Review

Glucagon Like Peptide-1 Receptor Agonists and Diabetic Kidney Disease: From Bench to Bed-Side

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Glucagon Like Peptide-1 Receptor Agonists and Diabetic Kidney Disease: From Bench to Bed-Side

Running Title: GLP-1 and DKD: Bench to Bed Side

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Abstract: Glucagon like peptide-1 (GLP-1) receptor agonists are currently available for the management of type 2 diabetes mellitus. They have been shown to help with diabetic kidney diseases through multiple mechanisms. In this review, we will shed light on the different mechanisms of actions through which GLP-1 receptor agonists may achieve their roles in renal protection in diabetics; both in animal and human studies as well as review their safety profile in diabetic patients

Keywords: GLP-1; DKD; albuminuria; mechanism of action; animal studies; human studies; safety

1. Introduction

Diabetic kidney disease (DKD) is a serious microvascular complication affecting approximately 20-50% of individuals with diabetes mellitus (DM) and is the leading cause of End Stage Kidney Disease (ESKD) worldwide [1].

Over the past decades, several medications have been developed to delay or reverse the progression of DKD, such as renin aldosterone angiotensin (RAAS) blockers, sodium-glucose cotransporter 2 inhibitors (SGLT2i), and the nonsteroidal selective mineralocorticoid receptor antagonist; Finerenone. Another group of drugs was evaluated to assess their role in managing patients with DKD; glucagon-like peptide-1 receptor agonists (GLP-1RAs).

Glucagon-like peptide 1 (GLP-1) belongs to the incretin group of gastrointestinal (GI) hormones that was demonstrated to help patients with diabetes mellitus (DM) as well as obesity [2]. Recent studies have also shown that GLP-1 might be helpful in patients with DKD.

In this review, we aim to explore the mechanism of action of GLP-1RAs, highlighting preclinical and clinical evidence regarding their potential role in diabetic kidney disease (DKD). We will also address their safety profile and common side effects.

2. Glucagon like Peptide 1

Glucagon-like peptide 1 (GLP-1) is an incretin hormone secreted by intestinal L cells and pancreatic α-cells [3]. GLP-1 is secreted and released by enteroendocrine L cells within the terminal ileum, colon, and brainstem neurons [4–7], through the action of prohormone convertase 1 [8] in response to meals. It has a rapid half-life and is degraded by dipeptidyl peptidase 4 (DPP-4) [4,5].

GLP-1 exerts various effects on pancreatic beta cells, such as enhancement of glucose-dependent insulin secretion, acceleration of beta cell proliferation, and inhibition of beta cell apoptosis, which occur through activation of GLP-1 receptors (GLP-1Rs) in the pancreas [9]. GLP-1 also inhibits glucagon secretion and decreases appetite and food intake [10]. In the GI tract and hypothalamus,

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GLP-1 inhibits motility, gastric emptying, and central regulation of feeding, resulting in body weight loss [11]. Thus, GLP-1, through these actions, helps improve glucose metabolism [12].

Besides GLP-1Rs expression in the pancreas and the GI tract, the GLP-1Rs are also expressed in other tissues such as the heart, brain, and kidneys [9]. In the kidneys, the GLP 1Rs are distributed in the cortical part of the kidney, the proximal convoluted tubules, and the glomeruli [13].

3. Glucagon Like Peptide Receptor Agonists

GLP-1 R agonists (GLP-1RAs) have been approved for the treatment of patients with type 2 DM [14], acting by activating GLP-1Rs [15]. They have been recommended for patients with DM who have not met their glycemic targets despite therapeutic optimization. A post hoc analysis of the cardiovascular outcome trials (CVOT) [16], have shown possible benefits of GLP-1RAs in delaying DKD progression [17].

