evidence of dehydration and no response to rehydration was seen. This patient had hematuria and proteinuria and interstitial nephritis was suspected; however, a kidney biopsy was not performed. The patient was treated with prednisolone and there was incomplete recovery of kidney function. The other patient had clinical evidence of dehydration and there was improvement in kidney function following rehydration[47].

Based on the above evidence FDA proposed that exenatide should not be used in patients with severe re-

Table 2	Studies of the effects of liraglutide on renal function	
Author	**Study details**	**Main findings**
Kim *et al*[89]	Liraglutide administration in *Glp1r*(-/-), *Nppa*(-/-) or wild type mice.	Liraglutide leaded to relaxation of aortic rings through a GLP-1 receptor-dependent but endothelium-independent manner. Liraglutide did not induce ANP secretion and did not result in vasorelaxation or blood pressure reduction in *Glp1r*(-/-) or *Nppa*(-/-) mice. Refeeding was associated with an increase in ANP levels in wild-type mice, whereas this effect was not observed in *Glp1r*(-/-) mice. Liraglutide administration led to increase of urine sodium excretion in wild-type, whereas this effect was abolished in *Nppa*(-/-) mice. These findings suggest a gut-heart axis, which is both GLP-1 receptor-dependent and ANP-dependent and regulates blood pressure.
Hendarto *et al*[90]	Liraglutide administration in streptozotocin-induced type 1 diabetes rats. Additionally, incubation of cultured renal mesangial cells with liraglutide for 48 h.	Liraglutide administration in streptozotocin-induced diabetic rats normalized the increased urinary albumin excretion and oxidative stress markers, as well as the expression of NADPH oxidase components, TGF-β1 and fibronectin in renal tissues. The incubation of cultured renal mesangial cells with liraglutide inhibited NADPH-dependent superoxide production in a dose-dependent manner, an effect that was abolished by a protein kinase A inhibitor and an adenylate cyclase inhibitor.
Malm-Erjefalt *et al*[82]	Administration of radio-labelled liraglutide in seven healthy males.	Liraglutide is metabolized by DPP-IV similarly with the native GLP-1, but at a much slower rate. No intact liraglutide was excreted in urine and feces.
Jacobsen *et al*[83]	A single dose of liraglutide 0.75 mg was given subcutaneously in 30 subjects (24 with varying degrees of renal impairment and 6 with normal renal function).	No significant effect of reduced creatinine clearance on the pharmacokinetics of liraglutide was observed. No association was found between the degree of renal impairment and the risk of adverse events.
Davidson *et al*[84]	A meta-analysis of the 6 LEAD (Liraglutide Effect and Action in Diabetes) studies which analysed data from patients with T2DM administered once-daily liraglutide (1.2 or 1.8 mg) or placebo as either monotherapy or in combination with oral antidiabetic drugs for 26 wk.	Mild renal impairment (determined by the Cockcroft-Gault equation) had no significant effect on the efficacy and safety of liraglutide. No significant differences in the rates of nausea, renal injury or minor hypoglycemia were observed between liraglutide and placebo in patients with mild renal impairment. No significant effect of mild renal impairment on HbA1c reduction was observed. However, a trend towards increased nausea was observed with liraglutide in the small number of patients with moderate or severe renal impairment.

GLP-1: Glucagon-like peptide 1; ANP: Atrial natriuretic peptide; TGF-β1: Transforming growth factor beta 1; DPP-IV: Dipeptidyl peptidase IV; T2DM: Type 2 diabetes mellitus; HbA1c: Glycated haemoglobin.

nal impairment (creatinine clearance < 30 mL/min) or ESRD and caution should be applied when initiating or increasing doses of exenatide from 5 to 10 μg in patients with moderate renal impairment (creatinine clearance 30-50 mL/min)[32]. Furthermore, the once weekly exenatide, which was recently approved by the FDA, is not recommended in patients with severe renal impairment or ESRD and caution is warranted in patients with renal transplantation or moderate renal impairment[48].

