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BEYOND GLYCEMIC CONTROL: ORGAN-PROTECTIVE EFFECTS AND SAFETY PROFILE OF GLP-1 RECEPTOR AGONISTS – A COMPREHENSIVE REVIEW

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have evolved from glucose-lowering agents for type 2 diabetes (T2D) into multifunctional therapies with effects extending across multiple metabolic and organ systems. This review summarizes current evidence regarding the pleiotropic effects, safety profile, and future therapeutic potential of GLP-1–based therapies beyond diabetes and obesity. Clinical evidence indicates that GLP-1RAs, particularly semaglutide, may reduce cardiovascular events and slow kidney disease progression, while also improving outcomes in heart failure with preserved ejection fraction. Beneficial effects have additionally been reported in metabolic dysfunction-associated steatohepatitis, osteoarthritis, obstructive sleep apnea, and peripheral artery disease. Emerging evidence suggests potential neuroprotective effects, although the role of GLP-1–based therapies in neurodegenerative diseases remains under investigation. Despite their generally favorable safety profile, gastrointestinal adverse events are common, while pancreatic, biliary, renal, ophthalmic, and other less frequent complications require appropriate clinical monitoring. The development of dual and triple receptor agonists, including tirzepatide, retatrutide, CagriSema, and amycletin, may further enhance weight loss and metabolic efficacy. Future treatment strategies may increasingly incorporate personalized selection of receptor profiles based on metabolic phenotype, comorbidities, therapeutic goals, and individual tolerability. Overall, GLP-1–based therapies represent an expanding therapeutic platform with potential applications extending well beyond glycemic control and weight management, although long-term clinical trials are required to establish their efficacy, safety, and organ-protective effects across broader patient populations.

KEYWORDS

GLP-1 Receptor Agonists, Incretin-based Therapies, Obesity, Type 2 Diabetes

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1. Pleiotropic Effects of GLP-1–Based Therapies Beyond Type 2 Diabetes and Obesity

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dual receptor agonists, collectively referred to as GLP-1–based therapies, include agents such as liraglutide, dulaglutide, and semaglutide, as well as tirzepatide, a dual agonist targeting the GLP-1 receptor (GLP-1R) and the glucose-dependent insulinotropic polypeptide receptor (GIPR). These therapies were initially developed for the management of type 2 diabetes (T2D), primarily because of their ability to enhance insulin secretion, suppress glucagon release, and delay gastric emptying through actions involving the pancreas and central nervous system. Activation of GLP-1R and GIPR pathways within the brain additionally suppresses appetite and enhances satiety. These effects have supported the subsequent development and approval of liraglutide, semaglutide, and tirzepatide as pharmacological treatments for obesity and overweight associated with at least one weight-related comorbidity.[1]

In addition to their established glucose-lowering and weight-reducing properties, GLP-1–based therapies have demonstrated clinically relevant benefits across a range of cardiometabolic conditions. In individuals with T2D, treatment with GLP-1–based agents has been associated with a reduced incidence of chronic kidney disease (CKD), myocardial infarction, stroke, and cardiovascular mortality. Evidence also indicates beneficial effects in patients with heart failure with preserved ejection fraction (HFpEF), a population in which obesity is highly prevalent and T2D frequently coexists. Furthermore, clinical trials have reported favorable outcomes in metabolic dysfunction-associated steatotic liver disease (MASLD), predominantly among patients with concomitant obesity and T2D, as well as in obstructive sleep apnea (OSA), which is strongly associated with obesity, and osteoarthritis (OA) in individuals with obesity irrespective of diabetes status. Emerging evidence also suggests potential benefits in peripheral artery disease (PAD). Collectively, these findings indicate that the therapeutic effects of GLP-1–based medications extend beyond glycemic control and weight reduction, with potential benefits involving the cardiovascular, renal, hepatic, musculoskeletal, respiratory, and peripheral vascular systems [1].

1.1. Cardiovascular Disease and Chronic Kidney Disease

GLP-1–based therapies, particularly semaglutide, have demonstrated cardiovascular and renal benefits that extend beyond their effects on body weight and glycemic control. In individuals with overweight or obesity and established cardiovascular disease, semaglutide significantly reduces the risk of major adverse cardiovascular events, including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. These effects appear to be largely independent of the degree of weight loss achieved.[1]

Semaglutide has also been associated with improvements in symptoms, physical limitations, and exercise capacity in patients with heart failure with preserved ejection fraction. Treatment may additionally reduce NT-proBNP concentrations and the risk of cardiovascular death or heart failure-related hospitalization or treatment intensification.[1]

