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Therapeutic Spectrum of GLP-1 Receptor Agonist: From Glycemic Control to Metabolic Protection

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ABSTRACT

Introduction. Type 2 diabetes mellitus (T2DM) and obesity are major global health challenges. They are associated with cardiovascular, renal, and metabolic complications. Traditional therapies primarily target glycemic control but do not fully prevent long-term complications. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as multi-organ protective agents, offering benefits beyond glucose lowering.

Aim of the study. This review provides a comprehensive overview of GLP-1 RAs. It covers their pharmacology, glycemic control, obesity management, cardiovascular and renal protection, safety profile, and emerging therapeutic indications. The objective is to highlight their therapeutic potential and support clinicians in individualized treatment planning.

Materials and methods. This narrative review is based on a structured literature search conducted in PubMed and Google Scholar up to September 2025, using the following terms: GLP-1 receptor agonist, type 2 diabetes, obesity, cardiovascular outcomes, renal outcomes, weight loss, and neuroprotection. Additional relevant articles were identified through manual review of reference lists from key publications.

Conclusion. GLP-1 RAs represent multifaceted therapeutic agents that improve glycemic control, induce significant weight loss and confer cardiovascular and renal protection. They are generally well tolerated, with gastrointestinal effects being the most common adverse events. Individualized therapy and ongoing research into novel agents and combination strategies may further enhance clinical outcomes in patients with T2DM, obesity, and cardiometabolic risk.

Keywords: GLP-1 receptor agonists, type 2 diabetes mellitus, obesity, cardiovascular protection, renal protection, weight loss, neuroprotection

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity represent major global health challenges. They are closely associated with cardiovascular and renal complications. Traditional therapy has focused on glycemic control. However, evidence shows that lowering glucose alone does not fully prevent long-term complications.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), developed from incretin biology, have emerged as a key advance in diabetes management. They enhance glucose-dependent insulin secretion, suppress glucagon, delay gastric emptying, and promote satiety. Importantly, GLP-1 receptor agonists also have effects beyond the pancreas. They influence the cardiovascular system, kidneys, and nervous system. This provides protective benefits across multiple organs. [1].

The 2025 American Diabetes Association (ADA) Standards of Care recommend GLP-1 RAs not only for glycemic management. They are also recommended for weight reduction and cardiovascular risk reduction in patients with type 2 diabetes, independent of baseline glycated hemoglobin (HbA1c) or metformin use [29]. This review highlights the therapeutic spectrum of GLP-1 RAs, from established glycemic benefits to emerging cardiometabolic, renal and neuroprotective effects.

AIM OF THE STUDY

This review aims to synthesize current evidence regarding glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in type 2 diabetes mellitus and obesity. It focuses on their pharmacology, clinical efficacy, metabolic and organ-protective benefits, safety profile and emerging therapeutic applications, with the goal of providing clinicians with an updated, practical overview for individualized patient management.

MATERIALS AND METHODS

This review was designed as a narrative synthesis of the scientific literature concerning glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in type 2 diabetes mellitus, obesity, and related cardiometabolic and renal outcomes. A structured search of PubMed and Google Scholar was performed for publications up to September 2025, using the following keywords: GLP-1 receptor agonist, type 2 diabetes, obesity, weight loss, cardiovascular outcomes, renal outcomes, neuroprotection. Additional publications were identified by reviewing reference lists of key articles. Only articles published in English were considered.

Pharmacology and mechanisms of action

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are synthetic analogs of the endogenous incretin hormone GLP-1. They are designed to enhance their physiological effects while resisting enzymatic degradation by dipeptidyl peptidase-4 (DPP-4). GLP-1 RAs improve glycemic control through a dual mechanism. They enhance glucose-dependent insulin secretion from pancreatic β-cells and suppress inappropriate glucagon release. This mechanism helps control postprandial and fasting glucose while minimizing the risk of hypoglycemia. [1,2,6].