However, it should be mentioned that the reported cases of altered renal function with exenatide represent a small percentage of the total number of patients who have used the drug (more than 6.6 million prescriptions)[32]. Furthermore, recent analyses do not associate exenatide use and acute kidney injury. In a pooled analysis of 19 completed, randomized, controlled clinical trials of exenatide twice daily (5 or 10 μg) 5594 intent-to-treat patients who were followed for 12-52 wk were included[49]. Transient, mild-to-moderate nausea was the most frequent adverse event with exenatide (36.9% *vs* 8.3% in the pooled comparator). Renal impairment-related adverse events, including acute renal failure, were low (1.6 per 100 person-years for both groups) and no significant difference was observed between groups (95%CI: -0.98 to 0.96)[49]. Additionally, a retrospective cohort study of a large medical and pharmacy claims database including data for 491539 patients was recently published[50]. The unadjusted incidence rates of acute kidney injury were higher in patients with T2DM (1.13 cases/100 patient-

years) compared with the subjects without T2DM (0.34 cases/100 patient-years). The unadjusted incidence rates of acute kidney injury were similar between exenatide users (0.94 cases/100 patient-years) and the other T2DM patients (1.02 cases/100 patient-years). Moreover, the adjusted risk of acute kidney injury did not differ between patients who received exenatide and T2DM patients who received other agents (HR = 0.77, 95%CI: 0.42-1.41, *P* = 0.40). Similar results were observed when analysis was restricted to the patients with at least one risk factor for acute kidney injury [(exenatide user: HR = 0.52, 95%CI: 0.45-1.50), *P* = 0.40]. Finally, when Kaplan-Meier curves of time to acute kidney injury were used, no significant differences between the groups receiving exenatide or other drugs were observed[50] (Table 1).

Effects of exenatide on renal function
Effects on diabetic nephropathy: Diabetic nephropathy is histologically characterized by the accumulation of extracellular matrix proteins in the glomerular mesangium[51]. It has been shown that these processes are mediated by the transforming growth factor-beta 1 (TGF-β1), which is expressed in renal tissues of patients with diabetic nephropathy[52-54]. The TGF-β1 is a major fibrogenic growth factor in the pathogenesis of glomerulosclerosis and interstitial fibrosis, since it induces collagen and matrix synthesis and the expression of connective tissue growth factor, mRNA and proteins[55]. Hence, TGF-β1 is a useful marker of the fibrotic response[56].

Treatment with exendin-4 improves the renal interstitial fibrosis in culture and animal models of diabetic nephropathy. The administration of exendin-4 in human mesangial cells decreased the mRNA and protein levels of TGF-β1 and connective tissue growth factor, effects that were mainly dependent on the activation of adenylate cyclase[57]. In a mouse model of diabetes (male *db/db* mice) the administration of 1 nmol/kg exendin-4 for 8 wk resulted in improvement of intraperitoneal glucose tolerance test compared with the control group (*P* < 0.05)[58]. Fasting blood glucose, glycated hemoglobin (HbA1c) and creatinine concentrations did not significantly differ among db/db mice, whereas urinary albumin excretion was significantly decreased in a dose-dependent manner with exendin-4 compared with control db/db mice (*P* < 0.005). Renal histology studies showed that treatment with exendin-4 resulted in a significant reduction of glomerular hypertrophy, mesangial matrix expansion, TGF-β1 expression, type Ⅳ collagen accumulation and associated glomerular lipid accumulation. Furthermore, fewer infiltrating inflammatory and apoptotic cells together with an increase in the renal immunoreactivity of peroxisome proliferator-activated receptor α and GLP-1 receptor-positive cells were observed in the glomeruli of *db/db* mice treated with exendin-4 compared with control group[58]. The administration of exendin-4 (10 μg/kg per day) in a streptozotocin-induced rat model of type 1 diabetes did not significantly alter blood pressure or body weight, but resulted in improvement of albuminuria, glomerular hyperfiltration, glomerular hypertrophy and mesangial matrix expansion. A reduction in protein levels of intercellular adhesion molecule-1 and type Ⅳ collagen together with a decrease in macrophage infiltration, oxidative stress and nuclear factor-κB activation were also observed in the kidney tissue of diabetic rats[59].