In patients with T2D and CKD, semaglutide has demonstrated renoprotective effects, reducing the risk of kidney failure, substantial declines in eGFR, and kidney- or cardiovascular-related mortality.[1] Furthermore, oral semaglutide has been shown to reduce major cardiovascular events in patients with T2D and established cardiovascular or kidney disease. These benefits were observed regardless of concomitant treatment with SGLT2 inhibitors, supporting the role of GLP-1–based therapies as an important component of comprehensive cardiometabolic management in patients with increased cardiovascular and renal risk.[1]

1.2. Metabolic Liver Disease

GLP-1–based therapies have shown promising effects in patients with metabolic dysfunction-associated steatohepatitis (MASH), particularly in those with obesity and moderate-to-advanced liver fibrosis. Semaglutide treatment has been associated with greater rates of MASH resolution without progression of fibrosis, as well as improvement in liver histological features such as steatosis, inflammation, and hepatocellular ballooning.[1] Since hepatocytes do not appear to directly express GLP-1 receptors, these effects may be mediated predominantly through weight reduction and indirect improvements in hepatic metabolism and systemic inflammation.

Other incretin-based therapies have demonstrated similar potential. Dual glucagon/GLP-1 receptor agonism with survodutide has been associated with improved MASH without worsening hepatic fibrosis. Tirzepatide, a GIP/GLP-1 receptor co-agonist, has likewise been shown to promote weight loss and improve steatohepatitis without progression of fibrosis.[1] Overall, the available evidence suggests that GLP-1–based and related multi-receptor therapies may have therapeutic potential in MASH, with improvements in liver disease partly related to the extent of weight reduction. [1,2]

1.3. Osteoarthritis

GLP-1–based therapy may also provide benefits in patients with obesity and knee osteoarthritis. Treatment with semaglutide has been associated with significant reductions in knee pain and improvements in physical function compared with placebo.[1] The substantial weight loss achieved during treatment is likely to contribute to these effects, although additional metabolic or anti-inflammatory mechanisms may also be involved.

1.4. Obstructive Sleep Apnea

Tirzepatide has demonstrated efficacy in adults with obesity and moderate-to-severe obstructive sleep apnea (OSA), leading to its approval for this indication. Treatment significantly reduced the apnea–hypopnea index compared with placebo, both in patients not receiving positive airway pressure therapy and in those already using such treatment.[1] These findings suggest that weight loss and the broader metabolic effects of incretin-based therapies may contribute to clinically meaningful improvements in OSA severity.

1.5. Peripheral Artery Disease

Semaglutide may also improve functional capacity in patients with peripheral artery disease (PAD) and intermittent claudication. Treatment was associated with a significant increase in maximum walking distance compared with placebo, accompanied by modest weight reduction.[1] The improvement in walking performance showed a moderate relationship with the extent of weight loss, suggesting that weight reduction may partially contribute to the observed benefit.

1.6. Neuroprotective Effects

GLP-1–based therapies have been associated with a reduced risk of stroke and may exert neuroprotective effects through multiple mechanisms, including improved metabolic function, modulation of neuroinflammation, reduced platelet aggregation and oxidative stress, and preservation of vascular integrity. Observational and clinical data also suggest a potential reduction in the risk of dementia, including Alzheimer’s disease, among individuals with T2D.[1] Ongoing clinical trials are evaluating whether semaglutide may have disease-modifying effects in patients with early symptomatic Alzheimer’s disease, although definitive evidence regarding its neuroprotective efficacy is still awaited.

2. Safety Profile of GLP-1 Receptor Agonists

GLP-1 receptor agonists (GLP-1RAs) generally have a favorable safety profile, with most adverse events being mild to moderate, transient, and manageable. Their cardiometabolic and organ-protective benefits outweigh the potential risks in most appropriately selected patients[3]. Real-world safety data for once-weekly semaglutide were consistent with randomized clinical trial findings, with no new safety concerns identified[4]. Oral small-molecule GLP-1RAs were associated with increased rates of treatment-emergent and general adverse events, but not with a significant increase in serious adverse events[5].

2.1. Gastrointestinal adverse events.

Nausea, vomiting, diarrhea, constipation, abdominal pain, dyspepsia, decreased appetite, eructation, gastro-esophageal reflux, and abdominal distension are the most frequently reported adverse effects of GLP-1RA therapy[3, 5–7]. They occur mainly during treatment initiation or dose escalation, are generally dose-dependent, and usually decrease with continued treatment[3, 4, 7]. Oral small-molecule GLP-1RAs also significantly increased the risk of gastrointestinal adverse events, particularly nausea and vomiting[5]. Gastrointestinal intolerance is the principal cause of treatment discontinuation and supports gradual dose escalation to improve tolerability[3, 7].