Beyond pancreatic effects, GLP-1 RAs slow gastric emptying and modulate central satiety pathways. They also confer additional benefits beyond the pancreas on cardiovascular, renal and metabolic systems [1,2]. GLP-1 RAs have different pharmacokinetic profiles that affect efficacy and tolerability. Short-acting agents mainly reduce postprandial glucose by delaying gastric emptying. Long-acting formulations provide greater reductions in fasting plasma glucose and overall HbA1c, with smoother plasma concentration profiles [7,8].

Routes and frequency of administration further influence adherence and outcomes. GLP-1 RAs are available as daily or weekly subcutaneous injections. Recently, oral semaglutide has become available, offering convenience and potentially improving long-term adherence [3,4]. Therapy choice and dosing can therefore be tailored to individual patient needs.

GLP-1 RAs in glycemic control

GLP-1 RAs have shown robust efficacy in lowering HbA1c and improving both fasting and postprandial glucose levels in patients with type 2 diabetes mellitus. Their dual mechanism of action involves both enhancement of glucose-dependent insulin secretion and suppression of inappropriate glucagon release, which together contribute to improved glycemic control. As a result, the intrinsic risk of hypoglycemia with GLP-1 receptor agonists is very low. This property clearly differentiates them from sulfonylureas and insulin, which can promote insulin release or activity regardless of ambient glucose concentrations, thereby increasing the likelihood of hypoglycemic episodes. [1,2,6].

Clinical trials and head-to-head studies of exenatide formulations, highlight clear pharmacodynamic differences between agents. Short-acting GLP-1 RAs, such as exenatide twice daily, predominantly target postprandial hyperglycemia by delaying gastric emptying. Long-acting preparations, including liraglutide and once-weekly exenatide, achieve stronger reductions in fasting plasma glucose and overall HbA1c. These trials consistently demonstrate

superior glycemic durability with long-acting agents, while both formulations improve glucose profiles across different phases of the day [7,8].

Overall, GLP-1 RAs represent a flexible therapeutic option, with agent selection and dosing tailored to individual glycemic patterns and treatment goals.

Obesity and Metabolic Effects

GLP-1 RAs have become effective therapies for weight reduction and metabolic improvement. In individuals with overweight or obesity, GLP-1 RAs consistently induce clinically meaningful weight loss, primarily through central mechanisms. These include modulation of hypothalamic satiety centers and mesolimbic reward pathways, which reduce appetite, enhance satiety and decrease hedonic feeding. Additionally, modest increases in energy expenditure may contribute to overall weight reduction [4,5]. It has been shown that once-weekly subcutaneous semaglutide 2.4 mg produces substantial weight loss in adults with overweight or obesity, with average reductions of approximately 10-15% of baseline body weight over 52 weeks. Clinically meaningful benefits are observed in individuals both with and without type 2 diabetes, and semaglutide demonstrates superior efficacy compared with other pharmacologic treatments for obesity [19]. Comparable reductions in body weight were observed in earlier trials with liraglutide 3.0 mg [20].

Beyond effects on body weight, GLP-1 RAs improve adipose tissue function and enhance insulin sensitivity. They also favorably influence liver metabolism. These agents reduce visceral and ectopic fat deposition and decrease adipocyte size. Additionally, GLP-1 RAs mitigate adipose tissue inflammation and modulate adipokine secretion. Collectively, these actions contribute to improved metabolic profiles [21].

Cardiovascular Benefits

GLP-1 RAs confer significant cardiovascular protection in patients with T2DM. Evidence from major cardiovascular outcome trials (CVOTs) has consistently demonstrated reductions in major adverse cardiovascular events (MACE). The LEADER trial showed that liraglutide significantly reduced the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke compared with placebo [9]. Similar cardioprotective effects were observed with semaglutide [10], dulaglutide [11], and albiglutide [12]. Exenatide once weekly and oral semaglutide also confirmed cardiovascular safety and suggested modest MACE reduction [13,14].

