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Emerging role of GLP-1 and dual agonists in modern obesity management: Beyond weight loss

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Abstract
Obesity is a chronic, relapsing, multifactorial disease associated with significant metabolic, cardiovascular, and psychosocial complications. Traditional obesity management strategies, including lifestyle modification, behavioural therapy, and bariatric surgery, often demonstrate limited long-term adherence or accessibility. The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual incretin agonists has transformed the therapeutic landscape of obesity treatment. Initially developed for type 2 diabetes mellitus, these agents have shown remarkable efficacy in inducing substantial and sustained weight reduction while simultaneously improving metabolic health. Recent evidence suggests that their benefits extend far beyond weight loss, including cardiovascular protection, improvement in non-alcoholic fatty liver disease, renal benefits, reduction in systemic inflammation, enhanced glycemic control, and possible neuroprotective and mental health effects. Dual agonists such as tirzepatide, which target both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, demonstrate superior efficacy compared with conventional GLP-1 monotherapy. Novel triple agonists and oral formulations are also under investigation, indicating a rapidly evolving therapeutic field. Despite promising outcomes, concerns remain regarding gastrointestinal adverse effects, long-term safety, affordability, accessibility, and maintenance of weight loss after discontinuation. This review discusses the mechanisms, clinical efficacy, systemic benefits, limitations, and future prospects of GLP-1 receptor agonists and dual agonists in modern obesity management, emphasizing their role beyond simple body weight reduction.

Keywords: Obesity, GLP-1 receptor agonists, dual agonists, tirzepatide, semaglutide, incretin therapy, metabolic health, cardiovascular protection, weight management

Introduction

Obesity has emerged as one of the most serious global public health concerns of the 21st century (James, 2018) [25]. According to the World Health Organization, obesity prevalence has increased dramatically over recent decades, affecting both developed and developing nations (Ellulu *et al*., 2014) [16]. Obesity is associated with numerous chronic diseases including type 2 diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, obstructive sleep apnea, osteoarthritis, certain cancers, and psychological disorders (Lopes, 2020) [30]. The pathophysiology of obesity is highly complex and involves genetic, environmental, hormonal, behavioural, and neuroendocrine mechanisms (Busebee *et al*., 2023) [7].

Conventional obesity treatment primarily focused on calorie restriction and physical activity. Although lifestyle interventions remain foundational, long-term maintenance of weight reduction is difficult due to adaptive metabolic responses, increased appetite, and hormonal changes favouring weight regain. Pharmacological interventions historically provided only modest benefits and were often associated with adverse effects or limited efficacy. Bariatric surgery remains highly effective but is invasive, costly, and unsuitable for all patients (Chin *et al*., 2016) [11].

The discovery of incretin hormones revolutionized obesity therapeutics. Glucagon-like peptide-1 (GLP-1), an endogenous gut hormone secreted from intestinal L-cells, regulates appetite, insulin secretion, gastric emptying, and satiety (Holst, 2019) [24]. GLP-1 receptor agonists mimic the action of native GLP-1 while resisting enzymatic degradation, thereby prolonging therapeutic activity (Sharma *et al*., 2018) [39]. These agents initially gained approval for diabetes management but later demonstrated significant weight reduction in individuals with obesity (Podder *et al*., 2026) [36].

More recently, dual agonists targeting both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors have shown even greater efficacy (Fisman and Tenenbaum, 2021) [17]. Tirzepatide, the first dual GIP/GLP-1 agonist, represents a major advancement in obesity medicine, producing weight reductions approaching outcomes seen with bariatric surgery in some studies (Singh and Nissen, 2024) [40].

Importantly, emerging evidence indicates that these medications provide benefits extending beyond body weight reduction (Korner and Aronne, 2003) [27]. Improvements in cardiovascular outcomes, fatty liver disease, renal function, systemic inflammation, mental health, and metabolic flexibility have expanded the therapeutic significance of incretin-based therapies. This review explores the evolving role of GLP-1 receptor agonists and dual agonists in obesity management and highlights their broader clinical implications (Newsome and Ambery, 2023) [34].