2.2. Delayed gastric emptying, gastroparesis, and bowel obstruction.

Delayed gastric emptying may alter the absorption of orally administered medications and increase the risk of perioperative aspiration[3]. Gastroparesis and bowel obstruction have also been reported, including among patients receiving GLP-1 agonists for weight management[3, 8]. Although uncommon, these complications should be considered in patients with persistent vomiting, abdominal pain, marked distension, or other severe gastrointestinal symptoms[3].

2.3. Pancreatic adverse events.

Acute pancreatitis has been reported during GLP-1RA therapy, and asymptomatic elevations in serum amylase and lipase may occur[3, 6, 7]. However, randomized trials and meta-analyses have not consistently demonstrated an increased overall risk of pancreatitis or pancreatic cancer[3, 6, 7]. An observational study of GLP-1 agonists used for weight loss found an increased risk of pancreatitis compared with bupropion–naltrexone[8]. Pancreatic symptoms therefore require clinical evaluation, while long-term post-marketing surveillance remains necessary[3].

2.4. Gallbladder and biliary disorders.

GLP-1RAs have been associated with cholelithiasis, cholecystitis, and other gallbladder disorders, particularly in patients experiencing substantial weight loss[3, 7]. Evidence regarding biliary tract malignancies remains inconsistent, and one observational study did not find an increased risk of biliary disease[3, 8]. New biliary symptoms developing during treatment should prompt further assessment[6].

2.5. Renal adverse events.

Acute kidney injury has been reported, usually secondary to dehydration caused by severe nausea, vomiting, diarrhea, or reduced fluid intake. Rare cases of acute interstitial nephritis and other immune-mediated renal injuries have also been described. Monitoring renal function is particularly important in older patients, individuals with chronic kidney disease, and those experiencing persistent gastrointestinal symptoms[3, 6, 7].

2.6. Hepatic adverse events.

Hepatic complications are uncommon and most frequently involve transient elevations in liver enzymes. Isolated cases of cholestatic liver injury and immune-mediated hepatic disorders have been reported. Biochemical evaluation should be considered in patients who develop clinical signs of liver dysfunction[3].

2.7. Ophthalmic complications.

Rapid improvement in glycemic control may temporarily worsen diabetic retinopathy, particularly in patients with pre-existing retinopathy, poor baseline glycemic control, or concomitant insulin therapy. Ophthalmologic monitoring should therefore be considered in high-risk patients during treatment initiation[3, 7]. An observational study also reported an association between semaglutide and nonarteritic anterior ischemic optic neuropathy; however, causality has not been established[9].

2.8. Thyroid malignancy.

Concerns regarding medullary thyroid carcinoma are based primarily on findings from rodent studies, while human clinical studies have not consistently confirmed an increased risk. Nevertheless, GLP-1RAs remain contraindicated in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2[3, 6, 7].

2.9. Cardiovascular effects.

GLP-1RAs may produce a modest increase in resting heart rate, although available evidence does not indicate a significant increase in major cardiovascular events, arrhythmias, or clinically relevant QT interval prolongation. Closer cardiovascular monitoring may be appropriate in patients receiving higher doses or presenting with additional arrhythmia risk factors[3, 6, 7].

2.10. Hypoglycemia.

The intrinsic risk of hypoglycemia is low because GLP-1RA-induced insulin secretion is glucose-dependent. The risk increases when GLP-1RAs are administered with insulin or sulfonylureas. Dose adjustment of these concomitant agents may therefore be required when initiating GLP-1RA treatment[6, 7].

2.11. Immunogenicity, hypersensitivity, and cutaneous reactions.

Antibody formation may occur, particularly with exenatide and lixisenatide, but is generally not associated with reduced efficacy or increased adverse events[5]. Rare hypersensitivity reactions include anaphylaxis, angioedema, urticaria, pruritus, vasculitis, bullous pemphigoid, and lupus-like syndromes[3, 6]. Injection-site reactions are usually mild and transient, while rare cutaneous events include panniculitis, alopecia, hyperhidrosis, and maculopapular rash[6].

2.12. Psychiatric adverse events.

Depression, anxiety, suicidal ideation, and suicidal behavior have been reported in pharmacovigilance and observational studies. However, the available findings are conflicting, and regulatory assessments have not established a causal relationship. Evaluation of psychiatric history and monitoring for new or worsening symptoms may be particularly relevant in patients treated for obesity[3, 10].