GLP-1RAs are classified as exendin-4- or human GLP-1- based compounds [18]. They are divided into short-acting (exenatide and lixisenatide) or long-acting (dulaglutide, liraglutide, exenatide long-acting release, and semaglutide) [19]. 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. Exenatide and lixisenatide are eliminated by the kidneys and are contraindicated below an eGFR of 30 mL/min/1.73 m^2 due to the risk of accumulation and toxicity [18]. Both experimental and clinical studies have demonstrated the renoprotective actions of GLP-RAs.

4. Mechanism of Renoprotective Action (Table 1)

It is not clear how GLP-1RAs elicit their specific renoprotective effects. However, the renoprotective effect might be due to a reduction in blood pressure, body weight, and plasma glucose (Table 1). In addition, GLP-1RAs also reduce inflammation, reactive oxygen species, and endothelial dysfunction, leading to a reduction in the development of albuminuria [9]. Further actions of GLP-1RAs that may help renal protection include reducing hyperlipidemia, induction of natriuresis, and reduction of intraglomerular pressure [17]. On the other hand, GLP-1 was not shown to affect renal hemodynamics. A double-blind, randomized, placebo-controlled trial by Tonneijck and colleagues assessed the GFR and effective renal plasma flow (ERPF) following the administration of either exenatide (n=24) or placebo (n=28) intravenously in overweight type 2 diabetic patients [20]. Other renal hemodynamic parameters were also assessed as filtration fraction, glomerular hydrostatic pressure, and vascular resistance in the afferent and efferent renal arterioles. The researchers demonstrated that exenatide alone does not have an acute effect on renal hemodynamics in the population studied [20]. Similar results were noted when comparing lixisenatide's effect on postprandial glomerular hemodynamics versus insulin-glulisine (iGlu) in diabetic patients, showing no effect of lixisenatide on renal hemodynamics compared to iGlu in an eight weeks study period [21].

Table 1. Possible mechanisms of renoprotective action of glucagon like peptide receptor agonists.

Reduction of oxidative stress
Reduction of inflammation
Natriuresis/Diuresis
Reduction of intraglomerular pressure
Reduction in hyperglycemia
Reduction in hypertension
Reduction in obesity
Reduction in endothelial dysfunction
Increase Renal Plasma Flow
Increase estimated Glomerular Filtration Rate
Increase Sympathetic Activity and Heart Rate

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5. Preclinical Studies (Table 2)

5.1. Liraglutide

Liraglutide (0.2-0.6 mg/kg/day) treatment for 8 weeks reduced renal pathologic findings and urinary albumin in early-phase DKD in spontaneously diabetic Torii fatty rats by preventing glomerular endothelial abnormality and preservation of autophagy. These renoprotective effects noted were independent of blood glucose and blood pressure levels [22]. Liraglutide (100 μg/kg and 200 μg/kg/day) treatment for 8 weeks delayed the progress of diabetic nephropathy in Sprague-Dawley rats that were fed a high-sugar and high-fat diet and received streptozotocin by reducing endoplasmic reticulum stress [23]. The effect of liraglutide on delaying the progression of diabetic nephropathy was confirmed in another study through other mechanisms. Liraglutide (0.3 mg/kg twice daily) was given for 8 weeks in streptozotocin-induced diabetes in Sprague Dawley rats, prevented the progression of diabetic nephropathy by modulating the crosstalk between transient receptor potential canonical 6 (TRPC6) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [24]. In high fat-high sugar fed Sprague Dawley rats that were treated with streptozotocin, liraglutide (0.6 mg/kg/day) for 12 weeks reduced albuminuria and the authors suggested that liraglutide may have a renoprotective effect in DKD through its effect on the Micro RNA-34A (miR-34a)/sirtuin 1 (SIRT1) pathway [25]. In Zucker diabetic fatty (ZDF) rats, liraglutide (200 μg/kg/12 h) for 9 weeks decreased urinary albumin and attenuated renal pathological changes. This renoprotective effect was due to the activation of autophagy by regulating the adenosine monokinase (AMP)-activated protein kinase-mammalian target of the rapamycin pathway [26]. Huang and colleagues [27] showed that administration of liraglutide (200 μg/kg/ 12 h) for 8 weeks to streptozotocin-induced diabetic Sprague Dawley rats improved renal function without lowering blood glucose levels and ameliorated glomerular histopathological changes. They further showed that liraglutide reduced the production of glomerular extracellular matrix proteins by enhancing Wnt/ β-catenin signaling [27]. In Sprague Dawley rats fed with high sugar and high-fat diet and injected with low dose streptozotocin to induce type 2 diabetes, liraglutide (0.2 mg/kg/12 h) for eight weeks had a renoprotective effect by activating forkhead box protein O1 (FoxO1) [28]. While in Wistar rats with streptozotocin-induced diabetes mellitus, liraglutide (0.3 mg/kg/12 h) for 12 weeks had a direct beneficial effect on diabetic nephropathy by improving endothelial nitrous oxide synthase (eNOS) activity via downregulating nuclear factor (NF)-κB (NF-κB) inflammatory pathway [29]. In streptozotocin-induced diabetic Wister rats, liraglutide (0.3 mg/kg/12 h) for four weeks reduced oxidative stress, expression of NAD(P)H oxidase components, transforming growth factor -beta (TGF-β), fibronectin in renal tissues and urinary albumin excretion [30]

