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GLP-1 RECEPTOR AGONISTS IN CHRONIC KIDNEY DISEASE: NEPHROPROTECTION BEYOND GLYCEMIC CONTROL - A REVIEW OF CURRENT LITERATURE

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is currently one of the major global health burdens and the number of people affected by this disease is still rising. CKD is strongly associated with type 2 diabetes mellitus (T2DM), obesity and cardiovascular diseases. Despite the fact that glucagon-like-peptide-1 receptor agonists were primarily developed as glucose-lowering agents, accumulating evidence suggests that their benefits extend beyond glycemic control and include significant renoprotective effects.
Aim: This review synthesises current evidence on the nephroprotective effects of GLP-1 receptor agonists in patients with CKD with emphasis on clinical trials outcomes and future therapeutic perspectives.
Materials and Methods: A narrative review of current literature was conducted in PubMed, Google Scholar, and Scopus. Relevant randomized controlled trials, meta-analyses, and recent review articles published between 2019 and 2026 were analyzed.
Results: GLP-1 receptor agonists expend nephroprotective effects through multiple pathways, including reduction of systemic inflammation, oxidative stress, endothelial dysfunction, albuminuria and intraglomerular hypertension. Additional benefits arise from weight reduction, blood pressure lowering and cardiovascular protection. Clinical trials such as LEADER, SUSTAIN-6, REWIND, and particularly the FLOW trial demonstrated significant reductions in renal composite outcomes and slower decline in estimated glomerular filtration rate (eGFR). The FLOW trial provided the first dedicated evidence that semaglutide significantly reduces the risk of kidney disease progression and cardiovascular death in patients with T2DM and CKD.
Conclusions: Current evidence suggests that GLP-1 receptor agonists represent an emerging nephroprotective therapy with benefits extending far beyond glycemic control. Their pleiotropic effects may position GLP-1 RAs as an important component of future cardio–renal–metabolic management strategies in CKD patients. Further studies are needed to clarify their role in non-diabetic CKD and advanced kidney disease.

KEYWORDS

GLP-1 Receptor Agonist, Chronic Kidney Disease, Glycemic Control, Kidney Failure, Nephroprotective Effects

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Introduction

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health.[1]. CKD represents a major global public health challenge, affecting more than 850 million people worldwide - contributing to morbidity, mortality and healthcare costs. The number of people with this disease is still rising, with the condition now the ninth leading cause of death globally, accounting for around 1,5 million deaths a year [2,3]. Moreover, the prevalence of CKD continues to rise due to the growing incidence of type 2 diabetes mellitus, obesity, hypertension and population aging [1,4]. Diabetic kidney disease is currently recognized as the leading cause of end-stage kidney disease worldwide and significantly contributes to cardiovascular complications and premature mortality [4,5].

Over the past two decades, therapeutic strategies in CKD management have focused predominantly on glycemic control, blood pressure reduction and renin-angiotensin-aldosterone system inhibition [1,6]. Although these interventions slow down CKD progression, residual renal and cardiovascular risk remains substantial [6,7]. Consequently, there is increasing interest in new pharmacological agents capable of exerting nephroprotective effects beyond conventional metabolic control [7].

Glucagon-like-peptide-1 receptor agonists (GLP-1 RAs), initially developed as antihyperglycemic agents for treatment of T2DM, have emerged as promising drugs with pleiotropic cardiovascular and renal effects [7-9]. Beyond glucose lowering, GLP-1 RAs demonstrate anti-inflammatory, antioxidative, natriuretic, antiatherogenic and antifibrotic properties that may contribute to kidney protection [7,8]. Large cardiovascular

outcome trials and dedicated renal analyses have shown reductions in albuminuria and slower decline in estimated glomerular filtration rate (eGFR) among patients receiving GLP-1 RAs [10-13].

Recent evidence suggests that nephroprotection associated with GLP-1 receptor agonists may be partially independent of glycemic control, indicating broader pathophysiological mechanisms involved in CKD progression [8, 14]. This has led to increasing incorporation of GLP-1 RAs into contemporary clinical guidelines for patients with T2DM and CKD [1,15].