Physiology of GLP-1 and Incretin System

GLP-1 is an incretin hormone released from enteroendocrine L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses

glucagon secretion, delays gastric emptying, and promotes satiety through central nervous system pathways. However, endogenous GLP-1 has a very short half-life due to rapid degradation by dipeptidyl peptidase-4 (DPP-4) (Spreckley and Murphy, 2015) [41].

GLP-1 receptor agonists are synthetic analogues engineered to resist DPP-4 degradation, resulting in prolonged action. These agents activate GLP-1 receptors located in the pancreas, gastrointestinal tract, cardiovascular system, kidneys, and brain. Central appetite suppression occurs primarily through hypothalamic pathways regulating hunger and satiety (Wang *et al*., 2026) [44].

GIP is another incretin hormone secreted from K-cells in the proximal intestine (Liu *et al*., 2025) [29]. Although historically considered less significant in obesity treatment, combined activation of GIP and GLP-1 receptors has demonstrated synergistic metabolic effects (Yamanouchi, 2025) [47]. Dual agonists enhance insulin secretion, reduce appetite, improve energy expenditure, and produce greater reductions in adiposity compared with GLP-1 monotherapy (Moiz *et al*., 2025) [31].

GLP-1 Receptor Agonists in Obesity Management

GLP-1 receptor agonists have emerged as a cornerstone in the pharmacological management of obesity, offering both weight reduction and metabolic benefits (Alharbi, 2025) [46]. Several agents are currently in clinical use, including Liraglutide, Semaglutide, Dulaglutide, and Exenatide, all of which function by enhancing glucose-dependent insulin secretion, delaying gastric emptying, and promoting satiety through central appetite regulation (Cabré *et al*., 2025) [8]. These agents have demonstrated significant efficacy not only in glycemic control but also in reducing body weight, making them valuable in patients with obesity, with or without type 2 diabetes (García-Compeán *et al*., 2023) [18]. Among them, semaglutide administered at a dose of 2.4 mg once weekly has shown particularly impressive results, with large-scale clinical trials reporting average weight reductions of approximately 15–17% in individuals without diabetes (Bikou *et al*., 2024) [5]. This degree of weight loss approaches outcomes seen with some surgical interventions and highlights the growing importance of GLP-1 receptor agonists as a non-invasive yet highly effective strategy in modern obesity management (Steven *et al*., 2026) [10].

Mechanisms of Weight Reduction

GLP-1 receptor agonists promote weight reduction through a combination of central and peripheral mechanisms that collectively decrease energy intake and improve metabolic regulation (Moiz *et al*., 2025) [31]. These agents suppress appetite and enhance satiety by acting on hypothalamic centers that regulate hunger, leading to earlier meal termination and reduced portion sizes (Halford and Blundell, 2000) [21]. They also delay gastric emptying, which prolongs the feeling of fullness after eating and helps stabilize postprandial glucose levels. Additionally, GLP-1 agonists reduce food cravings and modulate reward-related eating behaviour by influencing neural pathways associated with hedonic eating and food motivation. Improved glycemic regulation further contributes to reduced hunger fluctuations and better energy balance. Neuroimaging studies have demonstrated that these drugs alter activity in key brain reward regions, diminishing the appeal of high-calorie foods and supporting sustained reductions in caloric intake without the need for extreme dietary restriction (Kenny, 2011) [26].

Emergence of Dual Agonists

Dual agonists simultaneously target GLP-1 and GIP receptors. Tirzepatide is the most notable example and has demonstrated unprecedented efficacy in obesity treatment (Liu, 2024) [37]. Clinical trials revealed weight reductions exceeding 20% in some individuals, surpassing outcomes observed with semaglutide.

