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GLP-1 receptor agonists in diabetic kidney disease: current evidence and future directions

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With the emergence of various classes of blood glucose-lowering agents, choosing the appropriate drug for each patient is emphasized in diabetes management. Among incretin-based drugs, glucagon-like peptide 1 (GLP-1) receptor agonists are a promising therapeutic option for patients with diabetic kidney disease (DKD). Several cardiovascular outcome trials have demonstrated that GLP-1 receptor agonists have beneficial effects on cardiorenal outcomes beyond their blood glucose-lowering effects in patients with type 2 diabetes mellitus (T2DM). The renal protective effects of GLP-1 receptor agonists likely result from their direct actions on the kidney, in addition to their indirect actions that improve conventional risk factors for DKD, such as reducing blood glucose levels, blood pressure, and body weight. Inhibition of oxidative stress and inflammation and induction of natriuresis are major renoprotective mechanisms of GLP-1 analogues. Early evidence from the development of dual and triple combination agents suggests that GLP-1 receptor agonists will probably become popular treatment options for patients with T2DM.

Keywords: Diabetic nephropathies, Glucagon-like peptide 1, Type 2 diabetes mellitus

Introduction

The number of patients with diabetes mellitus (DM) continues to increase worldwide, and DM is the main cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1]. In Korea, the prevalence of diabetes was 13.8% in adults older than 30 years in 2018 [2], and it was predicted to be 29.2% in men and 19.7% in women by 2030 [3]. The total number of new patients who started renal replacement therapy (RRT) for ESRD increased from 10,000 in 2011 to 18,642 in 2019 [4], and the proportion of patients with DM as the underlying cause of ESRD increased from 19.5% in 1992 to 50.6% in 2012 [5], making DM the most common cause of ESRD in Korea [4]. Despite advances in medical technology and treatments, the need for RRT is increasing worldwide and is expected to more than double by 2030 compared with 2010 [6].

Diabetic kidney disease (DKD) is the main cause of morbidity and mortality in diabetes [7,8]. Therefore, inhibiting the onset and progression of DKD, in part by developing therapeutic approaches to prevent or delay it, is critical. Controlling blood sugar and blood pressure using

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angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is the current goal in DKD management [9], and no special drugs or other therapeutic options are widely used to delay DKD progression. However, several cardiovascular outcome trials (CVOTs) have demonstrated that sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have beneficial effects on cardiorenal outcomes, especially in patients with type 2 DM (T2DM) who are at high risk for cardiovascular disease (CVD) [10–12]. Based on the results of clinical trials, the current guidelines of the American Diabetes Association and Korean Diabetes Association recommend that clinicians consider prescribing SGLT2 inhibitors or GLP-1 receptor agonists after metformin as part of the glucose-lowering regimen for patients with T2DM and CKD [13,14]. In this review article, we focus on GLP-1 agonists and discuss the clinical and preclinical evidence for their nephroprotective effects and the potential mechanisms underlying those effects.

Physiology and metabolic effects of glucagon-like peptide 1

Oral intake of glucose causes the secretion of more insulin than does an injection of glucose due to the presence of gut hormones called *incretins* [15]. Gastrointestinal peptide (GIP) and the GLPs (GLP-1, GLP-2) are incretin hormones produced by enteroendocrine L-cells of the distal small bowel and colon [16]. In humans, fasting concentration of total GLP-1 ranges from 5 to 10 pmol/L and can increase to 40–50 pmol/L in response to meals [17]. Plasma concentration of biologically active, intact GLP-1 is much lower than that (fasting, <2 pmol/L; peak postprandial concentrations, 5–10 pmol/L) [18].

GLP-1 release after a meal occurs in a biphasic manner. An initial rapid rise in circulating GLP-1 level occurs 15 to 30 minutes after a meal, followed by a second minor peak at 90 to 120 minutes [19,20]. The rapid increase in GLP-1 secretion after meals is related to the proximal-distal loop regulated by neurotransmitters such as acetylcholine and gastrin-releasing peptide [21]. The second later peak of GLP-1 is believed to occur as ingested nutrients travel down the lumen and interact directly with distal L-cells [22,23].