Table 2. Effects of glucagon like peptide-1 receptor agonists on Experimental Animals Models of Diabetic Nephropathy.

Drug	Animal	Effects of GLP-1 receptor agonists	Ref.
Liraglutide	- Spontaneously diabetic Torii fatty rats. - Sprague-Dawley rats fed a high-sugar and high-fat diet and received streptozotocin.	- Reduced renal pathologic findings and urinary albumin in in early-phase diabetic kidney disease by preventing glomerular endothelial abnormality and preservation of autophagy.	[22] [23] [24] [25] [26]

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	- Streptozotocin induced diabetes in Sprague Dawley rats.	- Delayed the progress of diabetic nephropathy by reducing endoplasmic reticulum stress.	[27]
	- High fat-high sugar fed Sprague Dawley rats that were treated with streptozotocin.	- Prevented the progression of diabetic nephropathy by modulating the crosstalk between TRPC6 and NADPH oxidases.	[28] [29] [30]
	- Zucker diabetic fatty (ZDF) rats	- Reduced albuminuria, renoprotective effect in DN through its effect on miR-34a/ SIRT1 pathway.	[3] [31]
	- Streptozotocin induced diabetic in Sprague Dawley rats	- Decreased urinary albumin and attenuated renal pathological changes. Renoprotective effect due to activation of autophagy by regulating AMP-activated protein kinase-mammalian target of rapamycin pathway.	[32] [33] [34]
Exanti de	- Wistar rats with streptozotocin induced diabetes mellitus.	-Improved renal function and ameliorated glomerular histopathological changes. Liraglutide reduced the production of glomerular extracellular matrix proteins by enhancing Wnt/ β-catenin signaling.	[35] [11] [36] [37] [38]
	- Diabetic Ins2Akita mice	- Had a renoprotective effect	[39]

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Semaglutide	(C57BL/6-Ins2Akita/J).	by the activation of forkhead box protein O1 (FoxO1).	[40]
Lixisenatide	- C57BL/6J mice fed on high fat diet and treated with streptozotocin.	- Had a direct beneficial effect on diabetic nephropathy by improving eNOS activity via downregulating NF-κB.	[41]
	- C57BLKS/J db/db diabetic mice. - Diabetic nephropathy prone KK/Ta-Akita mice.	- Reduced albuminuria, glomerulosclerosis and glomerular basement membranous thickness Kidney protective effect due to dampening the receptor for advanced glycation end products–induced inflammation.	
	- Wistar rats fed high-fat diet and followed by injection of streptozotocin. - Sprague Dawley rats injected with streptozotocin.	- Reduced urinary protein, attenuated podocyte damage and glomerular injury via reducing NLRP3-mediated inflammation.	
	- Streptozotocin induced diabetes in Sprague Dawley rats. - C57BL/6J mice fed high fat diet and were injected with streptozotocin.	- Induced browning **of white adipose tissue which protects podocytes by decreasing TNF-α secretion and activation of** PI3K)/AKT pathway. - Reduced albuminuria and mesangial expansion.	