Furthermore, there are other possible mechanisms that GLP-1 receptor agonists improve diabetic nephropathy. Exendin-4 *in vitro* improved endothelium-dependent relaxation and restored renal blood flow in spontaneously hypertensive rat renal arteries and increased nitric oxide production in spontaneously hypertensive rat aortic endothelial cells[60]. Furthermore, *ex vivo* exendin-4 administration improved endothelial function of renal arteries from hypertensive patients. It seems that GLP-1 receptor agonists improve endothelial function by restoring nitric oxide bioavailability[60].

Other authors have shown that the protective action of GLP-1 in glomerular endothelial cells is partly mediated *via* its own receptor by the activation of protein kinase A[61]. It was also proposed that the presence of T2DM induces the activation of protein kinase Cβ isoform, which results in a reduction of GLP-1 receptor expression and an increase of its degradation through ubiquitination and/or enhancement of angiotensin Ⅱ-mediated mechanisms[61]. Specifically, mice overexpressing protein kinase Cβ2 in endothelial cells (EC-PKCβ2Tg) had decreased GLP-1 receptor expression

and enhanced angiotensin Ⅱ-mediated effects. Although diabetes and hyperglycemia blunted *via* PKCβ activation the protective actions of GLP-1, treatment with exendin-4 *in vivo* was still partially effective to reduce glomerular pathology of both diabetic wild type and EC-PKCβ2Tg mice[61]. In this context, exendin-4 has been described to exert anti-hypertensive effects through the attenuation of angiotensin Ⅱ-mediated effects. A study showed that treatment with exendin-4 for 12 wk inhibited the development of hypertension in *db/db* mice with increased intra-renal angiotensin Ⅱ concentration[62]. Furthermore, exendin-4 attenuated the delay of urinary sodium excretion and the elevation of blood pressure induced by a high-salt load in *db/db* mice. Exendin-4 also prevented angiotensin Ⅱ-induced hypertension in angiotensin Ⅱ-infused non-diabetic mice[62]. Of note, a 2-h infusion of GLP-1 in 12 healthy young males was associated with a significant reduction of angiotensin Ⅱ levels with no parallel change in the concentration of renin and aldosterone or the urinary excretion of angiotensinogen[63].

There is also evidence of a beneficial role of the combination of GLP-1 receptor agonists with angiotensin converting enzyme inhibitors. A peptide analogue with exenatide (AC3174 1.7 pmol/kg per minute) was given for 4 wk *via* subcutaneous infusion in Dahl salt-sensitive (DSS) rats[64]. The administration of AC3174, captopril or AC3174 plus captopril improved renal function (*P* < 0.05), but the combination of AC3174 with captopril produced the most effective improvement in renal morphology (reduction of extensive sclerosis) in these high salt diet rats. The combination of AC3174 with captopril also reduced the deleterious effects of high salt on posterior wall thickness and left ventricular mass (*P* < 0.05). It should be mentioned that the administration of GLP-1 did not result in improvement of cardiovascular parameters and survival, implying that GLP-1 receptor agonists are more potent peptides or have at least partly different mechanism of action[64].

The effects of exenatide on diabetic nephropathy were examined in 31 patients with T2DM and microalbuminuria, who randomly received exenatide (*n* = 13) or glimepiride treatment (*n* = 18) for 16 wk[65]. Exenatide resulted in a significant reduction of body mass index (BMI) by 5.95% (from 24.9 to 23.3 kg/m²), whereas glimepiride treatment did not significantly alter BMI levels (-0.25%, from 24.8 to 24.7 kg/m²). Similar reductions of fasting plasma glucose and HbA1c were observed between the two groups. Exenatide resulted in a significant reduction of 24 h urinary albumin and urinary TGF-β1 (all *P* < 0.01), whereas these variables did not significantly change with glimepiride. Additionally, the excretion of urinary type Ⅳ collagen was significantly decreased with exenatide (-25.3%) compared with glimepiride (-1.6%, *P* < 0.005)[65].