Aim

The main goal of this narrative review is to evaluate evidence on the nephroprotective effects of using GLP-1 receptor agonists and related outcomes in adults with chronic kidney disease with particular emphasis on mechanisms extending beyond glycemic control. Addictionally, this review explores physiological mechanisms, pathophysiological pathways and evidence from major clinical trials assessing renal outcomes associated with GLP-1 RA therapy.

Methodology

This narrative review follows the standard methodology for narrative literature reviews. The main focus was on integrating the latest research evidence regarding how using the GLP-1 receptor agonists affects development or progression of chronic kidney disease.

The literature search was conducted in multiple electronic databases, including PubMed, Google Scholar, and Scopus.

It was mainly limited to articles published during the last 3-5 years with particular emphasis on the newest articles published in last year (2025) to reflect the most recent outlook. The older articles providing foundational clinical information were included when necessary.

Search terms were combined as follows: ‘’GLP-1 receptor agonist’’, ‘’Chronic Kidney Disease’’, ‘’Glycemic Control’’, ‘’Obesity’’, ‘’Kidney Failure’’, ‘’eGFR’’, ‘’Nephroprotective effects’’.

Boolean operators AND/OR were used to refine searches. Manual searches were additionally performed on reference lists of all retrieved studies.

Because of the narrative structure of this review, a formal risk-of-bias assessment and statistical synthesis of results were not performed. Instead, a qualitative synthesis of key findings is provided, grouped thematically according to the categories described in the Results section. High-quality systematic reviews and meta-analyses were prioritised, with individual RCTs included when synthesis-level evidence was lacking.

Results

Physiology of GLP-1 and mechanism of action

Glucagon-like-peptide-1 (GLP-1) is an incretin hormone secreted primarily by enteroendocrine L-cells located in the distal small intestine and colon in response to nutrient intake [16]. Following food ingestion, GLP-1 is released into the circulation and contributes to postprandial glucose homeostasis by enhancing glucose-dependent insulin secretion and suppressing glucagon release from pancreatic α-cells [16,17]. In addition, GLP-1 delays gastric emptying and promotes satiety through central nervous system pathways, thereby contributing to reduced caloric intake and body weight reduction [17,18].

Native GLP-1 has a short half-life due to rapid degradation by dipeptidyl peptidase (DPP-4) [17]. This limitation led to the development of long-acting GLP-1 receptor agonists that are resistant to enzymatic degradation and capable of providing sustained receptor activation [17, 19].

GLP-1 receptors are widely distributed throughout the body and are expressed not only in pancreatic β-cells but also in cardiovascular tissues, the gastrointestinal tract, the central nervous system, and the kidneys [20]. In renal tissue, GLP-1 receptor expression has been identified in proximal tubular cells, renal vasculature, and other nephron-associated structures, suggesting that GLP-1 receptor agonists may exert direct renal effects independent of their glucose-lowering properties [20,21].

Currently available GLP-1 receptor agonists include short-acting and long-acting agents such as exenatide, liraglutide, dulaglutide, semaglutide and lixisenatide. These agents differ in pharmacokinetic properties, administration frequency and receptor affinity - although they share common metabolic and cardioprotective actions [19,20].

The activation of GLP-1 receptors stimulates intracellular cyclic adenosine monophosphate (cAMP) signaling pathways, resulting in activation of protein kinase A (PKA) and exchange proteins directly activated by cAMP (EPAC) [17, 23]. These pathways regulate insulin secretion, improve cellular energy metabolism,

and influence inflammatory and oxidative stress responses. Experimental evidence indicates that GLP-1 receptor signaling may reduce reactive oxygen species generation, attenuate inflammatory pathway activation, and improve endothelial function [20,23].

Importantly, many of these biological effects are directly involved in the pathogenesis of chronic kidney disease. Consequently, activation of GLP-1 signaling pathways has been proposed as a potential mechanism linking GLP-1 receptor agonist therapy with nephroprotection beyond glycemic control [20,21].