Tirzepatide

Tirzepatide is a novel dual incretin agonist that simultaneously targets both GLP-1 and GIP receptors, resulting in enhanced metabolic effects compared to traditional monotherapy (Fisman and Tenenbaum, 2021) [17]. By activating these complementary pathways, Tirzepatide promotes greater appetite suppression and improved satiety, leading to a significant reduction in caloric intake. It also enhances insulin sensitivity and glycemic control by facilitating glucose-dependent insulin secretion while reducing glucagon levels. Additionally, tirzepatide has been shown to increase fat oxidation and reduce adipose tissue inflammation, contributing to improved body composition and metabolic health. Evidence from the SURMOUNT trials demonstrates substantial reductions in body weight, waist circumference, HbA1c levels, and overall cardiometabolic risk factors, positioning tirzepatide as a highly effective therapeutic option in modern obesity management (Garvey *et al*., 2023) [19].

Comparative Efficacy

Comparative clinical studies evaluating the efficacy of Tirzepatide and Semaglutide consistently demonstrate superior outcomes with tirzepatide across multiple metabolic parameters (Cetiner, 2026) [10]. Patients treated with tirzepatide exhibit greater percentage weight loss, often exceeding 20% in clinical trials, compared to slightly lower reductions observed with semaglutide (Rodriguez *et al*., 2024) [38]. In addition, tirzepatide shows more pronounced decreases in body mass index (BMI) and waist circumference, indicating a stronger effect on both overall and central adiposity (Borlaug *et al*., 2025) [6]. Improvements in glycemic control are also significantly enhanced with tirzepatide, with greater reductions in HbA1c levels due to its dual incretin mechanism (Zhou *et al*., 2023) [49]. These findings highlight the added therapeutic advantage of targeting both GLP-1 and GIP pathways, making tirzepatide a more potent option in the pharmacological management of obesity and related metabolic disorders.

Beyond Weight Loss: Expanded Clinical Benefits

1. Cardiovascular Protection

One of the most significant advancements in incretin-based therapy is its demonstrated ability to reduce cardiovascular risk, extending benefits well beyond weight loss. GLP-1 receptor agonists have been shown to lower the incidence of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality. Evidence from the SELECT trial highlights that Semaglutide significantly reduces cardiovascular risk in individuals with obesity, even in the absence of type 2 diabetes, underscoring a weight-independent protective effect. These

cardioprotective actions are mediated through multiple mechanisms, including improved endothelial function, reduction in systemic inflammation, lowering of blood pressure, and favorable modulation of lipid profiles. Additionally, GLP-1 receptor activation reduces oxidative stress and enhances vascular health, contributing to overall cardiovascular resilience. Collectively, these effects position GLP-1 receptor agonists as not only anti-obesity agents but also important therapeutic tools in cardiovascular disease prevention and management (Alluri *et al*., 2025) [46].

2. Improvement in Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)

Obesity is a major driver of Metabolic Dysfunction-Associated Fatty Liver Disease, and incretin-based therapies have shown promising benefits in its management. GLP-1 receptor agonists improve hepatic steatosis through multiple interrelated mechanisms, including reduction of hepatic fat accumulation, enhancement of insulin sensitivity, suppression of *de novo* lipogenesis, and attenuation of hepatic inflammation. These effects collectively contribute to improved liver function and metabolic regulation. Notably, agents such as Semaglutide and Tirzepatide have demonstrated potential not only in reducing liver fat content but also in improving histological features of liver disease, including fibrosis and steatohepatitis progression. Emerging clinical evidence suggests that these therapies may play a significant role in slowing or even reversing disease progression, positioning them as promising pharmacological options in the management of MAFLD associated with obesity and metabolic dysfunction (Elangovan *et al*., 2025) [46].

