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GLP-1 Receptor Agonists in Diabetic Kidney Disease: From Clinical Outcomes to Mechanisms

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Diabetic Kidney Disease (DKD) is the leading cause of end stage renal disease (ESRD) worldwide. Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are now widely used in the treatment of patients with type 2 diabetes (T2D). A series of clinical and experimental studies demonstrated that GLP-1RAs have beneficial effects on DKD, independent of their glucose-lowering abilities, which are mediated by natriuresis, anti-inflammatory and anti-oxidative stress properties. Furthermore, GLP-1RAs have been shown to suppress renal fibrosis. Recent clinical trials have demonstrated that GLP-1RAs have beneficial effects on renal outcomes, especially in patients with T2D who are at high risk for CVD. These findings suggest that GLP-1RAs hold great promise in preventing the onset and progression of DKD. However, GLP-1RAs have only been shown to reduce albuminuria, and their ability to reduce progression to ESRD remains to be elucidated. In this review article, we highlight the current understanding of the clinical efficacy and the mechanisms underlying the effects of GLP-1RAs in DKD.

Keywords: diabetic kidney disease, diabetic nephropathy, GLP-1 receptor agonists, liraglutide, semaglutide, dulaglutide

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INTRODUCTION

Diabetic kidney disease (DKD) is a global concern because it causes end stage renal disease (ESRD) and affects mortality in diabetic patients. The inhibition of the onset and progression of DKD is an urgent issue, and the development of therapeutic approaches against DKD is required. Furthermore, DKD is an established risk factor for cardiovascular disease (CVD) (Rawshani et al., 2018). Thus, anti-diabetic agents that can attenuate both DKD and CVD have been awaited. A recent meta-analysis demonstrated that SGLT2 inhibitors and glucagon-like 1 receptor agonists (GLP-1RAs) have favorable effects on the cardiorenal outcomes in type 2 diabetes (T2D) (Giugliano et al., 2019; Kristensen et al., 2019). GLP-1RAs improve glucose metabolism by increasing glucose-dependent insulin secretion and suppress the release of glucagon. They have also been shown to have beneficial effects on cardiovascular (CV) risk factors by improving obesity, hypertension, and the lipid profile (Drucker, 2018). Recent CV outcome trials utilizing GLP-1RAs have also investigated renal outcomes. In addition, the elucidation of basic mechanisms underlying the renoprotective effect of GLP-1RAs is progressing. In this review article, we

discuss the current understanding of the renoprotective effects of GLP-1RAs from clinical and mechanistic standpoints.

THERAPEUTIC TARGETS IN DIABETIC KIDNEY DISEASE

DKD is a risk factor for both ESRD and CVD. Intensive glycemic control is effective for preventing the onset and progression of the early-middle stage of DKD. However, its usefulness for progressed DKD and established CVD remains unclear. Recent clinical trials demonstrated that SGLT2 inhibitors and GLP-1RAs bring beneficial effects on the cardiorenal outcomes of T2D subjects who are at high risk for CVD. T2D patients with severe renal impairment are not eligible for SGLT2 inhibitors, and GLP-1RAs could be an important therapeutic option for these patients. DKD is developed by glucose-dependent and -independent mechanisms, including oxidative stress and inflammation. GLP-1RAs have been shown to have beneficial effects on these factors.

GLP-1RAS AND RENAL OUTCOMES

Accumulating clinical evidence demonstrates that GLP-1 RAs have beneficial effects on renal outcomes. The results of major trials are summarized in **Table 1**.