Native GLP-1 has an extremely short half-life, less than 2 minutes, due to cleavage by dipeptidyl-peptidase IV (DPP IV) enzymes and renal elimination [24]. DPP IV enzymes cleave the active forms of GLP-1^{7-36} and GLP-1^{7-37} to produce inactive GLP-1^{9-36} or GLP-1^{9-37}, respectively, which have low affinity for the GLP-1 receptor [25,26]. Only 10% to 15% of secreted GLP-1 reaches the pancreas via systemic circulation [25], and both the active and inactive forms of GLP-1 are rapidly cleared from the circulation via the kidneys. Although the initial DPP IV-mediated degradation of GLP-1 is unaffected by impairments in renal function, GLP-1 clearance is delayed in patients with renal insufficiency [24].

In humans, the GLP-1 receptor is expressed in the pancreas, lungs, brain, kidneys, stomach, and heart but not in the liver, skeletal muscle, or adipose tissue [27]. Binding between GLP-1 and its receptor activates adenylate cyclase, which is followed by increase in cyclic AMP level and cytoplasmic Ca^{+2} that induces insulin secretion [28]. In addition to GLP-1's short-term effect of enhancing the glucose-dependent stimulation of insulin secretion, continuous GLP-1 activation also increases insulin synthesis [29], modulates β-cell proliferation [30], and inhibits β-cell apoptosis [31] and glucagon release [32]. Incretin hormones also decrease gastric emptying [33], inhibit food intake [34], and increase natriuresis and diuresis [35,36].

Classification of glucagon-like peptide 1 receptor agonists

GLP-1 receptor agonists have two main backbone structures and are classified as exendin-4- or human GLP-1-based compounds [37]. They are divided into short- and long-acting agents, and some formulations are mixed with insulin (Table 1). Exendin-4 is a protein isolated in 1992 from the saliva of the Gila monster lizard (*Heloderma suspectum*) [38]. This protein is composed of 39 amino acids and has 53% similarity in base sequence to native human GLP-1. Exenatide and lixisenatide are based on the structure of exendin-4. Exenatide is a recombinant form of the peptide exendin-4 and was the first GLP-1 receptor agonist to be developed for T2DM treatment. Lixisenatide is an exendin-4 analog with an additional six lysines attached to the C-terminus, which gives it a longer half-life than exenatide. These exendin-4-based agents have relatively short half-lives (~3 hours) and strongly inhibit gastric emptying [39], which can cause gastrointestinal side-effects such as

Table 1. Characteristics of GLP-1 receptor agonists

Generic	Commercial	Backbone	Dosage	Administration	Half-life	Renal dose adjustment	Route of elimination
Short-acting compound							
Exenatide	Byetta	Exendin-4	5 μg, 10 μg	Twice daily, SC	~2.4 hr	Not recommended for patients with CrCl < 30 mL/min; caution needed for patients with CrCl 30–50 mL/min	Glomerular filtration followed by proteolysis; eliminated in the urine
Lixisenatide	Lyxumia	Exendin-4	10 μg, 20 μg	Once daily, SC	~3 hr	Not recommended for patients with CrCl < 30 mL/min	Glomerular filtration and proteolysis; excreted in the urine
Long-acting compound							
Liraglutide	Victoza	Human GLP-1	0.6–1.8 mg	Once daily, SC	~13 hr	No dosage adjustment required; not recommended for patients with CrCl < 15 mL/min	Proteolysis; excreted via urine and feces
Liraglutide	Saxenda	Human GLP-1	0.6–3 mg	Once daily, SC	~13 hr	No dosage adjustment required; not recommended for patients with CrCl < 15 mL/min	Proteolysis; excreted via urine and feces
Exenatide ER	Bydureon	Exendin-4	2 mg	Once weekly, SC	~1 wk	Not recommended for patients with an eGFR < 45 mL/min/1.73 m^2 or ESRD	Glomerular filtration followed by proteolysis; eliminated in the urine
Dulaglutide	Trulicity	Human GLP-1	0.75 mg, 1.5 mg	Once weekly, SC	~5 day	No dosage adjustment required; not recommended for patients with CrCl < 15 mL/min	Proteolytic degradation
Semaglutide	Ozempic	Human GLP-1	0.5 mg, 1.0 mg	Once weekly, SC	~1 wk	No dosage adjustment required; not recommended for patients with CrCl < 15 mL/min	Proteolysis; excreted via urine and feces
Albiglutide[a]	Tanzeum	Human GLP-1	30 mg, 50 mg	Once weekly, SC	~5 day	No dosage adjustment required; not recommended for patients with CrCl < 15 mL/min	Not available
Oral agent							
Semaglutide	Rybelsus	Human GLP-1	3 mg, 7 mg, 14 mg	Once daily, oral	~1 wk	No dosage adjustment required	Proteolysis; excreted via urine and feces
Fixed-dose combination							
Lixisenatide + glargine	Soliqua	Exendin-4	20 μg/iGlar 40 IU, 20 μg/iGlar 60 IU	Once daily, SC	~3 hr	Closely monitor patients with CrCl 15–30 mL/min; not recommended for patients with CrCl < 15 mL/min	Glomerular filtration and proteolysis; excreted in the urine
Liraglutide + degludec	Xultophy	Human GLP-1	1.8 mg/iDeg 50 IU	Once daily, SC	~13 hr	Not studied in severe renal impairment; liraglutide is not recommended for patients with CrCl < 15 mL/min	Proteolysis; excreted via urine and feces

CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; ER, extended-release; ESRD, end-stage renal disease; GLP-1, glucagon-like peptide-1; iDeg, insulin degludec; iGlar, insulin glargine; SC, subcutaneous.

[a]Marketing was discontinued in 2018.

nausea. But they also have robust postprandial antihyperglycemic effects and could potentially replace rapid-acting mealtime insulin [39]. These shorter-acting agents are less effective at decreasing fasting glucose levels because of their short half-lives.

Human GLP-1–based agents are more structurally similar to native GLP-1 than to those based on exendin-4. They have 90% to 97% amino-acid homology to endogenous human GLP-1 and an extended half-life conferred by DPP IV resistance and noncovalent binding to serum albumin. These longer-acting agents lead to a greater reduction of fasting plasma glucose and hemoglobin A1c (HbA1c) levels than the shorter-acting agents [39,40]. The human GLP-1 compounds are liraglutide, albiglutide, dulaglutide, and semaglutide, all of which are injectable agents. Albiglutide and dulaglutide are large molecules conjugated to large proteins, which extends their half-life and enables once-weekly administration. Semaglutide is available in both injectable and oral forms. With withdrawal of albiglutide from the market for commercial reasons, liraglutide, dulaglutide, and semaglutide (oral and subcutaneous) are the currently available, approved human GLP-1 receptor agonists.

Table 1 shows the recommended uses of GLP-1 receptor agonists according to estimated glomerular filtration rate (eGFR). Human GLP-1–derived dulaglutide, liraglutide, and semaglutide are not excreted via the kidneys and can be used down to an eGFR of 15 mL/min/1.73 m^2; there is insufficient experience to recommend using those agents for eGFR values lower than that [41]. Conversely, exenatide and lixisenatide, which are eliminated by the kidneys, are contraindicated below an eGFR of 30 mL/min/1.73 m^2 due to the risk of accumulation and toxicity [24]. Exenatide should be used with caution in patients with an eGFR of 30–50 mL/min/1.73 m^2 (Table 1).

Renal effects of glucagon-like peptide 1 receptor agonists in patients with type 2 diabetes mellitus

Several CVOTs have examined GLP-1 receptor agonists; however, none have focused on the primary endpoint of renal events; renal outcomes have been reported as secondary outcomes after primary cardiovascular outcomes. This section focuses on the renal outcomes of GLP-1 receptor agonist treatment reported by randomized controlled trials (Table 2).

The first CVOT for a GLP-1 receptor agonist was the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) trial, the results of which were published in 2015 [42]. A total of 6,068 participants with T2DM, history of myocardial infarction or unstable angina, average baseline HbA1c of 7.7%, and a median follow-up of 25 months was enrolled. Although renal events were not investigated in the primary ELIXA trial, an exploratory analysis of renal outcomes was performed [43]. After a median follow-up of 108 weeks, lixisenatide reduced progression of the urinary albumin-to-creatinine ratio (UACR) in macroalbuminuric patients and was associated with a lower risk of new-onset macroalbuminuria after adjustment for baseline and on-trial HbA1c and other traditional renal risk factors. No significant differences in eGFR decline were identified between treatment groups. This study had a short follow-up period of 2 years, a high percentage of participants on statin therapy, and low compliance with the medication compared with the other trials in Table 2.