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- Diabetic apoE$^{-/-}$ mice (ApoE$^{-/-}$ DM) fed high fat diet and injected with streptozotocin. - Streptozotocin-induced diabetes in BALB/c mice.	- Reduced oxidative stress, expression of NAD(P)H oxidase components, TGF-β, fibronectin in renal tissues and urinary albumin excretion.
- *db/db* UNx-ReninAAV mice. - Lepr *db/db* (*db/db) mice*, a diabetic nephropathy model, - Wister rats fed a high fat diet and injected with streptozotocin.	- Improved renal function through correction of glycolipid intolerance as well as reducing oxidative stress - Ameliorated renal injury through decrease oxidative stress and inflammatory response in renal tissue. - Reduced albuminuria, glomerular hyperfiltration, glomerular hypertrophy and mesangial matrix expansion. - Reduced urinary albumin and attenuated the progress of diabetic nephropathy via activation of renal AMP-activated protein kinase. - Increased ABCA1 expression in glomerular endothelial cells and

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	attenuated renal lipid accumulation, inflammation, and proteinuria. - Decreased renal tubular injury of diabetic nephropathy by decreasing oxidative stress and inflammation. - Reduced albuminuria and glomerulosclerosis severity and hypertension. - Decreased collagen deposition, attenuated kidney fibrosis and kidney injury. - Has a nephroprotective effect, as shown by improved kidney function and renal histopathology.	

In diabetic Ins2Akita mice (C57BL/6-Ins2Akita/J), liraglutide (50 mg/kg/day for 20 weeks reduced albuminuria, glomerulosclerosis, and glomerular basement membranous thickness. The authors suggested that this kidney protective effect was due to dampening the receptor for advanced glycation end products–induced inflammation and that this is a glucose-independent effect [3]. In C57BL/6J mice fed on high-fat diet and treated with streptozotocin to induce type 2 diabetes model, liraglutide (400 μg/kg/day) treatment for 14 weeks reduced urinary protein, attenuated podocyte damage and glomerular injury via reducing nucleotide-binding domain, leucine-rich- containing family, pyrin domain-containing-3 (NLRP3)-mediated inflammation [31]. Liraglutide (400 mg/kg/day) treatment for 8 weeks induced browning **of white adipose tissue, which protects podocytes by decreasing tumor necrosis factor-alpha (TNF-α) secretion and activation of phosphoinositide 3-kinase** (PI3K)/protein kinase B (AKT) pathway in C57BLKS/J db/db diabetic mice [32]. Treatment with liraglutide (200μg/kg/day) for four weeks ameliorated the progression of nephropathy in a mouse model of progressive diabetic nephropathy (KK/Ta-Akita mice), as shown by reduced albuminuria and mesangial expansion [33].

5.2. Exenatide

In Wistar rats fed a high-fat diet and followed after injection of streptozotocin, exenatide (5 μg/kg/day) for four weeks improved renal function through correction of glycolipid intolerance as

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well as reducing oxidative stress [34]. In Sprague Dawley rats injected with streptozotocin, exenatide (2, 4, and 8 μg/kg) for 8 weeks ameliorated renal injury through decreased oxidative stress and inflammatory response in renal tissue [35]. Exendin 4 (10 μg/kg/day) for 8 reduced albuminuria, glomerular hyperfiltration, glomerular hypertrophy, and mesangial matrix expansion in streptozotocin-induced diabetes in Sprague Dawley rats [12].