Liraglutide

In an observational study, 52 weeks of liraglutide treatment was shown to increase the glomerular filtration rate (GFR) (5.4 ml/min/1.73 m^2) and reduce albuminuria by 50% in overweight T2D patients with stage 3 CKD (De Lucas et al., 2017). A small size randomized controlled trial (RCT) demonstrated that treatment with liraglutide (1.8 mg) for 12 weeks resulted in a reduction of albuminuria by 32% in T2D patients (Von Scholten et al., 2017). In the Satiety and Clinical Adiposity–Liraglutide Evidence (SCALE) Diabetes trial, a total of 846 overweight and obese patients with T2D were randomly assigned to receive 3.0 or 1.8 mg of liraglutide or placebo for 56 weeks. At the end of the study period, the reductions in the albumin-to-creatine ratios (UACR) of the liraglutide (3.0 mg), liraglutide (1.8 mg), and placebo groups were 18.36, 10.79, 2.34%, respectively (Davies et al., 2015). In the LIRA-RENAL trial, 279 T2D subjects with moderate renal impairment [estimated glomerular filtration rate (eGFR) 30–59 ml/min/1.73 m^2] were randomly assigned to receive liraglutide (1.8 mg) or placebo for 26 weeks. However, liraglutide treatment failed to show significant improvement of the UACR and eGFR trajectory in comparison to placebo (Davies et al., 2016).

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study assessed the CV outcome of liraglutide (1.8 mg) in comparison to placebo (Marso et al., 2016b). A total of 9340 participants with a high CV

TABLE 1 | Clinical effects of GLP-1RAs on DKD.

Trial	Agents, Follow-up Duration	Subjects	Renal Outcomes	Results
LEADER (n=9,340)	Liraglutide (1.8 mg) vs. placebo, 3.84 years	T2D with high CV risk	New-onset macroalbuminuria, doubling of the serum creatinine level, ESRD, renal death	HR 0.78 (95% CI: 0.67-0.92)
SUSTAIN-6 (n=3,297)	Semaglutide (0.5 mg, 1.0 mg) vs. placebo, 104 weeks	T2D Age >50 with established CVD or CKD stage 3-5 Age >60 with CV risk factors	New or worsening of nephropathy (persistent macroalbuminuria, doubling of the serum creatinine level and CCr < 45 mL/min/1.73 m2, RRT)	HR 0.64 (95% CI: 0.46-0.88)
REWIND (n=9,901)	Dulaglutide (1.5 mg) vs. placebo, 5.4 years	T2D with a previous CV event or CV risk factors	New onset of macroalbuminuria, sustained eGFR decline (≥30%) or RRT	HR 0.85 (95% CI: 0.77-0.93)
AWARD-7 (n=576)	Dulaglutide (0.75 mg, 1.5 mg) vs. placebo, 52 weeks	T2D with moderate to severe CKD (stage 3-4)	Changes in eGFR decline and UACR from baseline	eGFR decline: -1.1 (1.5 mg), -1.5 (0.75 mg), -2.9 (glargine) UACR: no significant differences among groups
ELIXA (n=6068)	Lixisenatide (10-20 μg) vs. placebo, 108 weeks	T2D with recent acute coronary syndrome	Percent change in UACR and eGFR from baseline	eGFR decline: no significant differences among groups UACR: -1.69% (95% CI: -11.69% to 8.30%) in patients with normoalbuminuria, -21.10% (95% CI: -42.25% to 0.04%) in patients with microalbuminuria, -39.18% (95% CI: -68.53% to -9.84%) in patients with macroalbuminuria

These effects are mainly driven by the reduction of albuminuria.

risk, who were ≥50 years of age, with HbA1c ≥7% were randomly assigned to receive placebo or liraglutide (1.8 mg). At baseline, 20.7% of the patients had an eGFR of 30–59 ml/min/1.73 m^2 and 2.4% had an eGFR of <30 ml/min/1.73 m^2. Microalbuminuria and macroalbuminuria were present in 26.3 and 10.5% of the participants, respectively. The definitions used for the renal outcomes in the LEADER study were a composite of new-onset persistent macroalbuminuria, persistent doubling of serum creatinine, ESRD, or death due to renal disease (Mann et al., 2017). Over a median follow-up of 3.8 years, liraglutide treatment resulted in less renal outcomes in comparison to placebo [HR 0.78 (95% CI: 0.67–0.92, p=0.03)] (Mann et al., 2017). This observation was largely driven by a reduction in new-onset macroalbuminuria in the liraglutide group in comparison to the placebo group [HR 0.74 (95% CI: 0.60–0.91, p=0.004)]. No significant differences in the doubling of the serum creatinine, initiation of renal replacement therapy (RRT), or renal death were observed between the liraglutide and placebo groups (Mann et al., 2017). In a *post-hoc* analysis of the LEADER trial, liraglutide was shown to reduce the risk of major adverse CV events and all-cause mortality in comparison to placebo in patients with chronic kidney disease (CKD), defined as eGFR < 60 ml/min/1.73 m^2 and albuminuria (UACR >30 mg/g) (Mann et al., 2018).

