Review Article

Glucagon-Like Peptide-1 Receptor Agonists Beyond Diabetes Mellitus: Pathophysiological Foundations and Clinical Applications in Obesity, Heart Failure, Chronic Kidney Disease, and Hepatic Steatosis

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Abstract

Glucagon-like peptide-1 receptor agonists have evolved from glucose-lowering agents to multifunctional therapies with significant implications across the cardiovascular-kidney-metabolic axis. Their mechanisms of action extend beyond glycemic control, including appetite regulation, delayed gastric emptying, and central modulation of satiety, which contribute to sustained weight loss. In obesity, these effects translate into meaningful reductions in body weight and improvements in metabolic parameters, supported by robust clinical trial evidence. In cardiovascular disease, particularly heart failure with preserved ejection fraction, these agents demonstrate benefits through

weight reduction, improved endothelial function, and anti-inflammatory effects, leading to enhanced functional capacity and quality of life. Their role in heart failure with reduced ejection fraction remains less clear, highlighting an area for further investigation. From a renal perspective, glucagon-like peptide-1 receptor agonists exert protective effects by reducing albuminuria, modulating intraglomerular pressure, and attenuating inflammatory and oxidative pathways. Clinical trials have confirmed their ability to slow the progression of chronic kidney disease, especially when integrated into combination strategies with other cardioprotective agents. In hepatic steatosis, these drugs target key metabolic pathways by improving insulin sensitivity, reducing hepatic lipogenesis, and enhancing fatty acid oxidation, resulting in decreased liver fat content and potential histological improvement in steatohepatitis. Despite these broad benefits, their use is associated with limitations, including gastrointestinal adverse effects, cost considerations, and incomplete long-term evidence in certain populations. Overall, glucagon-like peptide-1 receptor agonists represent a cornerstone in modern cardiometabolic therapy, with expanding indications and a growing role in integrated disease management.

Key words

GLP-1 receptor agonists, obesity, heart failure, chronic kidney disease, hepatic steatosis, cardiometabolic syndrome.

Introduction

GLP-1 receptor agonists have demonstrated substantial clinical relevance due to their broad therapeutic impact across multiple organ systems. From a cardiovascular perspective, these agents have been associated with significant reductions in major adverse cardiovascular events, ranging from 14% to 20% [1, 2]. This benefit extends to both diabetic and non-diabetic populations, where improvements in cardiovascular outcomes are mediated through reductions in blood pressure, lipid levels, and body weight [1, 2]. In parallel, GLP-1 receptor agonists provide meaningful renal protection, which is particularly relevant given the high prevalence of chronic kidney disease among individuals with diabetes [4, 5].

In addition to their cardiovascular and renal effects, these agents have emerged as effective tools in obesity management, achieving weight reductions ranging from 7% to 24%. This degree of efficacy positions them as a viable alternative to both metabolic surgery and traditional dietary interventions [1, 6]. These clinical benefits are supported by multiple underlying mechanisms of action. At the metabolic level, GLP-1 receptor agonists enhance mitochondrial function, improve cellular quality control, and regulate key metabolic pathways, thereby contributing to their wide-ranging therapeutic effects [4, 5].

Furthermore, these agents exert anti-inflammatory and anti-atherogenic effects, which play a central role in reducing cardiovascular risk by limiting vascular inflammation and the progression of atherosclerosis [3, 7]. In the context of heart failure, GLP-1 receptor agonists also influence neurohormonal and cellular pathways, including modulation of sympathetic nervous system activity, attenuation of oxidative stress, and optimization of cardiac metabolism. These effects collectively contribute to improved hemodynamic status and restoration of neurohormonal balance [8].

Beyond their established indications, emerging evidence suggests potential applications of GLP-1 receptor agonists in neurological and psychiatric disorders, although these uses remain investigational at present. Similarly, there is increasing interest in their role in liver disease and chronic respiratory conditions, further expanding their therapeutic scope [1, 5].