Interestingly, a study showed that exenatide exerts protective effects on liver injury induced by renal ischemia reperfusion in diabetes[66]. Specifically, a previous treat-

ment with exenatide for 14 d in T2DM rats with induced renal ischemia for 30 min followed by reperfusion for 24 h significantly normalized serum creatinine phosphokinase activity, liver function enzymes and antioxidant enzymes such as glutathione, superoxide dismutase, catalase and glutathione peroxidase (all $P < 0.01$)[66].

Overall, GLP-1 receptor agonists seem to improve the histologic changes and markers of diabetic nephropathy. These effects seem promising for the treatment of T2DM patients. However, it should be mentioned that most of the evidence is based on animal studies and the extrapolation of these observations to human physiology should be done with caution.

Effects on water and electrolyte balance: Excreted sodium is re-absorbed by 60%-70% in the proximal nephron, mainly by the Na^+/H^+ exchanger isoform 3 (NHE3)[67]. GLP-1 receptors are expressed in the proximal tubule[68]. There is evidence from animal studies that GLP-1 modulates sodium homeostasis in the kidney *via* the GLP-1 receptor in proximal tubular cells. Specifically, GLP-1 administration in porcine proximal tubular kidney cells led to an inhibition of sodium re-absorption after 3 h of incubation. In contrast, the use of a DPP-Ⅳ inhibitor in combination with exendin-4 or GLP-1 did not alter significantly glucose and sodium uptake and transport[68].

It was also demonstrated that GLP-1 can stimulate renal excretion of sodium in rats and humans, most likely by affecting NHE3 activity[41,69,70]. The administration of GLP-1 in rats (1 μg/kg per minute intravenously for 60 min) increased urine flow, fractional excretion of sodium, potassium and bicarbonate and was accompanied by increases in renal plasma flow and glomerular filtration rate (GFR)[71]. GLP-1 receptor-mRNA expression was restricted to glomerulus and proximal convoluted tubule. It was also shown that GLP-1 significantly reduced NHE3-mediated bicarbonate reabsorption in rat renal proximal tubule, through a protein kinase A-dependent mechanism[71].

Another study reported that parenteral administration of exendin-4 in wild-type mice induced diuresis and natriuresis[72]. These effects were associated with increases in glomerular filtration rate, fractional urinary fluid and Na^+ excretion. Furthermore, these effects were associated with renal membrane expression of the NHE3, a site for cAMP-dependent protein kinase A. These effects were abolished in mice lacking the GLP-1 receptor and were independent of adenylate cyclase 6. Of interest, the administration of parenteral DPP-Ⅳ inhibitor alogliptin in these wild-type mice induced diuresis and natriuresis, which were independent of the presence of the GLP-1 receptor or alterations in the phosphorylated NHE3. These results may imply mechanistic differences between exendin-4 and DPP-Ⅳ inhibition in the induction of diuresis and natriuresis under normal states. Notably, the administration of exendin-4 in diabetic *db/db* mice resulted in a reduction of renal fluid and Na^+

reabsorption, whereas these effects were not observed when diabetic *db/db* mice were given alogliptin. These results imply significant differences between exendin-4 and DPP-Ⅳ inhibition in a T2DM mice model, since GLP-1 receptor-mediated natriuretic mechanisms were preserved, whereas DPP-Ⅳ inhibitor-dependent mechanisms were abolished[72].

A recent study described a role of exenatide as a proximal diuretic and renal vasodilator[73]. Exenatide infusion (1 nmol/h *iv*) in hydropenic male Wistar and Wistar-Froemter rats increased single-nephron glomerular filtration rate by 33%-50%, reduced proximal tubular reabsorption by 20%-40%, doubled early distal flow rate and increased urine flow rate six-fold without altering the efficiency of glomerulotubular balance, tubuloglomerular feedback responsiveness or the tonic influence of tubuloglomerular feedback[73].