2.13. Sexual and hormonal effects.

In an observational study of non-diabetic men with obesity, semaglutide use was associated with higher rates of newly diagnosed erectile dysfunction, phosphodiesterase-5 inhibitor use, and testosterone deficiency. These findings require confirmation and should be interpreted cautiously because of the observational study design[11].

Overall, serious adverse events associated with GLP-1RAs remain uncommon. Appropriate patient selection, gradual dose escalation, adjustment of concomitant glucose-lowering therapy, and targeted monitoring of gastrointestinal, renal, ophthalmic, biliary, and psychiatric symptoms are essential to maintain a favorable benefit–risk balance[3, 6, 7].

3. Future Perspectives

The therapeutic role of incretin-based agents is rapidly expanding beyond conventional glycemic control and weight management. Over the past decade, drug development has focused on two main strategies: orally bioavailable small-molecule GLP-1 receptor agonists and peptide-based compounds capable of activating multiple complementary metabolic receptors[12]. The latter approach aims to enhance metabolic efficacy by simultaneously influencing pathways involved in appetite regulation, energy balance, glucose homeostasis, and organ function. Although next-generation incretin therapies may provide greater clinical benefits than selective GLP-1 receptor agonists, large phase 3 trials remain necessary to establish their long-term efficacy, safety, tolerability, and effects on cardiovascular and renal outcomes[12].

3.1. Next-generation incretin therapies

Tirzepatide represents an important step in the evolution of multi-receptor incretin therapy. It is a dual GLP-1/GIP receptor agonist and is currently the only approved peptide-based agent specifically developed to interact with more than one incretin-related receptor[12, 13]. Available evidence indicates that tirzepatide provides substantial improvements in body weight and glycemic control, with weight reductions exceeding 20% reported among next-generation entero-pancreatic hormone-based therapies[14].

Its clinical development has also provided important cardiovascular safety data. In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, tirzepatide was noninferior to dulaglutide with respect to the composite outcome of cardiovascular death, myocardial infarction, or stroke. The overall incidence of adverse events was similar between the treatment groups, although gastrointestinal adverse events occurred more frequently with tirzepatide[15]. These findings support its broader cardiometabolic potential while emphasizing the continued importance of monitoring treatment tolerability.

Retatrutide is the first unimolecular triple agonist targeting GLP-1, GIP, and glucagon receptors for which phase 2 results have been published in both obesity and type 2 diabetes. In individuals with obesity, retatrutide produced a mean body weight reduction of up to 24.2% after 48 weeks, whereas patients with type 2 diabetes achieved weight loss of up to 16.9% after 36 weeks. Glycemic improvement was also substantial, with a reduction in HbA1c of up to 2.2% and 82% of participants achieving an HbA1c level of 6.5% or lower[13].

Beyond weight reduction and glycemic control, retatrutide improved several cardiometabolic parameters, including blood pressure, lipid levels, waist circumference, and liver fat content. Gastrointestinal symptoms were the most frequently reported adverse events, while no major safety concerns were identified in the available phase 2 studies[13]. A comprehensive phase 3 development program is ongoing to evaluate its efficacy, safety, and potential cardiovascular and renal effects in people with obesity and/or type 2 diabetes. Retatrutide may therefore become one of the most effective pharmacological options for obesity while also providing clinically relevant benefits for glucose control and associated cardiometabolic risk factors[13].

CagriSema represents another emerging therapy combining complementary entero-pancreatic hormonal pathways. Available evidence indicates that CagriSema can achieve body weight reductions exceeding 20%, suggesting greater efficacy than selective GLP-1 receptor agonists, which typically produce weight loss of

approximately 10–15%. Its development reflects the broader strategy of combining mechanisms involved in appetite regulation, energy balance, and metabolic homeostasis to improve treatment outcomes[14].

Similarly, amycretin is part of the next generation of therapies designed to target multiple hormonal pathways. Reported weight reductions with amycretin have also exceeded 20%. Although the current evidence primarily emphasizes its effects on body weight, therapies targeting GLP-1, GIP, amylin, and glucagon pathways may provide benefits extending beyond weight reduction[14]. These potential effects include improved glycemic control, diabetes prevention, and organ-specific benefits involving the cardiovascular system, heart failure symptoms, obstructive sleep apnea, metabolic dysfunction-associated steatohepatitis, chronic kidney disease progression, and osteoarthritis-related pain[14].