Mechanistically, GLP-1 RAs improve endothelial function primarily by upregulating endothelial nitric oxide synthase (eNOS), which enhances nitric oxide bioavailability and promotes vasodilation. They reduce oxidative stress by decreasing NADPH oxidase activity and attenuate vascular inflammation through inhibition of pro-inflammatory cytokines, including IL-6 (interleukin-6) and TNF-α (Tumor Necrosis Factor alpha), thereby slowing the progression of atherosclerosis. Additionally, GLP-1 RAs modestly improve lipid profiles, reduce systolic blood pressure and enhance myocardial efficiency by increasing glucose uptake and reducing oxygen demand in the heart. Meta-analyses of CVOTs indicate that GLP-1 RAs reduce MACE by 14% overall, with consistent benefits across patient subgroups. [15,16].

Clinically, these cardiovascular benefits support preferential use of GLP-1 RAs in patients with T2DM who have high cardiovascular risk or established atherosclerotic cardiovascular disease. Implementing GLP-1 RAs therapy can reduce the risk of major cardiac events independent of glycemic control, making these agents a key component of guideline-recommended strategies for cardiometabolic risk reduction. They have multi-faceted effects that justify combining GLP-1 RAs with other glucose-lowering or cardioprotective therapies. SGLT2 inhibitors (sodium-glucose cotransporter 2 inhibitors) can be added in appropriately selected patients to maximize cardiovascular and renal protection [29-31].

Renal Protection

GLP-1 RAs demonstrate renoprotective effects in patients with T2DM. Clinical evidence has shown that GLP-1 RAs can slow the progression of chronic kidney disease (CKD), reduce albuminuria, and lower the risk of renal events. The FLOW trial specifically evaluated semaglutide in patients with T2DM and CKD and reported a significant reduction in the composite endpoint of persistent ≥50% decline in estimated glomerular filtration rate (eGFR), onset of end-stage kidney disease or renal death [17]. Similar renal benefits were observed in large cardiovascular outcome trials of GLP-1 receptor agonists, especially with consistent reductions in macroalbuminuria. [9–11].

GLP-1 RAs protect the kidneys through both direct and indirect mechanisms. These gut-derived hormones enhance natriuresis and regulate renal sodium handling, partly by affecting proximal tubular transport. They also improve glomerular haemodynamics, mitigating hyperfiltration commonly seen in diabetes. These kidney-specific actions are complemented by broader metabolic and hemodynamic benefits, supporting overall renal protection. Direct renal effects may include afferent arteriole vasodilation, modulation of tubuloglomerular feedback, and

reduction of renal inflammation and oxidative stress. Clinical trials indicate that GLP-1 RAs modestly improve surrogate renal outcomes [18].

Together, these systemic and kidney-specific mechanisms position GLP-1 RAs as an effective therapeutic option for renoprotection in patients with T2DM, complementing their established cardiovascular and metabolic benefits. Integration of GLP-1 RA therapy in patients at high renal risk is recommended in current guidelines from the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and Kidney Disease: Improving Global Outcomes (KDIGO) [29,30]. The multifaceted renal effects, together with cardiovascular protection, establish GLP-1 RAs as a cornerstone in the management of diabetes with coexisting kidney disease.

Emerging Therapeutic Areas

Beyond their established role in metabolic disease, GLP-1 RAs are being actively explored for novel therapeutic indications. Clinical data suggest neuroprotective effects, with trials in Parkinson's disease reporting improvements in motor symptoms and studies in Alzheimer's disease showing preservation of cognitive function and reductions in brain atrophy. These findings point to mechanisms extending beyond glucose control, including modulation of neuroinflammation, oxidative stress, and synaptic protection. [22].

GLP-1 RAs reduce systemic inflammation by lowering pro-inflammatory cytokines and oxidative stress while enhancing anti-inflammatory mediators. These actions may provide therapeutic benefits beyond glucose and weight control [23].

These agents also show promise in improving liver outcomes in patients with nonalcoholic fatty liver disease and type 2 diabetes. Meta-analytic data indicate reductions in hepatic fat, inflammation, and markers of nonalcoholic steatohepatitis (NASH), alongside improvements in liver histology. Although gastrointestinal adverse events are the most commonly reported limitation, these findings highlight the potential of GLP-1 RAs and support their investigation as a therapeutic option in metabolic liver disease [24].