3. Renal Protection

GLP-1 receptor agonists have demonstrated significant nephroprotective effects, offering an additional therapeutic advantage in individuals with obesity and type 2 diabetes who are at increased risk of kidney complications (Mosterd *et al*., 2020) [33]. These agents contribute to renal protection by reducing albuminuria, a key marker of kidney damage, and by improving renal blood flow through favorable hemodynamic changes. They also decrease oxidative stress and systemic inflammation, both of which play crucial roles in the progression of kidney injury. Furthermore, GLP-1 receptor agonists help lower blood pressure, thereby reducing intraglomerular pressure and preventing further renal damage (Greco *et al*., 2019) [20]. Collectively, these mechanisms support the preservation of kidney function and may help delay the onset and progression of Chronic Kidney Disease in patients with obesity and diabetes, highlighting their expanding role beyond glycemic and weight management.

4. Mental Health and Quality of Life

Obesity is closely associated with psychological comorbidities such as Depression and Anxiety, often leading to a reduced quality of life. Emerging evidence indicates that GLP-1 receptor agonists may exert beneficial effects on mental health and overall wellbeing in addition to their metabolic actions. These improvements are thought to arise from multiple interconnected mechanisms, including reduction in systemic inflammatory signaling, which is increasingly linked to mood disorders, as well as enhanced metabolic stability that reduces fatigue and glycemic fluctuations. Improvements in body image following weight loss may further contribute to better self-esteem and psychological outcomes. Additionally, GLP-1 agonists may support better sleep quality and influence central neurotransmitter pathways involved in mood regulation and reward processing. Collectively, these effects suggest that incretin-based therapies not only address the physical burden of obesity but also contribute to meaningful improvements in psychological health and quality of life (Nigatu *et al*., 2016) [35].

5. Preservation of Lean Mass and Body Composition

Modern obesity management increasingly focuses on achieving "quality weight loss," characterized by a preferential reduction in fat mass while preserving lean muscle tissue (Harper *et al*., 2025) [22]. GLP-1 receptor agonists have been shown to primarily target adipose tissue, contributing to significant fat loss; however, some degree of lean mass reduction may also occur, particularly in the absence of supportive lifestyle interventions. Preserving skeletal muscle is crucial for maintaining metabolic rate, physical function, and long-term weight maintenance (Cava *et al*., 2017) [9]. Therefore, adjunct strategies such as ensuring adequate dietary protein intake, engaging in regular resistance exercise, and continuous nutritional monitoring are strongly recommended. Additionally, combination approaches integrating pharmacotherapy with structured lifestyle interventions or other metabolic agents may further optimize body composition outcomes. These strategies help maximize the therapeutic benefits of GLP-1 receptor agonists while minimizing unintended muscle loss, thereby promoting sustainable and metabolically healthy weight reduction (Moscucci *et al*., 2026) [32].

Novel and Future Therapies

Triple Agonists

The next frontier in obesity pharmacotherapy involves the development of triple agonists that simultaneously target the GLP-1, GIP, and glucagon receptors, offering a more comprehensive approach to metabolic regulation (Liu, 2024) [28]. These multi-receptor agents are designed to combine the appetite-suppressing and insulin-enhancing effects of incretin hormones with the energy expenditure–promoting action of glucagon receptor activation. One of the most promising candidates in this class is Retatrutide, which has demonstrated remarkable outcomes in early clinical trials. Studies report substantial weight loss exceeding that of current GLP-1 and dual agonists, along with significant improvements in glycemic control, lipid metabolism, and overall cardiometabolic health. By simultaneously addressing multiple physiological pathways involved in obesity, triple agonists like retatrutide represent a potential paradigm shift in treatment, moving closer to highly effective, multi-targeted, and precision-based obesity management strategies (Chu *et al*., 2025) [46].

Oral GLP-1 Therapies

Oral agents such as orforglipron may improve patient adherence and accessibility by eliminating injectable administration.