A recent randomized, double-blinded, single-day, crossover trial showed that the infusion of GLP-1 for 2 h in 12 healthy young males increased renal sodium clearance by 40% ($P = 0.007$) and decreased angiotensin Ⅱ levels by 19% ($P = 0.003$), whereas no change in renin, aldosterone or the urinary excretion of angiotensinogen was observed[63]. The infusion of GLP-1 did not significantly alter the GFR (assessed with ^{51}Cr-EDTA), renal plasma flow (assessed with ^{123}I-hippuran) or blood pressure levels, but induced a small transient increase in heart rate[63]. In another study the urinary sodium/creatinine ratio was significantly increased (12.4 mmol/mmol, 95%CI: 4.6-20.2, $P < 0.05$) compared with placebo 2 h after a single 10 μg subcutaneous injection of exenatide in eight healthy male volunteers[74]. Furthermore, exenatide administration was associated with a significant increase of heart rate (8.2 beats/min, 95%CI: 4.2-12.2, $P < 0.01$) and cardiac output (1.2 L/min, 95%CI: 0.42-20.3, $P < 0.05$), whereas a reduction in total peripheral resistance ($P < 0.05$) was observed. These effects were not linked with any change in blood pressure levels[74]. Therefore, exenatide has both vasodilator and natriuretic properties. Although the effects of short-time administration of exenatide were not associated with significant changes in blood pressure levels, they may be related with the reduction in blood pressure that was observed in clinical studies examining the use of GLP-1 receptor agonists in patients with T2DM[75,76].

Furthermore, a possible role of exenatide in the human osmoregulation system has been proposed. A study (article in Russian, so no more details than the abstract could be used) showed that water load of 0.7% of body weight caused significant increase in urine excretion in 55 subjects (38 patients with T2DM)[77], but the rise of diuresis was depended on the increase in solute-free water clearance when exenatide 10 μg was administered with the water load[77].

Finally, there is evidence of a possible role of exenatide in the normalization of potassium balance *via* renal mechanisms. The administration of exenatide (0.015-0.5 nmol/100 g body weight) to Wistar rats with

normal serum concentration of glucose and potassium increased renal excretion of potassium from 7 ± 1 to 16 ± 1 μmol/h per 100 g body weight ($P < 0.05$)[78]. Moreover, exenatide enhanced excretion of potassium in Wistar rats with hyperkalemia produced by intraperitoneal injection of 1.25% KCl solution; specifically, during the first post-injection hour, potassium excretion was increased from 47 ± 9 μmol/h per 100 g body weight with potassium load alone to 97±11 μmol/h per 100 g body weight with exenatide ($P < 0.05$)[78] (Table 1).

LIRAGLUTIDE

Effects of renal impairment on liraglutide metabolism
Liraglutide shares a 97% structural homology with human GLP-1, has a longer half-life than the native hormone and undergoes a generalized proteolysis without elimination *via* the kidneys[33,79-81]. A study in seven healthy males who received radio-labelled liraglutide showed that liraglutide is metabolized by DPP-Ⅳ and neutral endopeptidase, similarly with the native GLP-1 but at a much slower rate. Furthermore, the results of this study showed that liraglutide is mainly degraded within the body since no intact liraglutide was excreted in urine and feces[82].

Renal impairment does not alter significantly the pharmacokinetic profile of liraglutide[33]. In a study a single dose of liraglutide 0.75 mg subcutaneously was given in 30 subjects, 24 with varying degrees of renal impairment and six with normal renal function[83]. The regression analysis of log [area under the curve (AUC)] of liraglutide for subjects with normal renal function and mild-to-severe renal impairment did not show any significant effect of reduced creatinine clearance on the pharmacokinetics of liraglutide. Furthermore, the AUC ratio of the subject with the lowest and the subject with the highest creatinine clearance was not significant (0.88, 95%CI: 0.58-1.34, $P > 0.05$). It should be mentioned that the between-group comparisons of the AUC of liraglutide did not show equivalence, since the estimated ratio of AUC(severe)/AUC(healthy) was 0.73 (90% 0.57-0.94) and the ratio of AUC(continuous ambulatory peritoneal dialysis)/AUC(healthy) was 0.74 (90%CI: 0.56-0.97). However, no association was found between the degree of renal impairment and the risk of adverse events[83]. Based on this study, liraglutide can be used safely in patients with varying degrees of renal impairment.