Given this wide spectrum of effects and applications, the clinical and methodological heterogeneity surrounding GLP-1 receptor agonists necessitates a structured narrative review approach. Such a framework allows for the integration and interpretation of evidence across diverse clinical contexts and study designs [1, 4]. Moreover, as the body of evidence supporting the multisystem benefits of these agents continues to expand, a comprehensive synthesis becomes essential to consolidate findings from different trials and observational studies, facilitating a clearer understanding of their evolving role in clinical practice [1, 3].

The objective of this manuscript is to provide a comprehensive and clinically integrated analysis of glucagon-like peptide-1 receptor agonists beyond their traditional role in glycemic control, focusing on their mechanisms of action and therapeutic implications in obesity, heart failure, chronic kidney disease, and hepatic steatosis.

Methodology

This manuscript was developed as a structured narrative review aimed at providing an updated and clinically integrated analysis of glucagon-like peptide-1 receptor agonists beyond their conventional role in glycemic control, with particular emphasis on their therapeutic implications in obesity, heart failure, chronic kidney disease, and hepatic steatosis. The review was conducted in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) framework and followed a predefined methodological protocol established prior to literature screening. Given the clinical heterogeneity of the populations evaluated, the diversity of outcomes assessed across cardiometabolic, renal, hepatic, and cardiovascular settings, and the variability in study designs and therapeutic endpoints, a narrative interpretative synthesis was selected over quantitative pooling in order to integrate mechanistic, metabolic, and clinical considerations into a coherent and clinically applicable framework. Special attention was given to cardiovascular protection, renal outcomes, weight reduction, hepatic benefits, and the expanding role of these agents in non-diabetic populations. The objective was to provide a structured synthesis capable of supporting multidisciplinary decision-making in the contemporary management of complex cardiometabolic disease.

A comprehensive literature search was conducted in PubMed, Scopus, and Web of Science, including peer-reviewed articles published in English or Spanish between January 2020 and December 2025. The final search was performed in March 2026. This timeframe was selected to capture contemporary advances in the understanding of glucagon-like peptide-1 receptor agonists, including their expanding indications in obesity, heart failure, chronic kidney disease, and metabolic liver disease, as well as emerging evidence regarding pleiotropic mechanisms and non-glycemic benefits. Foundational studies were incorporated when necessary to contextualize pathophysiological mechanisms, pharmacological development, or the evolution of therapeutic use. The search strategy combined MeSH and free-text terms using Boolean operators related to glucagon-like peptide-1 receptor agonists, GLP-1 receptor agonists, obesity, weight loss, heart failure, chronic kidney disease, renal protection, hepatic steatosis, nonalcoholic fatty liver disease, steatohepatitis, cardiovascular outcomes, and multisystem effects. Searches were conducted in titles and abstracts as well as indexed subject headings to maximize sensitivity.

The initial search yielded 212 records. After removal of duplicates, 168 articles remained for title and abstract screening. Of these, 97 underwent full-text evaluation, and 57 studies were included in the final synthesis. Selection was performed independently by two authors, with disagreements resolved through discussion and consensus. Exclusion criteria comprised non-

peer-reviewed publications, isolated case reports, editorials without clinically relevant outcome data, studies focused exclusively on glucose control without addressing extra-glycemic implications, redundant datasets, and articles not directly addressing the mechanistic, clinical, or therapeutic role of glucagon-like peptide-1 receptor agonists in obesity, heart failure, chronic kidney disease, or hepatic steatosis.