Exendin 4, administered for 8 weeks to C57BL/6J mice fed a high-fat diet and were injected with streptozotocin, reduced urinary albumin and attenuated the progress of diabetic nephropathy via activation of renal AMP-activated protein kinase [36]. In diabetic apoE$^{-/-}$ mice (ApoE$^{-/-}$ DM) fed high-fat diet and injected with streptozotocin, exendin 4 (1 nmol/kg/day) for 8 weeks increased ABC Transporter A1 (ABCA1) expression in glomerular endothelial cells and attenuated renal lipid accumulation, inflammation, and proteinuria [37]. Sancar-Bas et al. [38] showed that exendin (3 μg/kg) decreased renal tubular injury of diabetic nephropathy by reducing oxidative stress and inflammation in streptozotocin-induced diabetes in BALB/c mice.

5.3. Semaglutide

In db/db UNx-ReninAAV mice, a model of hypertension accelerated diabetic kidney disease, semaglutide (30 nmol/kg/day) for 11 weeks reduced hyperglycemia, albuminuria, and glomerulosclerosis severity and hypertension [39]. Semaglutide (120.0 μg/kg/day) injection for eight weeks to Lepr *db/db* (*db/db) mice,* a diabetic nephropathy model, decreased collagen deposition, attenuated kidney fibrosis, and kidney injury [40].

5.4. Lixisenatide

In Wister rats fed a high-fat diet and injected with streptozotocin, lixisenatide (1 nmol/kg/day) for 2 weeks induced a nephroprotective effect as shown by improved kidney function and renal histopathology [41].

6. Clinical Studies

Several studies have evaluated the effect of GLP-1RAs on renal outcomes such as albuminuria and progression of renal disease as assessed by the estimated glomerular filtration rate (eGFR) and the safety of these drugs.

6.1. Renal Outcome

In a systemic review that included seven trials (n=56,004) using different GLP-1 RAs drugs, the researchers demonstrated a reduction of a broad composite of kidney outcomes, progression to ESKD, or death attributable to kidney causes by 17% when receiving a GLP-1 RAs [42]. These benefits in renal outcomes noted when using these drugs were mainly due to a reduction in urinary albumin excretion. No increased risk was associated with using these drugs.

Schechter and colleagues studied the effects of GLP-1RAs (exenatide, exenatide extended release, liraglutide, dulaglutide, semaglutide, and lixisenatide) versus basal insulin on albuminuria and composite kidney outcome in diabetic patients (n=3424) with a median follow-up of 81.1 months [43]. In an as-treated analysis, the researchers demonstrated a significant benefit of GLP-1RAs in decreasing the eGFR slope compared to basal insulin [43]. Similarly, Lin and colleagues [44], over a median follow-up of 2.1 years, showed an advantage of using GLP-1RAs (n=759) vs DPP-4 inhibitors (n=8163).

In pooled data from 2 major trials, SUSTAIN 6 trial [45] using semaglutide and the LEADER trial [46] using liraglutide (n=12, 637), the researchers showed that both these drugs lowered albuminuria, slowed the decline in the eGFR slope and lowered the risk of persistent eGFR reductions versus placebo [47].

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6.2. Individual Drug

6.2.1. Semaglutide

Tuttle And Coworkers [48] underwent a post-hoc analysis of data pooled from 2 studies; SUSTAIN 6 [45] and Pioneer 6 [49]. Both studies were done on patients with DM II with high cardiovascular risks. In this post-hoc analysis, the researchers focused on the effect of semaglutide on the decline of renal function, comparing semaglutide (n=3239) versus placebo (3241). The researchers demonstrated a significant reduction in the rate of decline of eGFR in the semaglutide group in the total population studied, in a subgroup with baseline eGFR 30 to <60 ml/min/1.73 m^2 and in the subgroup with baseline eGFR >60 ml/min/1.73 m^2 with P values <0.0001, 0.0007 and 0.0083 respectively [48].