In the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial published in 2016 [44], participants with T2DM were either 50 years of age or older with at least one cardiovascular condition or 60 years or older with at least one cardiovascular risk factor. A total of 9,340 participants with a median follow-up of 3.8 years was enrolled, and the average baseline HbA1c was 8.7%. Approximately 23% of participants had moderate-to-severe CKD, suggesting a very high-risk population. Of note, this trial included 220 individuals with an eGFR of 15–30 mL/min/1.73 m^2. Liraglutide decreased the risk of the secondary composite renal endpoint (new-onset macroalbuminuria, sustained serum creatinine duplication, initiation of RRT, or renal death) by 22% (hazard ratio, 0.78; 95% confidence interval [CI], 0.67–0.92; p = 0.003) [45]. This finding was driven primarily by a reduction in new-onset persistent macroalbuminuria. That study was the first to show that a GLP-1 agonist had cardiovascular benefit, although it might not apply in patients with low cardiovascular risk.

The SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) was the next CVOT, also published in 2016 [46]. A total of 3,297 patients was randomly assigned, and 3,232 patients completed the trial over a median fol-

Table 2. Renal endpoints in cardiovascular outcome trials of GLP-1 receptor agonists

	ELIXA [42]	LEADER [44]	SUSTAIN-6 [46]	EXSCEL [48]	HARMONY [51]	REWIND [53]	PIONEER-6 [55]	AMPLITUDE-O [56]
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide ER	Albiglutide[a]	Dulaglutide	Semaglutide (oral)	Efpeglenatide
Participants (n)	6,068	9,340	3,297	14,752	9,463	9,901	3,183	4,076
Median follow-up (yr)	2.1	3.8	2.1	3.2	1.6	5.4	1.3	1.8
Baseline HbA1c (%)	7.7	8.7	8.7	8	8.7	7.2	8.2	8.9
Baseline BP (mmHg)	130	136/77	136/77	135/78	135/77	137/78	136/76	135/77
Established CVD (%)	100	81	83.0	73.1	100	31	84.7	89.6
Baseline eGFR < 60 mL/min/1.73 m^2 (%)	23.2	23.1	24.1	21.6	23.5	22.2	26.9	31.6
Baseline eGFR, mL/min/1.73 m^2	78	80	80	77	79	75	74	72
Albuminuria (%)	25.3	11.0	NA	22.0	NA	34.5	33	48.5
ACEI or ARB (%)	85.0	82.8	83.5	79.9	81.6	81.5	NA	80.0
Renal composite outcomes[b]	0.84 (0.68–1.02)	0.78 (0.67–0.92)	0.64 (0.46–0.88)	0.88 (0.76–1.01)	NA	0.85 (0.77–0.93)	NA	0.68 (0.57–0.79)
New-onset persistent macroalbuminuria[b]	0.81 (0.66–0.99)	0.74 (0.60–0.91)	0.54 (0.37–0.77)	0.87(0.70–1.07)	NA	0.77 (0.68–0.87)	NA	0.68 (0.58–0.80)
Persistent doubling of serum creatinine[b]	1.16 (0.74–1.83)	0.89 (0.67–1.19)	1.28 (0.64–2.58)	NA	NA	NA	NA	NA
End-stage renal disease[b]	NA	0.87 (0.61–1.24)	0.91 (0.40–2.07)	NA	NA	0.75 (0.39–1.44)	NA	NA
Death due to renal disease[b]	NA	1.59 (0.52–4.87)	NA	NA	NA	NA	NA	NA

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ER, extended-release; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; NA, not assessed.