Pathophysiological rationale for nephroprotection

The progression of CKD is driven by a complex interplay of hemodynamic, metabolic, inflammatory, and fibrotic mechanisms. Persistent glomerular hyperfiltration, endothelial dysfunction, oxidative stress, chronic low-grade inflammation, and activation of profibrotic signaling pathways contribute to progressive nephron loss and decline in renal function [1,20,24]. Hyperglycemia is a major contributor to these pathological processes in diabetic kidney disease (DKD), promoting the formation of advanced glycation end-products, mitochondrial dysfunction, and activation of inflammatory cascades [4,25].

However, metabolic disturbances alone do not fully explain the progression of CKD. Increasing evidence suggests that obesity, insulin resistance, hypertension, and systemic inflammation independently contribute to renal injury [26]. Excess adipose tissue functions as an active endocrine organ that releases proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1), thereby promoting chronic low-grade inflammation and oxidative stress [26,27]. These alterations contribute to endothelial dysfunction, activation of the renin–angiotensin–aldosterone system (RAAS), and increased intraglomerular pressure, ultimately accelerating CKD progression [26,28]. Obesity-related glomerulopathy has emerged as an important clinical entity linking excess body weight with renal dysfunction. Increased metabolic demand and adaptive glomerular hyperfiltration initially maintain renal function but eventually result in glomerular hypertrophy, podocyte injury, albuminuria, and progressive nephron loss [29]. Furthermore, obesity frequently coexists with hypertension, dyslipidemia, and atherosclerotic cardiovascular disease, amplifying vascular and renal damage [26,29].

GLP-1 receptor agonists may counteract these pathological processes through multiple mechanisms. Significant weight reduction associated with GLP-1 receptor agonist therapy improves insulin sensitivity, decreases systemic inflammation, and reduces glomerular hyperfiltration [18,22]. In addition, GLP-1 receptor activation has been associated with improvements in endothelial function, blood pressure regulation, and vascular homeostasis, all of which may contribute to preservation of renal function [20,30].

Experimental studies further suggest direct renoprotective actions of GLP-1 signaling. Activation of GLP-1 receptors has been shown to attenuate mesangial cell expansion, reduce podocyte injury, suppress inflammatory signaling pathways, and inhibit fibrotic remodeling within renal tissue [21,31]. These observations support the hypothesis that GLP-1 receptor agonists may influence several key pathways involved in CKD progression independently of glycemic control [20,31].

Taken together, the multifactorial pathophysiology of CKD provides a strong biological rationale for the use of GLP-1 receptor agonists as nephroprotective agents. Their ability to target metabolic, inflammatory, hemodynamic, and fibrotic pathways simultaneously may explain the favorable renal outcomes observed in clinical studies and supports their growing role in contemporary cardiorenal-metabolic medicine [20,14,15].

Mechanisms of nephroprotection beyond glycemic control

Accumulating evidence suggests that the renal benefits associated with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) cannot be explained solely by improvements in glycemic control. Although reduction of hyperglycemia undoubtedly contributes to slowing the progression of diabetic kidney disease, numerous experimental and clinical studies indicate that GLP-1 receptor agonists exert direct and indirect effects on inflammatory, oxidative, hemodynamic, vascular, and fibrotic pathways involved in chronic kidney disease (CKD) progression [20,32].

Anti-inflammatory effects

Chronic low-grade inflammation is a hallmark of CKD and contributes substantially to progressive nephron injury. Elevated circulating concentrations of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) are associated with accelerated decline in renal function and increased cardiovascular risk [24,33].Experimental studies have demonstrated that GLP-1 receptor activation suppresses inflammatory signaling through inhibition of nuclear factor kappa B (NF-κB) pathways, leading to reduced cytokine production and diminished inflammatory cell infiltration within renal tissue [21,34]. In both animal models and clinical studies, treatment with GLP-1 receptor agonists has been

associated with reductions in systemic inflammatory biomarkers, suggesting an important role of anti-inflammatory mechanisms in nephroprotection [32,34].