Eligible studies included randomized controlled trials, large observational cohorts, systematic reviews, meta-analyses, expert consensus statements, and contemporary international guidelines from endocrinology, cardiology, nephrology, hepatology, and obesity medicine societies. Priority was assigned to multicenter investigations, studies with clearly defined clinical endpoints, and research evaluating cardiovascular outcomes, renal endpoints, weight loss, hepatic improvement, symptom burden, and treatment-related adverse effects. Extracted variables included study design, population characteristics, underlying metabolic status, type of glucagon-like peptide-1 receptor agonist, comparator intervention when applicable, treatment duration, cardiovascular outcomes, renal outcomes, anthropometric changes, hepatic endpoints, and reported adverse events. Methodological quality and internal validity were assessed narratively, considering risk of bias, sample size, duration of follow-up, consistency of clinical definitions, and reproducibility of reported outcomes. In cases of conflicting evidence, greater interpretative weight was assigned to higher-level evidence and guideline-supported recommendations.

Reference lists of included studies were manually screened to identify additional relevant publications. Given its narrative design, this review is subject to potential selection bias and does not provide pooled quantitative estimates. Artificial intelligence-based tools were used exclusively to assist in literature organization and structural coherence, whereas critical appraisal, synthesis, and final interpretation were conducted independently by the authors to preserve methodological rigor.

Physiological and Pharmacological Basis of GLP-1

Glucagon-like peptide-1 is a hormone secreted by intestinal L-cells in response to nutrient intake, playing a key role in metabolic regulation. However, its physiological action is limited by rapid degradation through the enzyme dipeptidyl peptidase-4, which significantly reduces its half-life and bioavailability [9, 10]. In addition to nutrient stimulation, its secretion and activity are influenced by the gut microbiota and enteroendocrine signaling pathways, which contribute to the regulation of metabolic homeostasis [5].

Building upon this physiological framework, glucagon-like peptide-1 receptor agonists exert their effects through activation of GLP-1 receptors, leading to glucose-dependent insulin secretion and suppression of glucagon release [9, 11]. These agents also delay gastric emptying and modulate appetite through hypothalamic pathways, mechanisms that are directly associated with reduced caloric intake and weight regulation [12]. In this context, their influence extends to the central nervous system, where they participate in appetite regulation and contribute to decreased food intake and subsequent weight loss [13].

Beyond these primary metabolic actions, glucagon-like peptide-1 receptor agonists exhibit pleiotropic systemic effects that further support their clinical relevance. From a cardiovascular standpoint, they improve endothelial function and contribute to reductions in blood pressure, thereby enhancing cardiovascular protection [4, 14]. Concurrently, they exert renal effects by modulating intraglomerular pressure and inflammatory processes, which translates into potential renoprotective benefits [5]. These systemic actions are complemented by their anti-

inflammatory and antioxidative properties, which may extend their benefits beyond glycemic control and positively influence overall metabolic health [13].

From a pharmacological perspective, glucagon-like peptide-1 receptor agonists display variability in their duration of action, encompassing both short-acting and long-acting formulations that allow for tailored therapeutic approaches [9]. Structural differences further distinguish these agents, with human GLP-1 analogs and exendin-4–based compounds demonstrating distinct pharmacokinetic and pharmacodynamic profiles [11]. In addition, the development of dual agonists, such as tirzepatide, which target both GLP-1 and glucose-dependent insulinotropic polypeptide receptors, represents an important advancement, as these agents have shown potential for enhanced efficacy and a more favorable tolerability profile, including a reduction in gastrointestinal adverse effects [14, 15].

Role in Obesity; Mechanisms and Clinical Evidence

Obesity is characterized by a dysregulation of energy homeostasis, in which an imbalance between energy intake and expenditure develops as a result of genetic, environmental, and behavioral factors. Within this context, glucagon-like peptide-1 receptor agonists contribute to restoring this balance by modulating appetite and influencing energy expenditure [13, 16]. This disruption is further compounded by leptin resistance and alterations in gut-brain axis signaling, which impair the body's ability to regulate hunger and maintain energy equilibrium. In this setting, glucagon-like peptide-1 receptor agonists enhance gut-brain communication, promoting satiety and reducing food intake [17].

