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Mini Review

Glucagon-Like Peptide-1 Receptor Agonists and their Influence on Renal Metabolism

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Abstract

Glucagon-like peptide-1 Receptor Agonists (GLP-1 RAs) have emerged as a cornerstone in the management of type 2 diabetes mellitus, with expanding roles in cardiovascular and renal protection. Beyond glycemic control, these agents exert pleiotropic effects that influence renal hemodynamics, tubular function, inflammation, oxidative stress, and metabolic signaling pathways. GLP-1 receptors are expressed in renal tubular and vascular tissues, particularly in proximal tubular cells, suggesting direct renal actions. GLP-1 RAs promote natriuresis and diuresis through inhibition of the Sodium-Hydrogen Exchanger 3 (NHE3), improve endothelial function, and reduce intraglomerular pressure. Additionally, they modulate mitochondrial function, lipid metabolism, inflammatory cascades, and emerging metabolic pathways involving Sirtuin 1 (SIRT1), thereby attenuating renal injury progression. Recent large-scale cardiovascular and renal outcome trials have demonstrated that GLP-1 RAs significantly reduce albuminuria and slow the decline in estimated glomerular filtration rate, although their effects are less pronounced than those of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) on hard renal endpoints. Nevertheless, GLP-1 RAs provide complementary benefits, especially in patients with obesity, insulin resistance, and residual cardiovascular risk. This review synthesizes current evidence on the molecular and physiological mechanisms underlying renal effects mediated by GLP-1 RAs, explores their role in metabolic reprogramming within the kidney, and evaluates their clinical impact on chronic kidney disease progression. Emerging data suggest that GLP-1 RAs may redefine nephroprotective strategies when used in combination with other agents, highlighting their importance in a multidimensional approach to cardiorenal-metabolic disease.

Keywords: Glucagon-like peptide 1; GLP-1 receptor agonists; Diabetic nephropathies; Kidney function tests; Renal insufficiency; Chronic; Sodium-hydrogen exchanger 3; Inflammation mediators; Oxidative stress

Abbreviations: GLP-1 RAs: Glucagon-Like Peptide-1 Receptor Agonists; GLP-1: Glucagon-Like Peptide-1; SGLT2: Sodium-Glucose Cotransporter 2; SIRT1: Sirtuin 1

Introduction

Chronic kidney disease represents a major global health burden, particularly among individuals with type 2 diabetes mellitus. The interplay between hyperglycemia, hypertension, and metabolic dysregulation accelerates renal injury through complex hemodynamic and inflammatory pathways. Traditional therapies have focused on glycemic and blood pressure control; however, recent pharmacological advances have expanded the therapeutic landscape [1]. Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs), initially developed as antihyperglycemic agents, have demonstrated significant cardiovascular and renal benefits. These agents mimic endogenous Glucagon-Like Peptide-1 (GLP-1), a gut-derived incretin hormone that enhances glucose-dependent insulin secretion while suppressing glucagon release. Beyond these actions, GLP-1 receptors are expressed in multiple tissues, including the kidney, where they mediate direct and indirect effects [2]. GLP-1 receptors are expressed in renal tubular and vascular tissues, particularly in proximal tubular cells and renal vasculature.

This distribution supports both tubular and vascular mechanisms of action. Experimental studies have shown that receptor activation leads to intracellular cyclic Adenosine Monophosphate (cAMP) accumulation and activation of Protein Kinase A (PKA), influencing sodium handling and cellular metabolism [2].

Effects on renal hemodynamics

GLP-1 RAs exert favorable effects on renal hemodynamics through multiple pathways.

Natriuresis and tubular effects

One of the key mechanisms is inhibition of the Sodium-Hydrogen Exchanger 3 (NHE3) in the proximal tubule, leading to increased sodium excretion, reduced extracellular fluid volume and decreased blood pressure [2].

Glomerular hemodynamics

GLP-1 RAs may reduce intraglomerular pressure through modulation of renal vascular tone and improvement of endothelial nitric oxide availability. These effects help mitigate hyperfiltration, a hallmark of early diabetic nephropathy [2].