Semaglutide

The SUSTAIN-6 (trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes) was a double-blind trial in which T2D patients were randomized to receive either 0.5 or 1.0 mg of once-weekly subcutaneous semaglutide or placebo (Marso et al., 2016a). At baseline, 25.2% of the participants had an eGFR of 30–59 ml/min/1.73 m^2 and 2.9% had an eGFR of <30 ml/min/1.73 m^2. The composite renal outcome of this study was new or worsening nephropathy, defined as persistent macroalbuminuria, persistent doubling of the serum creatinine level and creatinine clearance <45 ml/min/1.73 m^2 or the need for RRT. After a median follow-up of 2 years, the incidence of new or worsening nephropathy in the semaglutide group was lower than that in the placebo group [HR 0.64 (95% CI: 0.46–0.88, p=0.05)]. This result was largely driven by a reduction in new onset macroalbuminuria. No significant changes were observed in ESRD or renal death (Marso et al., 2016a).

The PIONEER-6 trial primarily evaluated the cardiovascular safety of oral semaglutide (14 mg) in comparison to placebo (Husain et al., 2019). A total of 3,183 participants of ≥50 years of age with established CVD or CKD, or ≥60 years of age with CV risk factors were only observed for a median of 15.9 months. At baseline, 26.9% of participants had an eGFR of <60 ml/min/1.73 m^2. There was no significant reported difference in the eGFR decline from baseline to the end of treatment or in the rate of renal death (Husain et al., 2019). The PIONEER-5 trial showed that semaglutide use in T2D patients with renal impairment (eGFR 30–59 ml/min/1.73 m^2) was safe and effective (Mosenzon et al., 2019a). Further study is needed to elucidate whether the renoprotective effects of semaglutide are consistent in those individuals.

Currently, the ongoing FLOW is assessing whether or not semaglutide can inhibit worsening of CKD in patients with T2D (https://clinicaltrials.gov/ct2/show/NCT03819153). Renal impairment defined as either an eGFR 50–75 ml/min/1.73 m^2 and UACR 300–5,000 mg/g or an eGFR 25–50 ml/min/1.73 m^2 and UACR 100–5,000 mg/g are included in this study. An estimated 3,160 participants are to receive once-weekly subcutaneous semaglutide (starting with 0.25 mg and the dose will be increased to 0.5 mg at 4 weeks and 1 mg at 8 weeks) for up to 5 years. The primary endpoint is the time to the first occurrence of a composite primary outcome event, defined as a persistent eGFR decline (≥50% from baseline), reaching ESRD, renal death, or CV death. This study will elucidate the effects of semaglutide in detail.

Dulaglutide

The AWARD-7 study assessed the efficacy and safety of dulaglutide in T2D patients with moderate-to-severe CKD (Tuttle et al., 2018). The baseline cystatin C–based eGFR (eGFRcys) and creatinine-based eGFR (eGFRcre) values of the participants were 35.3 ml/min/1.73 m^2 and 36.0 ml/min/1.73 m^2, respectively. A total of 577 patients were randomly assigned (1:1:1) to receive once-weekly dulaglutide (1.5 mg), once-weekly dulaglutide (0.75 mg), or daily insulin glargine as basal therapy, all in combination with insulin lispro, for 52 weeks. The renal outcomes were changes in the eGFR and UACR. At 52 weeks, the eGFR decline was −1.1 in the dulaglutide (1.5 mg) group, −1.5 in the dulaglutide (0.75 mg) group, and −2.9 in the glargine group. However, the UACR reduction was not significantly different (Tuttle et al., 2018).