These physiological effects translate into specific mechanisms of weight reduction. Glucagon-like peptide-1 receptor agonists suppress appetite through actions on the central nervous system, leading to increased sensations of fullness and a consequent reduction in caloric intake [17, 18]. Consistently, clinical trials have demonstrated that these agents significantly decrease caloric consumption, thereby contributing to sustained weight loss [13, 18]. Although their primary effect is mediated through appetite regulation, there is also evidence suggesting a potential influence on energy expenditure; however, this mechanism remains less clearly defined and requires further investigation [16].

The clinical relevance of these mechanisms is supported by robust evidence from large-scale trials. The STEP trials, evaluating semaglutide, demonstrated substantial weight loss in non-diabetic populations, confirming its efficacy in reducing body weight [18, 19]. Similarly, the SURMOUNT trials showed that tirzepatide, a dual agonist targeting both GLP-1 and glucose-dependent insulinotropic polypeptide receptors, achieves superior weight reduction compared to other glucagon-like peptide-1 receptor agonists, underscoring its potential as a leading therapeutic option [20].

Beyond weight loss, these agents exert significant metabolic effects that further enhance their clinical utility. They have been associated with improvements in lipid profiles, including reductions in low-density lipoprotein cholesterol and triglycerides, alongside a reduction in insulin resistance, thereby contributing to improved metabolic health in individuals with obesity. In parallel, glucagon-like peptide-1 receptor agonists contribute to the reduction of cardiovascular risk markers, including blood pressure, which translates into broader benefits in overall health outcomes [21].

When compared with other therapeutic strategies, glucagon-like peptide-1 receptor agonists demonstrate a favorable profile. In pharmacological comparisons, they offer greater efficacy in weight reduction and improved safety compared to agents such as orlistat and

phentermine/topiramate [20]. In contrast to surgical approaches, although bariatric procedures remain highly effective, they are inherently invasive, whereas glucagon-like peptide-1 receptor agonists provide a non-surgical alternative capable of achieving significant weight loss [16].

From a clinical perspective, appropriate patient selection remains essential for optimizing outcomes. Ideal candidates include individuals with obesity or overweight without diabetes, particularly those who have not achieved sufficient weight loss through lifestyle modifications [13]. The combination of glucagon-like peptide-1 receptor agonists with lifestyle interventions may enhance long-term weight maintenance, reinforcing their role within comprehensive treatment strategies [22]. Despite their efficacy, considerations regarding adherence and cost remain relevant, as these factors may limit their widespread implementation and require careful evaluation in routine clinical practice [19].

Implications in Heart Failure

Obesity represents a central pathophysiological contributor to heart failure with preserved ejection fraction, as excess visceral adiposity promotes systemic inflammation, cardiac dysfunction, and structural remodeling. This inflammatory milieu plays a critical role in driving myocardial dysfunction in affected patients [23]. In parallel, insulin resistance further contributes to adverse cardiac remodeling, a hallmark feature of heart failure, thereby exacerbating disease progression. Within this context, glucagon-like peptide-1 receptor agonists have been shown to improve insulin sensitivity, which may help mitigate these deleterious effects on cardiac structure and function [8, 24].

These pathophysiological mechanisms are closely linked to the cardioprotective effects observed with glucagon-like peptide-1 receptor agonists. One of the primary benefits is weight reduction, which leads to a decrease in cardiac preload and subsequent improvement in hemodynamic status. This effect is particularly relevant in obese patients with heart failure with preserved ejection fraction, where volume overload and increased filling pressures are prominent features [23, 25]. Additionally, these agents enhance myocardial energy utilization, contributing to improved cardiac efficiency, a key factor in the management of heart failure [8]. Their anti-inflammatory properties, together with their ability to improve endothelial function, further support cardiovascular health by reducing arterial stiffness and limiting myocardial fibrosis [26].