A meta-analysis of the 6 LEAD (Liraglutide Effect and Action in Diabetes) studies analysed data from patients with T2DM administered once-daily liraglutide (1.2 or 1.8 mg) or placebo as either monotherapy or in combination with oral antidiabetic drugs for 26 wk. The patients were grouped as having normal renal function (Cockcroft-Gault creatinine clearance > 89 mL/min), mild renal impairment (60 mL/min ≤ creatinine clearance ≤ 89 mL/min) and moderate or severe renal impairment (creatinine clearance < 60 mL/min)[84]. Liraglutide administration was well tolerated in patients with mild renal impairment since no significant differences in the rates of nausea, renal injury or minor hypoglycemia were observed compared with placebo. No significant effect of mild renal impairment on HbA1c reduction was observed. However, a trend towards increased nausea was observed with liraglutide in the small number of patients with moderate or severe renal impairment. Overall, this meta-analysis showed that mild renal impairment (determined by the Cockcroft-Gault equation) did not have a significant effect on the efficacy and safety of liraglutide[84].

However, the long-term data regarding the use of liraglutide in patients with moderate-to-severe renal impairment is limited. Hence, the summary of product characteristics of liraglutide proposes no dose adjustment for patients with mild renal impairment (creatinine clearance 60-90 mL/min), but does not recommend the use of the drug in patients with moderate and severe renal impairment including patients with ESRD[85].

A randomised, placebo-controlled, double-blinded trial aiming to test safety and efficacy of treatment with liraglutide in patients with T2DM and dialysis-dependent ESRD was recently announced[86]. In this trial 20 patients with T2DM and ESRD and 20 matched patients with T2DM and normal kidney function will receive liraglutide for 12 wk (9 visits) in an individually titrated dose of 0.6, 1.2 or 1.8 mg/d or placebo. The primary endpoint is dose-corrected plasma trough liraglutide concentration at the final trial visit aiming to determine potential accumulation in the ESRD group. Glycemic control, β-cell response, cardiovascular parameters, various biomarkers and adverse events will also be assessed[86] (Table 2).

Liraglutide-induced acute kidney injury
A case report described a 53-year-old Caucasian woman who had started 1 mo earlier subcutaneous liraglutide 1.8 mg/d for uncontrolled T2DM and was admitted with serum creatinine concentration of 22.8 mg/dL and blood urea nitrogen of 150 mg/dL[87]. She had lost 8.9 kg in the previous month after severe and progressively worsening gastrointestinal symptoms leading to dehydration. Other potential causes of renal failure and adverse drug reactions due to other drugs such as ciprofloxacin and quinapril were ruled out by laboratory investigation and renal biopsy. Renal biopsy showed that liraglutide was a likely cause of acute kidney injury through the development of acute tubular necrosis. The patient was treated with discontinuation of liraglutide, volume repletion, and hemodialysis[87].

Another case report described a 56-year-old man with T2DM who started liraglutide aiming to a gradual reduction of insulin because of hypoglycemic episodes[88]. Three months later the patient reported that his early morning glucose levels were elevated and he had nocturia. Laboratory results revealed an increase in his creatinine concentration [from 1.1 mg/dL (101 μmol/L) to 1.56 (138 μmol/L)]. Liraglutide, ramipril, indapamide and metformin were stopped and insulin was restarted.

His renal function was completely recovered a few weeks later. Similarly, a 65-year-old man receiving liraglutide had polyuria and polydipsia. His HbA1c was 12.9% and his urine dipstick showed glycosuria. Laboratory results revealed an increase in his serum creatinine [1.8 mg/dL (159 µmol/L)]. Liraglutide was discontinued and insulin was initiated. Serum creatinine levels returned to normal [1.2 mg/dL (109 µmol/L)] after 5 wk of withholding liraglutide. After 2 mo of initiation of insulin his HbA1c dropped by 1.9%. The most likely mechanism for the renal impairment in these patients is volume depletion causing renal impairment[88].

Overall, despite these case reports, liraglutide seems to be a safe drug in terms of kidney function. However, clinicians should be cautious in patients receiving liraglutide and have uncontrolled T2DM with polyuria and polydipsia or have symptoms that predispose to volume depletion (for example vomiting) (Table 2).