[a]Marketing was discontinued in 2018. [b]Hazard ratio (95% confidence interval).

low-up of 2.1 years. Eighty-three percent of participants had established CVD, CKD, or both, and the mean HbA1c of the total study population was 8.7%. Once-weekly semaglutide effected a 36% reduction (HR, 0.64; 95% CI, 0.46–0.88; p = 0.005) in the secondary combined renal endpoint (new-onset macroalbuminuria, doubling of serum creatinine, eGFR of <45 mL/min/1.73 m^2, initiation of RRT, or renal death). This result was mainly driven by a reduction in new-onset macroalbuminuria. Across the SUSTAIN 1–7 trials [47], semaglutide lowered albuminuria compared with placebo beginning as early as 16 weeks and lasting over the entire treatment period.

The next trial, published in 2017, was the EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial to evaluate the effect of once-weekly exenatide extended-release (ER) on cardiovascular outcomes in participants with T2DM [48]. A total of 14,752 patients, of whom 73.1% had previous CVD, was followed for a median of 3.2 years. Exenatide ER had no significant effects on renal outcomes in an additional analysis of EXSCEL trial data [49]. Twice-daily exenatide also did not affect eGFR or albuminuria compared with insulin glargine over the 52-week study period [50].

The cardiovascular effects of albiglutide were evaluated in patients with T2DM and CVD in the HARMONY trial (NCT02465515) [51], published in 2018. A total of 9,463 participants with a median HbA1c of 8.7% was enrolled; this was a relatively high-risk population with high baseline glucose levels. After a median of 1.6 years of follow-up, albiglutide conferred no significant benefit in slowing the rate of eGFR decline.

The renal outcomes of dulaglutide treatment were investigated in two representative trials. The first study was the AWARD-7 trial (NCT01621178), published in 2018 [52]. Five hundred seventy-seven participants with T2DM and moderate-to-severe CKD were included in this trial. A once-weekly injection of dulaglutide was associated with a significantly smaller decline in eGFR compared with insulin glargine over 52 weeks. The mean eGFR decline with 1.5-mg dulaglutide was about 10% of that observed with insulin glargine (–0.5 mL/min/1.73 m^2 in the 1.5-mg dulaglutide group compared with –5.5 mL/min/1.73 m^2 in the insulin glargine group). This association between dulaglutide and reduced eGFR decline was most evident in participants with macroalbuminuria. Another study of the effects of injectable dulaglutide on cardiovascular outcomes in T2DM was the REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial [53,54], published in 2019. This study was designed to demonstrate superiority, unlike the previous trials. A total of 9,901 participants with T2DM was followed up for a median of 5.4 years, a longer period than in the previous trials. This trial was unique in that the participants were low risk, with an average baseline HbA1c of 7.2%, median eGFR of 74.9 mL/min/1.73 m^2, baseline prevalence of CVD of 31.5%, and baseline prevalence of albuminuria of 35.0%. The composite renal outcome occurred significantly less frequently in the dulaglutide group than in the placebo group (HR, 0.85; 95% CI, 0.77–0.93; p = 0.0004), and the largest effect was a reduction in the development of macroalbuminuria in the dulaglutide group (HR, 0.77; 95% CI, 0.68–0.87; p < 0.0001).

The PIONEER 6 (Peptide Innovation for Early Diabetes Treatment) trial was designed to evaluate the cardiovascular outcomes from once-daily oral semaglutide in T2DM patients at high cardiovascular risk [55], and its results were published in 2019. This study recruited 3,183 participants who were followed up for a median of 15.9 months, which is the shortest duration of the trials listed in Table 2. However, no renal endpoint was predefined for assessment in this trial.

The most recent CVOT for GLP-1 agonists was the AMPLITUDE-O (Effect of Efpeglenatide on Cardiovascular Outcomes) trial in patients with T2DM and a history of either CVD or CKD [56]; the results were published in 2021. Once-weekly injectable efpeglenatide is a new exendin-4-based GLP-1 receptor agonist. A total of 4,076 participants was enrolled and followed up for a median of 1.81 years. Compared with placebo, efpeglenatide led to a 32% lower risk of a composite renal outcome event (incident macroalbuminuria, increase in UACR of ≥30% from baseline, sustained decrease in eGFR of ≥40%, initiation of RRT, or sustained eGFR of <15 mL/min/1.73 m^2), independently of baseline use of SGLT2 inhibitors or metformin and baseline eGFR (HR, 0.68; 95% CI, 0.57–0.79; p < 0.001). However, a kidney function outcome event, defined as a composite of a decrease in eGFR of at least 40% for ≥30 days, ESRD, or death from any cause, did not differ between the efpeglenatide group and the placebo group (HR, 0.77; 95% CI, 0.57–1.02; p = 0.07).