Reduction of oxidative stress

Oxidative stress is another major contributor to CKD progression. Excessive production of reactive oxygen species (ROS) promotes endothelial dysfunction, podocyte injury, mesangial expansion, and extracellular matrix accumulation [25,35]. GLP-1 receptor agonists appear to enhance antioxidant defense systems while simultaneously reducing ROS generation and mitochondrial dysfunction [35]. Experimental evidence suggests that activation of GLP-1 signaling pathways improves mitochondrial integrity and attenuates oxidative injury in renal tissues [35,36]. These effects may help preserve glomerular filtration barrier function and delay structural kidney damage.

Hemodynamic and natriuretic effects

Alterations in renal hemodynamics play a crucial role in the initiation and progression of CKD. Hyperfiltration and increased intraglomerular pressure contribute to glomerular injury and albuminuria [30]. LP-1 receptor agonists promote natriuresis and diuresis through inhibition of the sodium–hydrogen exchanger isoform 3 (NHE3) in proximal renal tubules [20,37]. Enhanced sodium excretion may improve volume regulation, reduce systemic blood pressure, and decrease intraglomerular hypertension [20,37]. Furthermore, modest but clinically meaningful reductions in systolic blood pressure observed during GLP-1 receptor agonist therapy may contribute to long-term renal protection [18, 22].

Antifibrotic activity

Renal fibrosis represents the final common pathway of CKD progression regardless of the underlying etiology. Transforming growth factor-beta (TGF-β) signaling plays a central role in extracellular matrix accumulation, fibroblast activation, and structural remodeling of renal tissue [24,38]. Experimental studies indicate that GLP-1 receptor agonists may attenuate TGF-β-mediated profibrotic signaling and reduce collagen deposition within the kidney [31,38]. By limiting fibrotic remodeling, GLP-1 receptor agonists may help preserve functional nephron mass and slow the progression toward end-stage kidney disease.

Improvement of endothelial function

Endothelial dysfunction is a characteristic feature of both CKD and cardiovascular disease. Reduced nitric oxide bioavailability, increased oxidative stress, and vascular inflammation contribute to impaired vasodilation and accelerated atherosclerosis [39]. GLP-1 receptor activation has been shown to improve endothelial function through enhanced nitric oxide production, reduced oxidative injury, and suppression of inflammatory signaling pathways [39,40]. These vascular effects may improve renal perfusion and reduce ischemic injury within the kidney microcirculation.

Weight reduction and metabolic benefits

Obesity and insulin resistance are increasingly recognized as independent risk factors for CKD progression [26]. Weight loss achieved with GLP-1 receptor agonists improves insulin sensitivity, reduces systemic inflammation, lowers blood pressure, and decreases glomerular hyperfiltration [18,22]. In addition, favorable effects on lipid metabolism and body composition may further reduce cardiovascular and renal risk [41]. The substantial weight reduction observed with newer GLP-1 receptor agonists, particularly semaglutide, has generated considerable interest in their potential role within integrated cardiorenal-metabolic management strategies [14,41].

Collectively, these mechanisms suggest that GLP-1 receptor agonists exert nephroprotective effects through multiple complementary pathways extending far beyond glycemic control alone. Their ability to simultaneously target inflammation, oxidative stress, hemodynamic abnormalities, endothelial dysfunction, fibrosis, and obesity provides a strong biological explanation for the favorable renal outcomes observed in major clinical trials [20,14,32].

Evidence from clinical trails

The nephroprotective potential of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has been progressively demonstrated through a series of large cardiovascular outcome trials (CVOTs) and, more recently, dedicated kidney outcome studies. Although early trials were primarily designed to evaluate cardiovascular safety, secondary renal analyses consistently suggested favorable effects on albuminuria, estimated glomerular filtration rate (eGFR) decline, and progression of diabetic kidney disease.

LEADER Trial

The LEADER trial was among the first large studies to demonstrate potential renal benefits of GLP-1 receptor agonist therapy. In this multicenter randomized controlled trial involving more than 9,000 patients with type 2 diabetes mellitus and high cardiovascular risk, liraglutide significantly reduced the occurrence of

nephropathy events compared with placebo. The observed benefit was driven primarily by a reduction in new-onset persistent macroalbuminuria, although favorable trends in other renal outcomes were also reported [10] These findings provided initial evidence that GLP-1 receptor agonists may influence kidney disease progression beyond glycemic control.