The REWIND study evaluated the cardiovascular safety of dulaglutide (1.5 mg) in comparison to placebo (Gerstein et al., 2019b). In total, 9,901 participants of ≥ 50 years of age with T2D and a history or a high risk of CVD were observed for a median of 5.4 years. The composite renal outcome (the first occurrence of new macroalbuminuria, a sustained decline in eGFR of ≥30% from baseline, or RRT) developed less frequently in participants using dulaglutide in comparison to those using placebo [HR 0.85 (95% CI: 0.77–0.93), p=0.0004]. This result was largely driven by a reduction of albuminuria [HR 0.77 (95% CI: 0.68–0.87), p < 0.001]. The rates of a sustained decline in eGFR [HR 0.89 (95% CI: 0.78–1.01), p=0.066] and the need for RRT showed a downward trend but were not statistically significant [HR 0.75 (95% CI: 0.39–1.44), p=0.39] (Gerstein et al., 2019a).

Exenatide

The EXSCEL (Exenatide Study of Cardiovascular Event Lowering) trial evaluated the CV safety of exenatide (2 mg weekly). In total, 14,752 participants with T2D (HbA1c 6.5–10.0%) with or without a history of CVD were observed for a median of 3.2 years (Holman et al., 2017). At baseline, 21.6% of the participants had an eGFR of <60 ml/min/1.73 m^2. Exenatide treatment did not change the eGFR significantly. Macroalbuminuria occurred less (2.2%) in exenatide group compared to placebo group (2.5%) [HR 0.87 (95% CI: 0.70–1.07)]. Neither renal composite 1 (40% eGFR decline, RRT, or renal death) nor composite 2 (composite 1 variables plus

macroalbuminuria) was reduced by exenatide in unadjusted analyses; however, renal composite 2 was reduced after adjustment [HR 0.85 (95% CI: 0.74–0.98)] (Bethel et al., 2020). In a *post hoc* analysis of a 52-week randomized trial, exenatide treatment did not alter the renal function (creatinine clearance or eGFR) or the onset/progression of albuminuria in comparison to titrated insulin glargine in overweight T2D patients (Muskiet et al., 2019). Finally, a pooled analysis of RCTs and open-label phase III studies showed that once-weekly exenatide reduced albuminuria 26% (95% CI%: −39.5 to −10%) compared with comparators (Van Der Aart-Van Der Beek et al., 2020). Furthermore, the change in the HbA1c value from baseline did not affect the result, suggesting that once-weekly exenatide reduced albuminuria independent of the glucose-lowering effect (Van Der Aart-Van Der Beek et al., 2020).

Lixisenatide

In the ELIXA (Evaluation of Lixisenatide in Acute Coronary Syndrome) study, T2D patients with a recent coronary artery event were randomly assigned (1:1) to a lixisenatide (10–20 μg) group or placebo group (Pfeffer et al., 2015). Baseline UACR data were available for 5,978 (99%) of the 6,068 patients who were included in the study. Among them, 19% of the participants had microalbuminuria, and 7% had macroalbuminuria. After 108 weeks, changes in UACR from baseline with lixisenatide were −1.69% [(95% CI: −11.69 to 8.30), p=0.7398] in patients with normoalbuminuria, −21.10% [(95% CI: −42.25 to 0.04), p=0.0502] in patients with microalbuminuria, and −39.18% [(95% CI: −68·53 to −9·84), p=0.0070] in patients with macroalbuminuria. No significant differences in eGFR decline were observed between the treatment groups (Muskiet et al., 2018).

Albiglutide

Harmony outcomes was a double-blind trial that included a total of 9,463 T2D participants of ≥40 years of age and a history of CVD, who were allocated to an albiglutide (30–50 mg weekly) group or placebo group (Hernandez et al., 2018). After a mean follow-up period of 1.6 years, no significant difference in eGFR decline was observed between the two groups (Hernandez et al., 2018).