Suggested nephroprotective mechanisms of glucagon-like peptide 1 receptor agonists

Indirect effects by improving conventional risk factors for diabetic kidney disease

Hyperglycemia plays a critical role in the pathogenesis of DKD [57,58], and GLP-1 receptor agonists have potent glucose-lowering effects [59–62]. The Kidney Disease: Improving Global Outcomes (KDIGO) 2020 clinical practice guidelines recommend GLP-1 receptor agonists as an excellent option for patients with DKD who have not achieved their glycemic target or as an alternative for patients unable to tolerate metformin or an SGLT2 inhibitor [63]. Although glucose-independent mechanisms are also emphasized, the antihyperglycemic effects of GLP-1 receptor agonists are thought to contribute to their nephroprotective effects in patients with DKD. Furthermore, GLP-1 receptor agonists induce reduction in body weight, blood pressure, and dyslipidemia, which could also contribute to their antialbuminuric effects [64,65].

In the LEADER trial [44], the liraglutide group showed a 0.4% reduction in HbA1c compared with the placebo group. Weight loss was 2.3 kg higher and systolic blood pressure was 1.2 mmHg lower in the liraglutide group than in the placebo group. In the REWIND trial [54], participants in the once-weekly 1.5-mg dulaglutide group had a 0.61% lower HbA1c, 1.46 kg lower body weight, and 1.7 mmHg lower systolic blood pressure than participants in the placebo group. In the SUSTAIN-6 trial [46], the mean HbA1c level was 1.0 percentage point lower, mean body weight was decreased by 4.3 kg more, and mean systolic blood pressure was 2.6 mmHg lower in the group receiving 1.0 mg of semaglutide once weekly than in the placebo group. In the PIONEER 5 trial [55], once-daily oral semaglutide (14 mg) was superior to placebo at reducing HbA1c and body weight in patients with T2DM. However, statistical correction for on-trial HbA1c level, blood pressure change, and bodyweight decrease did not significantly alter the observed decreases in albuminuria induced by GLP-1 receptor agonists in several CVOTs [66], suggesting that the renal protective effects of GLP-1 receptor agonists are not entirely due to improvements in risk factors.

In addition to its actions on body weight, blood pressure, and glucose, GLP-1 also regulates lipid metabolism. Dyslipidemia is a strong risk factor for both CKD and DKD. Experimental studies have provided data to support the notion that lipid abnormalities contribute to initiation and progression of glomerular disease [67]. A systematic review and meta-analysis of 35 trials showed that GLP-1 receptor agonists are associated with reductions in total and low-density lipoprotein cholesterol and triglyceride levels [68]. GLP-1 inhibits gastric lipase secretion [69] and intestinal lipoprotein and chylomicron production in humans [70]. GLP-1 receptor signaling reduces hepatic triglyceride content and impairs lipogenesis in the liver by stimulating the AMP-activated protein kinase pathway [71,72]. It also increases peripheral use of triglyceride-rich lipoproteins through increased burning of fat and activation of brown adipose tissue function [73,74]. However, it is uncertain whether those actions directly contribute to the nephroprotective effects of GLP-1 receptor agonists.

Potential direct mechanisms accounting for the renal protective effects of glucagon-like peptide 1 receptor agonists

The GLP-1 receptor is expressed in the renal cortex and vasculature, as well as proximal tubular cells [75,76], although uncertainties remain regarding receptor localization in the kidney due to lack of antibodies with high sensitivity and specificity. Inhibition of oxidative stress and inflammation, induction of natriuresis, and reduction of intraglomerular pressure are potential direct mechanisms underlying the renal protective effects of GLP-1 analogues (Fig. 1). Systemic oxidative stress increases the stage of incipient DKD [77]. A study in diabetic rats revealed that recombinant human GLP-1 attenuated oxidative stress in the glomeruli and in glomerular microvascular endothelial cells by inhibiting protein kinase C and activating protein kinase A (PKA) [78]. Liraglutide also reduced oxidative stress and albuminuria in streptozotocin-induced type 1 DM rats via PKA-mediated inhibition of renal nicotinamide adenine dinucleotide phosphate oxidases [79]. Exendin-4 was shown to activate the Nrf2 signaling pathway, which plays a key role in preventing oxidative stress and maintaining redox homeostasis, in vascular smooth muscle cells [80,81].