SUSTAIN-6 Trial

Further support for nephroprotection emerged from the SUSTAIN-6 trial evaluating semaglutide in patients with type 2 diabetes at high cardiovascular risk. Semaglutide significantly reduced the risk of new or worsening nephropathy compared with placebo, largely through reductions in persistent macroalbuminuria [11]. Subsequent post hoc analyses demonstrated beneficial effects across different chronic kidney disease risk categories, suggesting that semaglutide may provide renal protection even in patients with more advanced kidney impairment [15].

REWIND Trial

The REWIND trial expanded these observations to a broader population of patients with type 2 diabetes. In an exploratory renal analysis, dulaglutide reduced the incidence of a composite renal outcome consisting of new macroalbuminuria, sustained decline in eGFR, or need for renal replacement therapy [12]. Importantly, benefits were observed despite relatively preserved baseline renal function in many participants, indicating a potential role for GLP-1 receptor agonists in earlier stages of kidney disease.

AWARD-7 Trial

Unlike previous cardiovascular outcome trials, the AWARD-7 study specifically enrolled patients with moderate-to-severe chronic kidney disease. This randomized trial compared dulaglutide with insulin glargine in patients with type 2 diabetes and CKD stages 3–4. Over 52 weeks of follow-up, dulaglutide was associated with a slower decline in eGFR compared with insulin glargine while providing similar glycemic control [13]. These findings strengthened the hypothesis that renal benefits may extend beyond glucose lowering alone.

FLOW Trial

The most compelling evidence supporting nephroprotection with GLP-1 receptor agonists originates from the FLOW trial, the first dedicated kidney outcome trial evaluating a GLP-1 receptor agonist in patients with type 2 diabetes and chronic kidney disease. The study enrolled more than 3,500 participants with CKD and demonstrated that once-weekly semaglutide significantly reduced the risk of major kidney disease events, kidney failure, substantial eGFR decline, or cardiovascular death compared with placebo. The primary composite outcome was reduced by approximately 24%, leading to early trial termination because of clear efficacy.[14] Furthermore, semaglutide slowed the annual decline in kidney function and reduced both cardiovascular events and all-cause mortality. These findings represent the strongest evidence to date supporting the direct nephroprotective role of GLP-1 receptor agonists [14].

Meta-Analyses and Overall Evidence

Evidence from large meta-analyses has largely confirmed the renal benefits observed in individual clinical trials.[32] Across different GLP-1 receptor agonists, treatment has been associated with significant reductions in albuminuria progression and favorable effects on composite kidney outcomes [32]. Nevertheless, until the publication of FLOW, much of the evidence relied on secondary renal endpoints from cardiovascular outcome trials. Consequently, although confidence in the nephroprotective potential of GLP-1 receptor agonists has increased substantially, additional studies are still needed to clarify their role in non-diabetic CKD, advanced stages of kidney disease, and combination therapy with sodium-glucose cotransporter-2 inhibitors (SGLT2i) [14,32].

Overall, current clinical evidence supports GLP-1 receptor agonists as an important component of contemporary cardiorenal-metabolic therapy. Their demonstrated ability to reduce albuminuria, preserve kidney function, and improve cardiovascular outcomes provides strong clinical confirmation of the mechanistic pathways described in experimental studies [10-14].

Discussion

The accumulated evidence from experimental studies, mechanistic research, and large randomized clinical trials indicates that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) exert clinically meaningful nephroprotective effects in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). These effects appear to extend beyond improvements in glycemic control and involve multiple interrelated biological pathways, including anti-inflammatory, antioxidative, hemodynamic, antifibrotic, and metabolic mechanisms [14,20,32].