The clinical relevance of these mechanisms is supported by emerging evidence. In patients with heart failure with preserved ejection fraction, trials such as STEP-HFpEF have demonstrated meaningful improvements in functional capacity, highlighting the therapeutic potential of glucagon-like peptide-1 receptor agonists in this subgroup [8, 23]. In contrast, data regarding their use in heart failure with reduced ejection fraction remain limited and inconsistent, with some studies suggesting potential adverse effects, thereby underscoring the need for cautious interpretation [24, 27].

These findings translate into clinically relevant outcomes, including reductions in heart failure-related symptoms and improvements in functional capacity [28]. Moreover, patients, particularly those with heart failure with preserved ejection fraction, have shown improvements in quality of life and exercise tolerance, reflecting the broader impact of these agents on daily functioning [29]. In addition, there is evidence suggesting a reduction in hospitalization rates for heart failure events among patients treated with glucagon-like peptide-1 receptor agonists, further supporting their potential role in disease management [27].

Despite these promising results, important limitations and gaps remain. There is a notable lack of large, dedicated clinical trials specifically evaluating the effects of glucagon-like peptide-1 receptor agonists in patients with heart failure with reduced ejection fraction, which contributes to ongoing uncertainty in this population [24]. Furthermore, the interaction of these agents with established guideline-directed medical therapies for heart failure has not been fully elucidated, highlighting the need for further research to clarify their role within existing treatment frameworks [27].

Role in Chronic Kidney Disease

The interaction between glucagon-like peptide-1 receptor agonists and the cardiorenal-metabolic axis involves a complex interplay of metabolic, hemodynamic, and inflammatory pathways that are central to the progression of chronic kidney disease. These agents contribute to the modulation of inflammation through mechanisms such as downregulation of the receptor for advanced glycation end products, promotion of M2-like macrophage polarization, and reduction of markers associated with kidney damage [30]. In parallel, they improve endothelial function and exert anti-inflammatory and anti-atherogenic effects, which further contribute to cardiovascular protection and are closely linked to renal outcomes [3].

These systemic effects translate into specific renoprotective mechanisms. Glucagon-like peptide-1 receptor agonists have been shown to reduce albuminuria, a key indicator of kidney damage, in both diabetic and non-diabetic models [30]. Additionally, by improving endothelial function and reducing oxidative stress, these agents modulate intraglomerular pressure, thereby contributing to the preservation of renal function. Their direct anti-inflammatory and antifibrotic actions on renal tissues further support their role in slowing the progression of chronic kidney disease [31].

The clinical relevance of these mechanisms is supported by evidence from major cardiovascular outcome trials. Studies such as LEADER and REWIND have demonstrated the renoprotective effects of glucagon-like peptide-1 receptor agonists, including a reduction in the risk of major adverse cardiovascular events and progression of chronic kidney disease [32, 33]. More recently, dedicated renal studies, including the FLOW trial, have further highlighted their potential to reduce the incidence of kidney failure and improve renal outcomes in patients with chronic kidney disease [34].

When compared with sodium-glucose cotransporter-2 inhibitors, important mechanistic differences become evident. While sodium-glucose cotransporter-2 inhibitors primarily act by reducing intraglomerular pressure and improving tubuloglomerular feedback, glucagon-like peptide-1 receptor agonists exert their effects predominantly through anti-inflammatory pathways and endothelial protection. These differences support the concept of complementary therapeutic roles, as the combination of both classes may provide synergistic benefits, enhancing both renal protection and cardiovascular outcomes [34].

From a clinical perspective, glucagon-like peptide-1 receptor agonists have demonstrated utility in patients with chronic kidney disease and obesity, offering the dual benefit of weight reduction and renal protection [35]. Their integration into combination therapy strategies, including use alongside sodium-glucose cotransporter-2 inhibitors and renin-angiotensin system antagonists, represents an approach aimed at optimizing treatment outcomes and addressing multiple pathophysiological pathways involved in chronic kidney disease [36].