Inflammation plays a central role in the development of DKD. Accumulating experimental data suggest that anti-inflammatory activity underlies the nephroprotec-

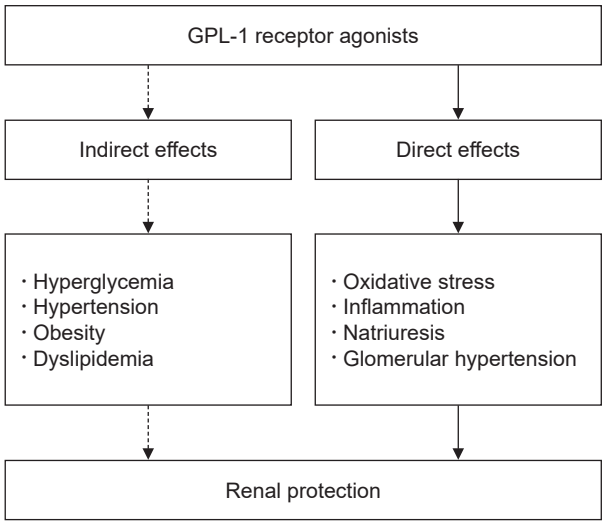

Figure 1. The mechanisms underlying the nephroprotective effects of GLP-1 receptor agonists.
GLP-1, glucagon-like peptide 1.

tive effects of GLP-1. GLP-1 receptor agonists decrease the production of proinflammatory cytokines, adhesion molecules, and profibrotic signaling [82–84]. Liraglutide inhibited renal tumor necrosis factor (TNF)-α-mediated nuclear factor kappa B (NF-κB) activation and mitogen-activated protein kinase pathway activation in the glomerular podocytes of an obesity-related glomerulopathy mouse model [82]. Exendin-4 attenuated albuminuria, glomerular hyperfiltration, glomerular hypertrophy, and mesangial matrix expansion without lowering blood glucose level in diabetic rats by inhibiting oxidative stress and NF-κB activation [83]. In humans, exenatide reduced reactive oxygen species generation and expression of NF-κB, TNF-α, interleukin-1β, c-Jun N-terminal kinase-1, toll-like receptor-4, and suppressor of cytokine signaling 3 in obese patients with T2DM, independent of weight loss [84]. Exenatide also reduced high-sensitivity C-reactive protein by 61% [85] and reduced urinary transforming growth factor-β_1 and type IV collagen excretion in patients with T2DM [86]. Liraglutide treatment was associated with decreased levels of inflammatory cytokines and an increase in serum adiponectin level in obese patients with T2DM [87]. Liraglutide also improved oxidative stress by increasing glutathione concentration and decreasing serum lipid hydroperoxides and heme oxygenase-1 levels in subjects with T2DM, independent of its glucose-lowering effects [88].

The natriuretic effect of GLP-1 receptor agonists has been proposed to underly the GLP-1–induced reduction in blood pressure reported in large CVOTs. GLP-1–mediated natriuresis and diuresis appear to involve redistribution and reduction of Na^+/H^+ exchanger 3 (NHE3) activity, which is located at the brush border of renal proximal tubules [89]. GLP-1 receptor agonists phosphorylated NHE3 at the PKA consensus sites Ser552 and Ser605, reducing its activity [36]. GLP-1 receptor agonists also increased natriuresis and diuresis by increasing renal blood flow in rats [90]. Human studies have shown that GLP-1 infusion reduces proximal tubular sodium reabsorption and decreases plasma angiotensin II concentration [91]. In addition, a single subcutaneous injection of liraglutide increased sodium excretion in people with T2DM [92]. Inhibition of NHE3 by GLP-1 could also affect glomerular hemodynamics by activating tubuloglomerular feedback. The increase in sodium delivery to the macula densa due to low NHE3 activity results in afferent arteriolar vasoconstriction and lower glomerular hyperfiltration and pressure. Liraglutide is associated with an acute reduction in eGFR and subsequent stabilization over time, suggesting that GLP-1 has renal hemodynamic effects [93].