RENOPROTECTION OF GLP-1RAS IS LARGELY DEPENDENT ON REDUCTION OF ALBUMINURIA

As described above, GLP-1RAs have no clinically important effect on eGFR and hard renal endpoints. In a meta-analysis of 60 studies involving 60,077 T2D patients, GLP-1RAs marginally reduced the UACR in comparison to placebo and other antidiabetic agents, but resulted in no clinically relevant changes in eGFR (Avgerinos et al., 2019). Consistently, a recent meta-analysis that included LEADER (liraglutide), SUSTAIN-6 (semaglutide), REWIND (dulaglutide), EXSCEL (exenatide), ELIXA (lixisenatide), Harmony outcomes (albiglutide), and PIONEER-6 (oral semaglutide), demonstrated that treatment with GLP-1 RAs reduced the composite kidney outcome (development of new-onset macroalbuminuria, decline in eGFR or increase in creatinine, ESRD, or renal death by 17% [HR0.83 (95% CI: 0.78–0.89, p < 0·0001)], mainly driven by a reduction in albuminuria (Kristensen et al., 2019).

RENOPROTECTIVE MECHANISMS OF GLP-1RAS

Experimental studies to elucidate the beneficial effects on DKD have been extensively reported. The inhibition of oxidative stress, inflammation, fibrosis, and induction of natriuresis have been mainly implicated as mechanisms underlying the attenuation of DKD by GLP-1RAs (**Figure 1**).

GLP-1 Receptors in the Kidney

The distribution of GLP-1R in the kidney is controversial. GLP-1R has been shown to be expressed in the renal cortex as well as the proximal tubules (Schlatter et al., 2007; Carraro-Lacroix et al., 2009). However, several investigations reported a lack of GLP-1R

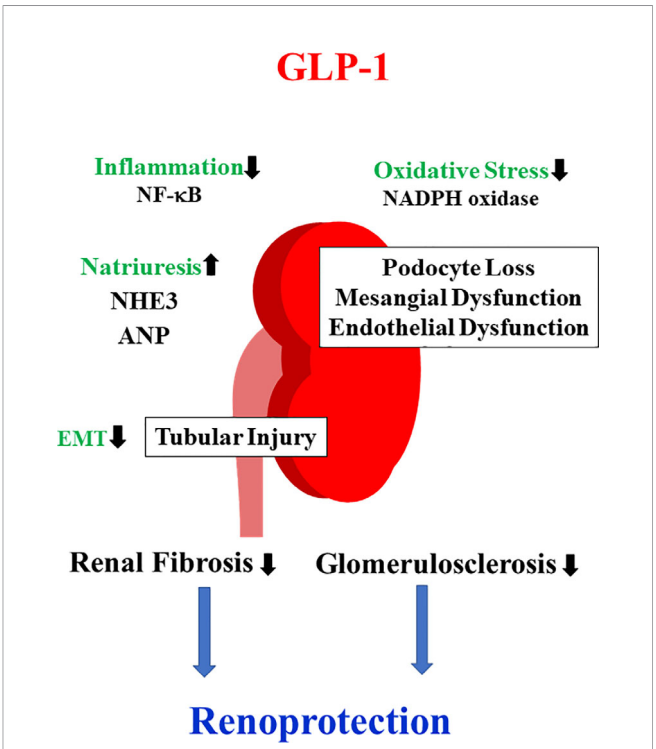

FIGURE 1 | Mechanisms of the renoprotective effects of GLP-1RAs. GLP-1RAs have been shown to activate PKA and increase the production of cyclic adenosine monophosphate (cAMP). As a consequence, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and NF-κB activity are inhibited, resulting in the attenuation of oxidative stress and inflammation. These favorable effects prevent podocyte loss as well as mesangial and endothelial dysfunction.. GLP-1RAs inactivate NHE3 and promote atrial natriuretic peptide (ANP) secretion, thereby inducing natriuresis. Furthermore, GLP-1RAs inhibit tubular injury and subsequent tubulointerstitial fibrosis.

in tubules (Pyke et al., 2014; Lee et al., 2015; Ronn et al., 2017). Studies using monoclonal antibodies against GLP-1R revealed that it is mainly present in the vasculature of the kidney (Pyke et al., 2014; Jensen et al., 2015; Ronn et al., 2017). To date, the presence of GLP-1R in the renal vasculature has been confirmed but not in the tubules (Hviid and Sorensen, 2020).