Safety and Adverse Effects

GLP-1 RAs are generally well tolerated. Their safety profile is primarily shaped by gastrointestinal effects. Nausea, vomiting, and diarrhea are the most common adverse events. These symptoms typically appear during dose escalation and tend to resolve over time. Gastrointestinal side effects are more frequent with long-acting agents at higher doses. However, they rarely lead to treatment discontinuation [1,2].

Concerns regarding pancreatitis and pancreatic cancer have been extensively investigated. Large-scale clinical trials and meta-analyses show no convincing evidence of an increased risk of pancreatic cancer, while findings on pancreatitis are mixed, with some analyses suggesting a small increase. Post-marketing surveillance continues to monitor for rare events [25,26].

Rodent studies suggested a potential risk of C-cell thyroid tumors. In humans, however, clinical data do not indicate a meaningful association with medullary thyroid carcinoma. GLP-1 RAs do not appear to increase long-term risk of thyroid cancer, including medullary thyroid carcinoma (MTC). Early increases in thyroid cancer diagnoses during the first year of therapy likely reflect increased monitoring rather than a true causal effect, though further research is needed to clarify this. Overall, GLP-1 RAs are considered safe for the thyroid, with guidelines recommending avoidance only in patients with a personal or family history of MTC or MEN2 [27,28].

GLP-1 RAs have a low intrinsic risk of hypoglycemia due to their glucose-dependent insulinotropic effects. Nonetheless, hypoglycemia can occur when these agents are combined with insulin or insulin secretagogues, such as sulfonylureas. In such cases, dose adjustments and careful monitoring are required [1,2].

Overall, GLP-1 RAs demonstrate a favorable safety profile. Their efficacy in glycemic control, weight reduction, and organ protection supports broad clinical use. Proper patient selection and ongoing monitoring are essential to optimize outcomes and minimize risks.

Future Directions and Novel Molecules

The therapeutic landscape of GLP-1 receptor agonists continues to evolve, with several novel agents and combination therapies emerging. Dual agonists targeting both the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors represent a particularly promising direction. Evidence from recent analyses demonstrated that tirzepatide, a dual GIP/GLP-1 receptor agonist, provides greater reductions in HbA1c and body weight compared with traditional GLP-1 RA monotherapy, with a higher proportion of patients achieving both glycemic and weight loss targets. These findings highlight the potential of co-agonist strategies to further enhance glycemic control and metabolic outcomes, marking a new frontier in incretin-based therapy [32].

Emerging formulations, including oral semaglutide and long-acting injectable agents, improve patient convenience and adherence. These innovations broaden therapeutic options for individuals with type 2 diabetes [3,4]. Ongoing research is also exploring additional pleiotropic

effects, including neuroprotection, anti-inflammatory actions, and hepatic benefits, as well as optimization of dosing regimens and combination therapy with SGLT2 inhibitors or other glucose-lowering agents [5,22–24].

Future studies will need to address cost-effectiveness, access to therapy, and long-term safety, particularly in diverse patient populations. The integration of new molecules and combination therapies may further shift the treatment paradigm from glucose-centered management toward comprehensive cardiometabolic risk reduction.

CONCLUSION

GLP-1 receptor agonists have evolved from glucose-lowering drugs to multifaceted therapies. They provide cardiometabolic, renal, and weight-related benefits. Evidence from cardiovascular outcome trials, renal studies, and weight management trials supports their use in patients with type 2 diabetes, obesity, and those at high cardiovascular or renal risk. Their safety profile is favorable. Gastrointestinal adverse events are the most common limitation, while the risk of hypoglycemia remains low when used appropriately.

Individualization of therapy is essential for maximizing clinical outcomes. Treatment decisions should consider patient comorbidities, tolerability, and preferences. The development of dual agonists and novel formulations promises to expand therapeutic options and improve adherence. Ongoing research into emerging indications may further broaden the clinical utility of GLP-1 RAs. Collectively, these agents exemplify the transition toward therapies that address multiple aspects of cardiometabolic disease.

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