Importantly, renal benefits observed in major cardiovascular outcome trials such as LEADER, SUSTAIN-6, and REWIND were primarily driven by reductions in albuminuria, with more modest effects on hard renal endpoints such as end-stage kidney disease or initiation of dialysis [10-12]. This pattern suggests that GLP-1 RAs may be particularly effective in the early and intermediate stages of CKD, where functional and hemodynamic abnormalities predominate over irreversible structural damage [13,3].

The recent FLOW trial provides the strongest evidence to date that GLP-1 receptor agonism can modify clinically relevant kidney outcomes, demonstrating a significant reduction in a composite endpoint of kidney failure, sustained decline in eGFR, and cardiovascular death in patients with T2DM and CKD. These results position GLP-1 RAs as agents with disease-modifying potential in diabetic kidney disease rather than merely glucose-lowering therapies with secondary renal benefits [14].

From a pathophysiological perspective, the nephroprotective effects of GLP-1 RAs are likely multifactorial. As previously discussed, these agents reduce systemic inflammation, oxidative stress, and intraglomerular hypertension, while simultaneously improving endothelial function and promoting weight loss [2026,32]. This multimodal action distinguishes GLP-1 RAs from traditional renin–angiotensin–aldosterone system (RAAS) blockade, which primarily targets hemodynamic pathways [6].

A key clinical consideration is the positioning of GLP-1 RAs within contemporary cardiorenal-metabolic therapy. Current KDIGO 2024 guidelines and ADA Standards of Care recommend GLP-1 receptor agonists in patients with T2DM and CKD, particularly in those with established cardiovascular disease or high cardiovascular risk, often in combination with sodium-glucose cotransporter-2 (SGLT2) inhibitors [1,15,16]. This reflects an evolving paradigm in which CKD is increasingly understood as part of a broader cardiorenal-metabolic syndrome requiring multifaceted therapeutic approaches.

Comparative data suggest that SGLT2 inhibitors remain the first-line agents for slowing CKD progression due to their robust effects on hard renal endpoints, while GLP-1 RAs provide complementary benefits, particularly in reducing albuminuria, body weight, and atherosclerotic cardiovascular risk. The combination of both drug classes may therefore offer additive or potentially synergistic renal and cardiovascular protection, although direct head-to-head and combination trials remain limited [14,32].

Despite these promising findings, several limitations should be acknowledged. First, many renal outcomes in earlier trials were secondary or exploratory endpoints, limiting causal inference [10-12]. Second, heterogeneity between GLP-1 receptor agonists in terms of molecular structure, pharmacokinetics, and receptor affinity may translate into variable renal effects that are not yet fully characterized [19]. Third, evidence in non-diabetic CKD populations remains scarce, and it is currently unclear whether GLP-1 RAs exert similar nephroprotective effects in the absence of diabetes [20].

Future research should focus on several key areas. Direct comparisons between GLP-1 RAs and SGLT2 inhibitors, as well as combination therapy trials, are needed to define optimal treatment strategies in CKD. Additionally, long-term studies evaluating hard renal endpoints such as dialysis initiation and kidney transplantation are required to confirm disease-modifying effects. Finally, further mechanistic studies may help identify patient subgroups most likely to benefit from GLP-1 receptor agonist therapy based on metabolic, inflammatory, or genetic profiles [20,32].

GLP-1 receptor agonists represent an important therapeutic advancement in the management of patients with T2DM and CKD. Their nephroprotective effects, mediated through multiple complementary mechanisms and supported by emerging clinical evidence, support their integration into modern cardiorenal-metabolic treatment strategies [14,16].

Conclusions

The GLP-1 receptor agonists represent a promising therapeutic class with significant nephroprotective potential extending beyond glycemic control. Through anti-inflammatory, antioxidative, antifibrotic, natriuretic and metabolic effects, these agents may slow down progression of chronic kidney disease and reduce cardiovascular risk in patients with type 2 diabetes mellitus.

Current clinical evidence supports the beneficial impact of GLP-1 receptor agonists on albuminuria reduction and preservation of renal function, although further studies are needed to establish their role in advanced CKD and non-diabetic populations. The expanding role of GLP-1 RAs highlights the importance of integrated cardiorenal-metabolic management strategies in modern nephrology and diabetology.

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