The development of tirzepatide, retatrutide, CagriSema, and amycretin demonstrates a transition from selective receptor activation toward coordinated modulation of several metabolic pathways. Multi-receptor agonism may increase therapeutic efficacy, but greater pharmacological complexity also requires careful evaluation of adverse effects and long-term clinical outcomes. The balance between efficacy and tolerability will remain a central issue, particularly because gastrointestinal symptoms continue to be the predominant adverse events associated with these therapies[13, 15]. Large-scale trials are therefore required to determine whether the substantial improvements in weight and metabolic parameters translate into durable reductions in cardiovascular, renal, hepatic, and other obesity-related complications[12].

3.2. Personalized medicine

The increasing number of selective, dual, and triple receptor agonists creates new opportunities for a more individualized approach to incretin-based therapy. In multi-receptor compounds, the relative potency of agonism at each target receptor can be modified to maximize therapeutic efficacy while limiting adverse effects. However, the clinical effects of different receptor combinations may be difficult to predict from animal studies, and the optimal balance of receptor activation is likely to vary between individual patients[13].

Personalized treatment may therefore involve selecting therapies according to the patient's metabolic phenotype, comorbidities, treatment goals, and individual susceptibility to adverse events. A patient requiring marked weight reduction may benefit from a different receptor profile than a patient in whom glycemic control, hepatic steatosis, cardiovascular protection, or preservation of kidney function is the principal therapeutic objective. The availability of agents targeting different combinations of GLP-1, GIP, glucagon, and amylin pathways may allow treatment to be better aligned with these individual clinical priorities[13, 14].

Another potential strategy involves combining mono- and dual-receptor agonists to achieve a personalized degree of triple receptor activation. Such combinations could make it possible to adjust the relative contribution of individual pathways and identify the most effective balance for a particular patient[13]. However, this approach also presents important challenges. Individual agents may differ in their pharmacokinetic and pharmacodynamic properties, including their half-lives, meaning that the relative intensity of receptor activation may change over time when several compounds are used together[13]. Consequently, personalized combinations would require careful dose selection and monitoring.

Artificial intelligence may further support individualized incretin therapy by helping predict the optimal combination of receptor agonists based on a patient's genetic and metabolomic characteristics. Such approaches may also accelerate drug development and assist in identifying individuals most likely to respond to a particular treatment strategy[12]. Biomarker-driven selection may be especially relevant in areas characterized by substantial heterogeneity of treatment response, including obesity-associated complications and potential neurological indications[16].

Personalization should also include assessment of tolerability and adherence. The most effective therapy may not provide sustained clinical benefit when adverse events lead to dose reduction or treatment discontinuation. Individual risk factors, previous gastrointestinal intolerance, concomitant medications, cardiovascular and renal status, and treatment preferences should therefore be considered when selecting an incretin-based agent. Future studies should aim not only to compare average treatment effects but also to identify clinical and biological predictors of efficacy, adverse events, and long-term adherence.

Overall, next-generation incretin therapies are expected to provide increasingly effective and individualized management of obesity, type 2 diabetes, and related organ complications. Multi-receptor agonists may offer greater metabolic efficacy than selective GLP-1 receptor agonists, while personalized selection of receptor profiles may improve the balance between therapeutic benefit and tolerability. However, their broader clinical role will depend on confirmation of long-term safety, organ-protective effects, and clinically meaningful outcomes in large, well-designed trials[12–14].

Conclusions

GLP-1–based therapies have emerged as multifunctional pharmacological agents whose clinical benefits extend beyond glycemic control and weight reduction. Current evidence supports their role in reducing cardiovascular and renal risk and suggests additional benefits in heart failure with preserved ejection fraction, metabolic liver disease, osteoarthritis, obstructive sleep apnea, and peripheral artery disease. Potential neuroprotective effects represent an important area of ongoing research, but further clinical evidence is required before these applications can be established.

Although GLP-1 receptor agonists generally demonstrate a favorable benefit–risk profile, gastrointestinal adverse events remain the most common limitation to treatment persistence. Appropriate patient selection, gradual dose escalation, consideration of concomitant medications, and targeted monitoring are therefore important for optimizing safety and adherence.

The development of dual- and triple-receptor agonists represents a further evolution of incretin-based therapy, with the potential to achieve greater weight loss and broader metabolic effects. However, increased pharmacological complexity requires confirmation of long-term safety and clinically meaningful cardiovascular, renal, hepatic, and other organ-specific outcomes. Future research should increasingly focus on personalized treatment strategies that account for individual metabolic characteristics, comorbidities, therapeutic priorities, and tolerability. Overall, GLP-1–based therapies are likely to become an increasingly important component of comprehensive cardiometabolic and obesity-related disease management, provided that their emerging benefits are confirmed in large, long-term clinical trial.

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