Oxidative Stress/Inflammation

GLP-1RAs have been shown to prevent renal oxidative stress by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase through the activation of PKA and the production of cyclic adenosine monophosphate (cAMP). Recombinant human GLP-1 inhibits protein kinase C (PKC)-β, but increases protein kinase A (PKA), which reduces oxidative stress in both glomeruli and tubules (Yin et al., 2019). Consistent with this observation, the combination of olmesartan and exenatide has been shown to attenuate the renal NADPH oxidase 4 (Nox4) expression in insulin-resistant Otsuka Long-Evans Tokushima Fatty (OLETF) rats (Rodriguez et al., 2020). Hendarto et. al. revealed that liraglutide attenuates oxidative stress and albuminuria in streptozotocin (STZ)-diabetic rats *via* the PKA-mediated inhibition of renal NADPH oxidases (Hendarto et al., 2012). Liljedahl et al. performed label-free shotgun mass spectrometry (MS) and demonstrated that liraglutide increased the abundance of structurally involved proteins as well as proteins involved in oxidative stress responses in the kidney of STZ-induced diabetic mice (Liljedahl et al., 2019). Moreover, it is reported that exendin-4 inhibits mesangial fibrotic responses (Li et al., 2012; Xu et al., 2014). Exendin-4 has been shown to reduce advanced glycation end product (AGE)-induced interleukin (IL)-6 and TNF-α production, the expression of receptor for AGE (RAGE), and cell death in mesangial cells (Chang et al., 2017). The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and Kelch-like ECH-associated protein1 (Keap1) signaling pathways play an important role in preventing oxidative stress (Wang et al., 2014). Nrf2 activator bardoxolone methyl is known to have renoprotective effects (Ito et al., 2020). Interestingly, exendin-4 has been shown to activate the Nrf2 signaling pathway in vascular smooth muscle cells (Zhou et al., 2016) and retinal pigment epithelial cells (Cui et al., 2019). A further study to investigate whether a similar mechanism exists in kidney under diabetic conditions would be intriguing.

NF-κB plays a central role in the inflammatory pathway in the development of DKD (Kawanami et al., 2016). The hyperglycemia-induced downregulation of GLP-1R is involved in NF-κB activation and the subsequent inflammatory response in mesangial cells (Kang et al., 2019). Liraglutide has been shown to increase renal endothelial nitric oxide synthase (eNOS) levels by downregulating NF-κB in STZ-induced diabetic rats (Zhou et al., 2014). Furthermore, liraglutide inhibits the expression levels of TNF-α-mediated NF-κB activation in podocytes (Ye et al., 2019). Kodera et. al. reported that exendin-4 attenuates albuminuria and glomerulosclerosis independent of the glucose-lowering effect in STZ-induced diabetic rats by inhibiting oxidative stress and NF-κB activation. From a mechanistic standpoint, these observations are mediated by GLP-1R in monocytes/macrophages and glomerular endothelial cells (Kodera et al., 2011). Ye et al. showed that liraglutide attenuated the morphology and structure damage of podocytes in obesity-related glomerulopathy model mice (Ye et al., 2019). Mechanistically, they found that liraglutide inhibited the renal TNF-α expression and NF-κB as well as the MAPK pathway activation in these mice (Ye et al., 2019). Similarly, liraglutide has been shown to reduce renal lipid accumulation and improve the mitochondrial function by activating the Sirt1/AMPK/PGC1α pathways in an obesity-induced rat CKD model (Wang et al., 2018). In addition to the MAPK pathway, the JAK/STAT signaling pathway is also involved in liraglutide-induced renoprotection. Zitman-Gal et al. revealed that liraglutide attenuated the phosphorylation of JAK2 and STAT3 in AGE-stimulated endothelial cells and the kidney of db/db mice (Zitman-Gal et al., 2019). Furthermore, it has been reported that the administration of exenatide attenuates the renal inflammation index, including reducing the TNF-α, IL-6, hsCRP, and CCL5 levels, in STZ-induced diabetic rats by increasing the superoxide dismutase and decreasing malondialdehyde levels (Wang et al., 2019). Taken together, the prevention of oxidative stress and inflammation is a key mechanism for the renoprotective effects of GLP-1RAs.