Ongoing studies and candidate drugs under development

The FLOW trial (NCT03819153) to evaluate the effect of once-weekly semaglutide on progression of renal impairment is currently in progress. The primary renal outcome comprises a persistent ≥50% reduction in eGFR or a persistent eGFR of <15 mL/min/1.73 m^2, initiation of RRT, or death from kidney disease or CVD. This study recently began recruiting more than 3,000 T2DM patients with moderate/advanced CKD and albuminuria, and its estimated completion date is 2024. This trial will be the first to investigate the effects of a GLP-1 receptor agonist on primary kidney outcomes.

In addition, the SOUL trial (NCT03914326) is a currently ongoing CVOT to evaluate the hypothesis that oral semaglutide lowers the risk of cardiovascular events in T2DM patients at high risk for CVD. In this trial, the composite renal endpoint is a secondary outcome consisting of a persistent ≥50% reduction in eGFR or a persistent eGFR of <15 mL/min/1.73 m^2, initiation of RRT, and renal death. Oral

semaglutide received the approval of the U.S. Food and Drug Administration in September 2019.

Polypharmacology refers to the combination of several structurally related hormones into a single entity. Treatment with GLP-1/glucagon dual agonists produced weight loss and antihyperglycemic efficacy superior to that of GLP-1 selective agonists alone in mice with diet-induced obesity [94]. GLP-1 and glucagon are structurally similar, and glucagon also acts on the GLP-1 receptor [95], raising expectations that a combination of the two drugs could be more efficacious than the use of either drug on its own. Several phase 2 clinical trials of GLP-1/glucagon dual agonists are currently in progress. In addition, dual GLP-1/GIP agonists have prolonged half-lives due to fatty acylation or PEGylation. A once-weekly GLP-1/GIP co-agonist, named tirzepatide (LY3298176), was superior to dulaglutide in terms of weight loss and improved HbA1c level in a phase 2 study of patients with T2DM [96]. Phase 1 clinical trials for GLP-1/glucagon/GIP triple combination agents have been performed by Hanmi Pharmaceuticals (HM15211) and Novo Nordisk (NNC9204-1706).

GLP-1-based combination therapies have been found to offer metabolic benefits greater than those achieved by treatment with either compound alone. Based on the improved efficacy of GLP-1/glucagon and GLP-1/GIP co-agonists, it is reasonable to determine whether dual or triple agonists might provide greater efficacy than the respective mono-agonists. Various possible combinations are GLP-1 with GLP-2 [97], leptin [98], gastrin [99], amylin [100], peptide YY [101], cholecystokinin [102], insulin [103], adrenomedullin [104], fibroblast growth factor 21 [105], estrogen [106], dexamethasone [107], a proprotein convertase subtilisin/kexin type 9 antibody [108], melanocortin-4 agonist [109], farnesoid-x [110], or an SGLT2 inhibitor [111]. Future studies are required to evaluate whether any of these combinations of agents have nephroprotective effects superior to those of GLP-1 mono-agonists in DKD patients.

Conclusions and future perspectives

GLP-1 receptor agonists are promising therapeutic options for patients with DKD, with benefits beyond their blood glucose-lowering activity. These agents seem to predominantly affect macroalbuminuria, whereas their effects on hard renal endpoints are less clear. Although these agents can be used in CKD patients with an eGFR down to 15 mL/min/1.73 m^2, the safety of GLP-1 receptor agonists in DKD patients with stage 5 CKD needs to be investigated. In terms of future research direction, more studies similar to the ongoing FLOW trial should be conducted to evaluate the primary kidney outcomes of GLP-1 receptor agonist treatment. In addition, it is necessary to explore whether combination treatment with GLP-1 receptor agonists and other classes of agents with beneficial effects on the kidney will have synergistic renoprotective effects in patients with DKD.

Conflicts of interest

All authors have no conflicts of interest to declare.

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