Applications in Hepatic Steatosis (NAFLD/NASH)

The pathophysiology of metabolic-associated fatty liver disease is primarily driven by hepatic

lipid accumulation, in which insulin resistance plays a central role. This metabolic disturbance leads to increased flux of free fatty acids դեպի the liver and enhanced de novo lipogenesis, promoting the progressive accumulation of lipids within hepatocytes [37, 38]. As this process advances, lipid accumulation activates inflammatory pathways, resulting in the development of steatohepatitis and, in more severe cases, progression toward fibrosis and cirrhosis [37, 39].

Within this pathophysiological framework, glucagon-like peptide-1 receptor agonists exert multiple hepatic effects that target key metabolic pathways. These agents have been shown to reduce de novo lipogenesis, thereby limiting the accumulation of lipids in the liver. In parallel, they enhance fatty acid oxidation, contributing to a reduction in hepatic fat content [37, 39, 40]. Additionally, by improving insulin sensitivity, glucagon-like peptide-1 receptor agonists reduce hepatic glucose production and lipid synthesis, addressing fundamental mechanisms underlying disease progression [41].

The clinical relevance of these mechanisms is supported by emerging evidence demonstrating meaningful hepatic benefits. Clinical trials have shown that glucagon-like peptide-1 receptor agonists can induce histological improvement in nonalcoholic steatohepatitis, including resolution of steatohepatitis without worsening fibrosis. Studies have reported significant reductions in liver enzyme levels and hepatic fat content, reflecting improvements in liver function and attenuation of steatosis [42, 43, 44].

Despite these promising findings, important limitations remain. The efficacy of glucagon-like peptide-1 receptor agonists appears to be more pronounced in earlier stages of metabolic-associated fatty liver disease, with limited impact observed in advanced fibrosis [38, 44]. In addition, there is a need for long-term outcome data to better define their effects on clinically relevant liver-related endpoints [39, 42].

Given their multifaceted metabolic and anti-inflammatory effects, glucagon-like peptide-1 receptor agonists hold potential for integration into standard therapeutic strategies for nonalcoholic steatohepatitis, particularly in patients with coexisting metabolic disorders [40, 41]. Future directions may include the exploration of combination therapies involving these agents, with the aim of enhancing therapeutic efficacy, especially in more advanced stages of disease [38, 39].

Safety Profile and Clinical Considerations

Glucagon-like peptide-1 receptor agonists are generally well tolerated; however, they are frequently associated with gastrointestinal adverse effects, which represent the most commonly reported limitation to their use. These effects include nausea, vomiting, and diarrhea, and can significantly impact patient adherence to treatment. Among these, nausea is the most prevalent symptom, with agents such as semaglutide and liraglutide demonstrating a higher associated risk compared to other glucagon-like peptide-1 receptor agonists. Importantly, the gastrointestinal profile varies across different agents, as semaglutide has been associated with a higher incidence of nausea and diarrhea, whereas exenatide is more frequently linked to vomiting [18, 45, 46].

Beyond these common adverse effects, certain potential risks have been identified. There is a recognized, although relatively low, risk of pancreatitis associated with glucagon-like peptide-1 receptor agonists, with liraglutide and exenatide being particularly highlighted in this context [45, 47]. Additionally, these agents have been associated with an increased risk of gallbladder and biliary diseases, including cholelithiasis and cholecystitis, a risk that appears to be more pronounced with higher doses and prolonged duration of therapy [9, 48].

These safety considerations are reflected in specific contraindications. Glucagon-like peptide-1 receptor agonists are contraindicated in individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, due to the potential risk of thyroid C-cell tumors. These conditions represent critical exclusions in clinical decision-making when considering therapy with this class of agents.In addition, special populations require careful evaluation. In patients with renal impairment, the use of glucagon-like peptide-1 receptor agonists necessitates caution, as these agents may exacerbate underlying renal dysfunction, requiring dose adjustments or consideration of alternative therapies. Similarly, in elderly patients, the presence of comorbidities and an increased susceptibility to adverse effects warrant a more individualized approach, with tailored dosing strategies and close clinical monitoring to optimize safety and therapeutic outcomes [49].