Natriuresis

Acute infusion of GLP-1 has been shown to stimulate diuresis and natriuresis in both experimental (Crajoinas et al., 2011; Jensen et al., 2015) and human studies (Gutzwiller et al., 2004; Skov et al., 2013; Muskiet et al., 2016). These observations seem to be associated with the inhibition of Na^+/H^+ exchanger 3 (NHE3) in the proximal tubules. NHE3 plays an important role in reabsorbing filtered Na^+ in the proximal tubules (Schultheis et al., 1998). Therefore, inactivation of NHE3 can result in natriuresis. GLP-1 RAs have been shown to induce phosphorylation and inactivation of NHE3 (Carraro-Lacroix et al., 2009; Crajoinas et al., 2011; Farah et al., 2016; Muskiet et al., 2017). The long-term administration of lixisenatide has been shown to decrease NHE3 activity in overweight T2D patients. In this study, 35 participants were randomly allocated to a lixisenatide (20 mg) group or once-daily insulin glulisine treatment group. After 8 weeks of follow-up, the administration of lixisenatide increased the phosphorylation of NHE3, which reduced its activity in urinary extracellular vesicles in comparison to once-daily insulin glulisine treatment (Tonneijck et al., 2019). However, it remains unclear whether these natriuretic responses are direct effects of GLP-1RA because a lack of GLP-1R in the proximal tubules has been reported (Pyke et al., 2014; Lee et al., 2015; Ronn et al., 2017). Furthermore, cardiomyocyte GLP-1R plays an important role in natriuresis. It has been shown that liraglutide promotes natriuresis by atrial natriuretic peptide (ANP) secretion from cardiomyocytes in an Epac2-depdenent manner (Kim et al., 2013).

Fibrosis

GLP-1RAs have been shown to attenuate renal fibrosis. For instance, exendin-4 has been shown to ameliorate the high glucose-induced fibronectin (FN) and type I collagen (Col1) expression in tubular epithelial cells by inhibiting the secretion of miR-192, an microRNA (miRNA) that is regulated by p53 and plays a role in renal fibrosis (Jia et al., 2018). Consistent with this observation, liraglutide has been shown to attenuate unilateral ureteral obstruction (UUO)-induced tubulointerstitial fibrosis by suppressing TGF-β and its downstream signaling pathways, including Smad3 and ERK1/2 (Li et al., 2018). These protective effects of GLP-1RAs for renal fibrosis are also mediated by attenuating the epithelial-to-mesenchymal transition (EMT) of tubular cells (Li et al., 2018; Yin et al., 2018).

The Endothelial Function

DKD is associated with endothelial dysfunction (Chen et al., 2020). Endothelial GLP-1R has been shown to be involved in endothelial dysfunction in a mouse angiotensin II-induced hypertension model (Helmstadter et al., 2020). Liraglutide was found to increase eNOS phosphorylation and nitric oxide (NO) production *via* AMPK-dependent pathways in endothelial cells (Li et al., 2016; Honda et al., 2018; Han et al., 2019). Lixisenatide has also been shown to prevent the free fatty acid-induced reduction of eNOS phosphorylation in endothelial cells (Zhao et al., 2019). Sukumaran et al. showed that liraglutide improves the renal endothelial dysfunction in obese Zucker rats on a high-salt diet by increasing the renal eNOS expression (Sukumaran et al., 2019). They also found that liraglutide increases the NO-mediated vasodilation of small intrarenal arteries using X-ray microangiography (Sukumaran et al., 2019). Furthermore, exendin-4 has been shown to attenuate lipotoxicity-induced glomerular endothelial cell dysfunction in diabetic ApoE-deficient mice by increasing the ABC transporter A1-mediated cholesterol efflux (Yin et al., 2016). Taken together, these findings highlight the improvement of the glomerular endothelial dysfunction as an important renoprotective effect of GLP-1RA.

Cleavage Products of GLP-1

Moellmann et al. reported that cleavage products derived from GLP-1 reduced tubulointerstitial renal damage, lowered the expression of tubular injury markers, and attenuated the renal accumulation of macrophages and T cells (Moellmann et al., 2018). These findings suggest that GLP-1R-independent renoprotective effects are mediated by GLP-1 cleavage products. Since distribution of GLP-1R in the kidney remains controversial, the renoprotective effects of GLP-1RAs may be partially explained by this mechanism.