A post-hoc analysis of the patients (n=8416) that were enrolled in SUSTAIN 1-5, SUSTAIN 7 [50–52] and SUSTAIN 6 [45] trials was done aiming to evaluate the effectiveness and safety of once-weekly semaglutide given in 2 different doses (0.5 mg and 1.0 mg) compared to the drugs used in the above studies (sitagliptin, exenatide, insulin glargine, dulaglutide and placebo [53]. While the duration of the SUSTAIN studies 1 through 7 ranged between 30-104 weeks, analysis for the post-hoc trial was done on data pooled up to 30 weeks for eGFR and to week 56 for UACR for SUSTAIN 1-5 and SUSTAIN 7, and up to 104 weeks in SUSTAIN 6. The authors showed that both doses of semaglutide showed marked reduction in UACR compared to placebo [53].

More recently, in 2023, Rossing and colleagues published an article to detail the rationale, design, and baseline data of the FLOW trial [54], a year later the results of the trial were published [55–58]. The FLOW trial, a randomized, double-blind, parallel-group, multinational trial, was done on diabetic patients with chronic kidney disease (CKD), aiming to investigate the effects of semaglutide versus placebo on kidney outcomes. Two groups of patients were included based on the eGFR and proteinuria; the first group had eGFR >50 - ≤75 ml/min/1.73 m^2 with urine albumin; creatinine ratio (UACR) > 300 to ≤5000, while the second group had eGFR >25 - <50 ml/min/1.73 m^2 with UACR >100 - ≤5000. The composite primary endpoint was time to first kidney failure, persistent >50% reduction in eGFR or death from kidney or cardiovascular (CV) causes [54]. After a median follow-up of 3.4 years, the researchers demonstrated a 24% decrease in the primary endpoint in the semaglutide group (n=1767) compared to the placebo group (n=1766) [55]. The severity of the baseline CKD had no significant effect on the beneficial effects noted in the semaglutide-treated group on the risk of CV death, myocardial infarction, or strokes [56]. To further study the effect of adding SGLT2 inhibitors to semaglutide for patients in the FLOW trial, the researchers found that regardless of the presence or absence of SGLT2i, semaglutide was beneficial in reducing composed renal outcomes [57].

6.2.2. Liraglutide

Mali and colleagues underwent a meta-analysis using randomized controlled trials that studied the effect of liraglutide on renal function in patients with DN. They reviewed 18 studies (n=1580) and showed that liraglutide efficiently controlled diabetes, overweight, and renal outcomes [59].

A randomized control trial by Mann and colleagues [46] (LEADER trial) assessed the renal outcome (new-onset macroalbuminuria, doubling of serum creatinine, ESKD, or renal-related death) in patients

(n=9,349) with DM II and high cardiovascular risk over a median follow-up period of 3.84 years. The researchers compared liraglutide versus placebo and showed the renal outcome to be significantly better in the liraglutide group. This result was mainly driven by the fewer new onsets of persistent macroalbuminuria, which occurred in fewer participants in the liraglutide group than in the placebo group.

6.2.3. Dulaglutide

The randomized control trial REWIND [60] was a study on patients with DM II (n=9,901). In this trial, which had a median follow-up of 5.4 years, the effects of dulaglutide (n=4,949) on renal outcome

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were compared with those of placebo (n=4952). The study demonstrated a significant decrease in renal outcomes with dulaglutide compared to placebo. The study also showed a superior effect of dulaglutide compared to placebo in decreasing new macroalbuminuria.

Dulaglutide in 2 doses, 1.5 mg (n=193) and 0.75 mg (n=190) were compared to insulin glargine (n=194) in diabetic patients with CKD stage 3 to 4 (AWARD 7 trial) [61] with the primary outcome being HBA1c and the secondary being eGFR and albuminuria. Dulaglutide in both doses was non-inferior to insulin glargine, with a significant improvement in eGFR in the dulaglutide-treated group. No difference was noted in UACR in both groups.