Metabolic effects in renal tissue

Mitochondrial function: GLP-1 RAs improve mitochondrial biogenesis and function through activation of Adenosine Monophosphate-Activated Protein Kinase (AMPK) and upregulation of peroxisome Proliferator-activated Receptor-Gamma Coactivator-1alpha (PGC-1α). This results in improved energy homeostasis and reduced cellular stress [2].

Lipid metabolism

Renal lipotoxicity is a key contributor to chronic kidney disease progression. GLP-1 RAs reduce lipid accumulation in renal cells, enhance fatty acid oxidation and decrease ectopic lipid deposition [2].

Glucose handling

Although Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors dominate this pathway, GLP-1 RAs contribute by improving systemic glycemic control and reducing glucotoxicity [1].

Anti-inflammatory and antioxidant effects

Chronic inflammation and oxidative stress are central to chronic kidney disease progression. GLP-1 RAs suppress Nuclear Factor Kappa B (NF-kB) signaling, reduce pro-inflammatory cytokines [Tumor Necrosis Factor Alpha (TNF-α), Interleukin-6 (IL-6)] and decrease Reactive Oxygen Species (ROS) production. These actions collectively protect renal structures from progressive damage [2].

Sirtuin 1 (SIRT1)-mediated metabolic regulation

Recent experimental evidence indicates that part of the pleiotropic effects of GLP-1 RAs may involve activation of the Nicotinamide Adenine Dinucleotide (NAD^+)-dependent deacetylase SIRT1, a key regulator of cellular metabolism, mitochondrial homeostasis, oxidative stress, inflammation and aging [3,4]. SIRT1 modulates several downstream targets, including peroxisome Proliferator-Activated Receptor Gamma Coactivator-1 Alpha (PGC-1α), Forkhead Box O (FOXO) transcription factors, Nuclear Factor Kappa B (NF-κB) and p53, thereby promoting mitochondrial biogenesis, improving energy metabolism and attenuating inflammatory responses [3,4]. Experimental studies suggest that GLP-1 receptor activation may enhance AMP-Activated Protein Kinase (AMPK)-SIRT1 signaling, contributing to improved mitochondrial function, increased fatty acid oxidation and reduced oxidative stress. Experimental evidence with exenatide has demonstrated SIRT1-dependent metabolic effects, whereas renal protective mechanisms are supported by experimental and translational studies investigating the role of SIRT1 in kidney disease [4-6].

Clinical Evidence

Cardiovascular outcome trials

Recent trials have demonstrated reduction in albuminuria, slower decline in estimated glomerular filtration rate and cardiovascular risk reduction [7-10].

Notable studies include

Researching Cardiovascular Events with a Weekly INcretin in Diabetes - REWIND (dulaglutide), SUSTAIN-6 (semaglutide) and LEADER (liraglutide) [8-10].

Dedicated renal outcomes

The FLOW trial (2024) provided strong evidence of kidney protection with semaglutide, showing reduced progression to kidney failure and lower risk of sustained estimated glomerular filtration rate decline [11].

Comparison with SGLT2 inhibitors

while SGLT2 inhibitors remain the first-line nephroprotective agents, GLP-1 RAs offer greater weight reduction, superior glycemic control and complementary cardiovascular benefits. Combination therapy is increasingly recommended [1].

Therapeutic implications

GLP-1 RAs are particularly beneficial in patients with type 2 diabetes mellitus and obesity, early-stage chronic kidney disease and high cardiovascular risk. They may be used alongside SGLT2 inhibitors and Renin-Angiotensin-Aldosterone System (RAAS) blockers [1].

Future directions

Emerging research areas include dual agonists (GLP-1/GIP), precision medicine approaches and direct renal-targeted therapies. Further trials are needed to clarify long-term renal outcomes [7-11].

Conclusion

GLP-1 receptor agonists represent a significant advancement in the management of cardiorenal-metabolic disease. Their multifaceted effects on renal metabolism, inflammation, and hemodynamics provide a strong rationale for their use in chronic

kidney disease prevention and treatment. As evidence continues to evolve, these agents are likely to play an increasingly central role in nephrology [7].

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