Glycemic Control

Although the glucose-independent mechanisms are emphasized, glycemic control by GLP-1RAs is considered to be involved in its renoprotective effects. In LEADER, the use of liraglutide was associated with a 0.4% HbA1c reduction compared with the placebo (Marso et al., 2016b; Zinman et al., 2018). As a reduction of 0.5% in HbA1c is a clinically important difference (Zinman et al., 2018), a greater reduction by liraglutide may contribute to the renoprotective effects. Furthermore, liraglutide use was associated with a reduction in weight of 2.3 kg. In SUSTAIN-6, semaglutide use *vs*. placebo was associated with respective reductions in HbA1c of −0.66% (0.5 mg) *vs*. −1.05% (1.0 mg) and body weight of −2.9 kg (0.5 mg) *vs*. −4.4 kg (1.0 mg) (Kaul, 2018). In REWIND, dulaglutide use reduced the HbA1c value by −0.61% and body weight by −1.46 kg compared with placebo (Gerstein et al., 2019b). In these trails, GLP-1RAs exerted renoprotection, irrespective of the baseline HbA1c (Kristensen et al., 2019).

LIMITATIONS OF RENOPROTECTION BY GLP-1RAS

A series of experimental studies revealed that GLP-1RAs can exert renoprotective effects independent of their glucose-lowering activities; however, clinical evidence at present is insufficient to support these observations. For instance, there are no established methods for assessing the reduction in oxidative stress and inflammation by GLP-1RAs. It is difficult to evaluate the extent to which glucose-independent mechanisms are involved in renoprotection by GLP-1RAs. In clinical settings, glucose-lowering, weight loss, natriuresis, and blood pressure reduction may account for the renoprotective effects of GLP-1RAs. As described above, GLP-1RAs attenuate albuminuria and marginally reduce eGFR decline. However, whether or not albuminuria is a clinically relevant renal outcome remains unclear. Long-term clinical trials will be needed to address this question. The additive effects of combination treatment of GLP-1RAs and SGLT2 inhibitors on DKD are uncertain. In DELIGHT, the combination of saxagliptin and dapagliflozin showed potentially additive but marginal albuminuria-lowering effects in T2D subjects (Pollock et al., 2019). A meta-analysis showed that GLP-1RA and SGLT2 inhibitor combination therapy was associated with a greater reduction in HbA1c (−0.74%), body weight (−1.61 kg), and systolic blood pressure (−3.32 mmHg) than SGLT2 inhibitor monotherapy (Castellana et al., 2019), suggesting that this combination may induce additive renoprotective effects. Further studies will be required to address this issue.

CONCLUSION AND PERSPECTIVES

GLP-1RAs are widely used in the treatment of T2D. The treatment of DKD has been largely dependent on the management of hyperglycemia and hypertension. Thus, novel therapeutic approaches that exert renoprotective effects independently of these factors have been awaited. A series of clinical trials and experimental studies support the beneficial effects of GLP-1RAs on DKD. Lessons from clinical trials demonstrate these effects are mainly driven by reductions in albuminuria. In contrast, the beneficial effects of SGLT2 inhibitors on albuminuria and eGFR decline in DKD were demonstrated by EMPA-REG OUTCOME (Wanner et al., 2016), CANagliflozin cardioVascular Assessment Study (CANVAS) (Perkovic et al., 2018), DECLARE-TIMI58

(Mosenzon et al., 2019b), and Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) (Perkovic et al., 2019). It remains unclear why these differences were observed. The effects of SGLT2s inhibitors on hemodynamics and glomerular hyperfiltration seem to be robust whereas those of GLP-1RAs have not been established. In addition, the different distribution of SGLT2 and GLP-1R may be involved. Further studies are required to clarify the differences in their effects on the kidney and how to use them appropriately in clinical practice. Nevertheless, GLP-1RAs are a promising therapeutic option for DKD.

AUTHOR CONTRIBUTIONS

DK and YT wrote and revised the manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.