Effects of liraglutide on renal function

A recent study in mice showed that GLP-1 receptors are localized and expressed in cardiac atria[89]. Furthermore, it was shown that GLP-1 receptor activation is associated with the secretion of atrial natriuretic peptide (ANP) and a reduction of blood pressure. Specifically, liraglutide did not induce ANP secretion and did not result in vasorelaxation or blood pressure reduction in *Glp1r(-/-)* or *Nppa(-/-)* mice. Moreover, refeeding was associated with an increase in ANP levels in wild-type mice, whereas this effect was not observed in *Glp1r(-/-)* mice. On the other hand, liraglutide administration increased urine sodium excretion in wild-type mice, whereas this effect was abolished in *Nppa(-/-)* mice. These findings suggest a gut-heart axis that regulates blood pressure, which is both GLP-1 receptor-dependent and ANP-dependent. Furthermore, it was shown that liraglutide leaded to relaxation of aortic rings through a GLP-1 receptor-dependent, indirect ANP-dependent and endothelium-independent manner, since a conditioned medium from liraglutide-treated hearts resulted in relaxation of aortic rings but did not directly increase the amount of cyclic guanosine monophosphate (cGMP, associated with the function of ANP) or relax pre-constricted aortic rings. There is evidence that the Rap guanine nucleotide exchange factor Epac2 (also known as Rapgef4, an exchange protein activated by cAMP) may mediate the association of GLP-1 receptor activation and ANP secretion, since cardiomyocyte GLP-1 receptor activation induced the translocation of the Epac2 to the membrane, whereas Epac2 deficiency did not induce ANP secretion through GLP-1 receptor stimulation[89].

A study showed that liraglutide inhibits oxidative stress and albuminuria in streptozotocin-induced type 1 diabetes mellitus rats through a protein kinase A-mediated inhibition of renal NADPH oxidases[90]. Specifically, diabetic rats were randomly treated with liraglutide (0.3 mg/kg 12 h subcutaneously) for 4 wk. The administration of liraglutide normalized the increased urinary albu-

min excretion and oxidative stress markers, as well as the expression of NADPH oxidase components, TGF-β1 and fibronectin in renal tissues, without affecting plasma glucose levels or body weight of streptozotocin-induced diabetic rats. Additionally, the authors conducted *in vitro* experiments which showed that incubation of cultured renal mesangial cells with liraglutide for 48 h inhibited NADPH-dependent superoxide production in a dose-dependent manner, an effect that was abolished by a protein kinase A inhibitor and an adenylate cyclase inhibitor[90].

Another study evaluated the effects of liraglutide on tumour necrosis factor-α-induced injury of the human umbilical vein endothelial cells and showed that the drug inhibits protein kinase A, NADPH oxidase and nuclear factor-κB signaling and upregulates protective antioxidative enzymes. Consequently, liraglutide exerts significant anti-oxidative and anti-inflammatory effects on endothelial cells[91]. If these protective effects are also evident in renal cells remains to be established (Table 2).

CONCLUSION

Chronic kidney disease is a common complication of T2DM resulting in a progressive deterioration of renal function[92]. However, many of the antidiabetic drugs are contraindicated or require dosage adjustments in patients with renal impairment. Based on the current evidence, exenatide should not be given in patients with severe renal impairment or ESRD because the drug is eliminated by renal mechanisms. Liraglutide, although it is not eliminated by renal or hepatic mechanisms, should be used with caution since there are only limited data in patients with renal or hepatic impairment[80,81,93].

Furthermore, current evidence shows that these drugs exert protective role in diabetic nephropathy with mechanisms that many times are independent of their glucose-lowering effect. GLP-1 receptor agonists have also been shown to influence water and electrolyte balance. Although most of these effects have been demonstrated in culture or animal models and their mechanism of action need to be better elucidated, they may represent new ways to improve or even prevent diabetic nephropathy. It should be mentioned that animal studies should be interpreted with caution, since a number of drugs evaluated in rodents with induced diabetes were ineffective in clinical trials (for example the advanced glycation endproduct inhibitors).

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