6.2.4. Efpeglenatide

Another drug studied was efpeglenatide in the AMPLITUDE-O trial [62]. This randomized placebo-controlled trial was done in 28 countries over 344 sites (n=4076). The study aimed to assess the effect of efpeglenatide versus placebo in patients with DM II with either a history of cardiovascular disease or current kidney disease on renal outcome; a decrease in kidney function, or macroalbuminuria. Follow up period was 1.81 years. The authors showed that the composite of renal outcome events was significantly lower in the Efpeglenatide-treated group but had more GI side effects in the treatment group.

6.3. Safety

Several studies compared the effects and safety of different GLP-1 drugs in diabetic patients. SUSTAIN 10 [63] compared the efficacy and safety between semaglutide and liraglutide. Both were given subcutaneously, showing the superiority of semaglutide over liraglutide in controlling diabetes but with more GI side effects.

The LEADER Trial Investigators [64] underwent a post-hoc analysis of the LEADER trial evaluating the safety of liraglutide. The authors focused on the effect of the presence (n=2158) or absence (n=7182) of CKD and the presence of macroalbuminuria (n=966) or microalbuminuria (n=2456) on the safety of the drug. The authors demonstrated that while the serious adverse events were higher in patients with CKD, no difference was noted in these adverse effects between the liraglutide-treated group versus those on placebo. No significant added adverse events were reported in patients with macroalbuminuria versus those with microalbuminuria.

To evaluate the efficacy and safety of oral semaglutide, the PIONEER 5 trial [65] was done on patients with DM II and CKD 3 (n=324). The trial was a multicenter randomized, double-blind study comparing semaglutide (n=163) to placebo (n=161), with an outcome being a change in hemoglobin A1c, body weight, and safety. The trial team demonstrated that oral semaglutide was effective and superior to placebo in lowering hemoglobin A1c and decreasing body weight and that aside from GI symptoms, semaglutide was safe in this population.

Similarly, the FLOW trial showed no serious adverse events on using semaglutide compared to placebo [54], and the SUSTAIN 1-7 trials demonstrated no added risk with semaglutide compared to the other drugs used in these trials [45,50–52].

7. Future Directions

Future directions for GLP-1RAs in DKD should focus on several key areas. Firstly, expanding the scope of clinical trials to include a broader range of patient populations with varying degrees of kidney function, particularly those with more advanced stages of CKD, will be essential. Recent trials, such as the FLOW trial, have demonstrated the renoprotective effects of semaglutide, but further research is needed to confirm these benefits in broader populations and over more extended follow-up periods. Additionally, investigating the potential synergistic effects of combining GLP-1RAs with other renoprotective therapies, such as SGLT2 inhibitors, could improve clinical outcomes by targeting multiple pathways in DKD progression. Moreover, preclinical studies suggest that GLP-1RAs exert protective effects beyond glycemic control, such as anti-inflammatory and anti-fibrotic actions, which warrants further exploration in non-diabetic CKD. Future research should also

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address the potential use of GLP-1RAs in earlier stages of DKD, focusing on prevention strategies rather than just treating established diseases. Lastly, as new GLP-1RAs and formulations (e.g., oral agents) become available, ongoing assessments of their long-term safety, efficacy, and impact on quality of life will be crucial to optimizing patient care.

8. Conclusions

Preclinical and clinical studies highlight the significant benefits of GLP-1 receptor agonists in improving renal outcomes for patients with diabetic kidney disease (DKD), mainly by reducing albuminuria. The data also confirm their safety in patients with diabetes and DKD. Multiple mechanisms likely contribute to their protective effects on kidney function. In summary, GLP-1RAs offer an exciting and valuable addition to our therapeutic options in the ongoing battle against DKD.

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