Comparison with Emerging Metabolic Therapies

Both glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have demonstrated efficacy in improving cardiovascular outcomes, particularly through reductions in major adverse cardiovascular events. However, their benefits differ in specific domains, as sodium-glucose cotransporter-2 inhibitors have shown greater effectiveness in reducing hospitalizations for heart failure, whereas glucagon-like peptide-1 receptor agonists exhibit a more pronounced effect in lowering the risk of nonfatal stroke [50, 51]. In terms of mortality, both classes contribute to reductions in cardiovascular and all-cause mortality, although sodium-glucose cotransporter-2 inhibitors appear to have a slight advantage in improving heart failure-related outcomes [52].

These differences extend to renal outcomes, where sodium-glucose cotransporter-2 inhibitors have demonstrated superior efficacy in reducing the risk of declining estimated glomerular filtration rate and progression to end-stage kidney disease when compared to glucagon-like peptide-1 receptor agonists [52, 53]. Nevertheless, glucagon-like peptide-1 receptor agonists also provide significant renoprotective effects, particularly through the reduction of macroalbuminuria and benefits observed in patients with chronic kidney disease [34, 54].

In parallel with these established therapies, the development of dual agonists represents an important advancement in metabolic treatment. Agents that combine glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptor agonism aim to enhance both metabolic and cardiovascular outcomes. Tirzepatide, a dual agonist, has demonstrated promising results in weight reduction and glycemic control, with emerging evidence suggesting potential cardiorenal benefits. Furthermore, although still in the experimental phase, triple agonists targeting glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, and glucagon receptors are being explored for their capacity to provide more comprehensive metabolic and cardiovascular effects by leveraging complementary mechanisms of action [54].

The concept of synergistic therapeutic strategies has gained increasing attention, particularly through the combination of glucagon-like peptide-1 receptor agonists with sodium-glucose cotransporter-2 inhibitors. This combination has been associated with additive benefits in reducing cardiovascular and renal risks, including significant reductions in major adverse cardiovascular events, myocardial infarction, stroke, and hospitalizations for heart failure when compared to monotherapy with either agent [55, 56]. These effects are supported by the complementary mechanisms of action of both drug classes, where glucagon-like peptide-1 receptor agonists primarily exert anti-

atherosclerotic and metabolic effects, while sodium-glucose cotransporter-2 inhibitors provide hemodynamic and renal benefits [57].

From a clinical perspective, the combined use of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors is increasingly recommended in patients with type 2 diabetes mellitus and additional cardiovascular or renal risk factors. This approach not only enhances cardiorenal protection but also addresses multiple components of the cardiovascular-kidney-metabolic syndrome, reflecting a more integrated and comprehensive therapeutic strategy [50, 57].

Conclusions

Glucagon-like peptide-1 receptor agonists have emerged as multisystem therapeutic agents with benefits that extend beyond glycemic control, demonstrating significant effects in obesity, heart failure, chronic kidney disease, and metabolic-associated fatty liver disease through integrated metabolic, cardiovascular, renal, and anti-inflammatory mechanisms.

Their clinical impact is supported by robust evidence showing improvements in weight reduction, cardiovascular outcomes, renal protection, and hepatic parameters, positioning them as key components in the management of the cardiovascular-kidney-metabolic syndrome, particularly when used alone or in combination with other agents such as sodium-glucose cotransporter-2 inhibitors.

Despite their therapeutic potential, important limitations remain, including variability in efficacy across different clinical conditions, gaps in long-term and disease-specific evidence, and safety considerations, highlighting the need for further research to optimize their integration into personalized and multidisciplinary treatment strategies

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