Personalized Obesity Medicine

The future of obesity management is shifting toward precision-based approaches that tailor interventions to

individual biological and behavioural characteristics. Personalized obesity medicine integrates genetic profiling to identify predispositions affecting metabolism and treatment response, metabolic phenotyping to classify patients based on underlying physiological drivers of weight gain, and analysis of the gut microbiome, which plays a crucial role in energy balance, inflammation, and nutrient metabolism. In addition, behavioral assessment helps to understand eating patterns, psychological triggers, and lifestyle factors that influence adherence and long-term outcomes. By combining these multidimensional insights, clinicians can design targeted therapeutic strategies—including optimized pharmacotherapy, nutrition plans, and lifestyle interventions—thereby improving efficacy, minimizing trial-and-error treatment, and enhancing sustainable weight management outcomes (Woolf *et al*., 2025) [46].

Adverse Effects and Limitations

Despite major therapeutic advances, several limitations remain.

Gastrointestinal Side Effects

Despite their substantial therapeutic benefits, GLP-1 receptor agonists and related incretin-based therapies are commonly associated with gastrointestinal adverse effects, which represent the most frequently reported limitation of these agents. Patients often experience symptoms such as nausea, vomiting, diarrhea, constipation, and abdominal discomfort, particularly during the initial phase of treatment or following dose escalation. These effects are primarily related to delayed gastric emptying and central appetite regulation mechanisms induced by drugs such as Semaglutide and Tirzepatide. In most cases, these symptoms are dose-dependent, mild to moderate in severity, and tend to diminish over time as the body adapts to the medication. Gradual dose titration, dietary modifications, and patient counseling are effective strategies to improve tolerability and ensure better adherence to therapy (Podder *et al*., 2026) [36].

Weight Regain

Discontinuation often leads to partial weight regain, suggesting obesity requires chronic long-term management similar to hypertension or diabetes.

Comparison with Bariatric Surgery

Bariatric surgery remains the most effective intervention for severe obesity. However, GLP-1 agonists provide a less invasive alternative with substantial efficacy. Studies comparing surgery and pharmacotherapy indicate that bariatric surgery often achieves greater long-term weight reduction, though medications offer broader accessibility and lower procedural risk. Combination approaches integrating pharmacotherapy before or after surgery may optimize outcomes.

Public Health Implications

The growing use of GLP-1 receptor agonists may significantly influence future obesity management strategies. Their integration into public health systems could reduce the burden of obesity-related diseases including diabetes, cardiovascular disease, and fatty liver disease (Wang *et al*., 2023) [43].

However, equitable access remains a major challenge. Healthcare systems must balance innovation with affordability and ensure responsible prescribing practices.

The World Health Organization has already begun developing guidance regarding the use of GLP-1 therapies in obesity management.

Table 1: Summary of Published Studies on GLP-1 and Dual Agonists in Obesity Management

Author (Year)	Study Type	Intervention	Population	Key Findings	Beyond Weight Loss Benefits
Qin *et al*. (2024) [37]	RCT (STEP 1)	Semaglutide 2.4 mg weekly	Non-diabetic adults with obesity	~15–17% weight loss	Improved cardiovascular risk factors, reduced inflammation
Zhou *et al*. (2025) [12]	RCT (STEP 4)	Semaglutide continuation vs withdrawal	Overweight/obese adults	Sustained weight loss with continued therapy	Better glycemic control and metabolic stability
Aronne *et al*. (2024) [4]	RCT (SURMOUNT-1)	Tirzepatide	Obese adults without diabetes	Up to 20–22% weight loss	Improved insulin sensitivity, reduced cardiometabolic risk
de Mendonça *et al*. (2025) [14]	RCT	Tirzepatide vs insulin	Type 2 diabetes patients	Superior HbA1c reduction and weight loss	Cardiovascular and glycemic improvement
Heerspink *et al*. (2023) [23]	RCT (STEP 2)	Semaglutide	Obesity with T2DM	Significant weight loss vs placebo	Renal and cardiovascular protection
Ahmed *et al*. (2025) [1]	RCT	Semaglutide	Patients with NASH	Reduction in liver fat and inflammation	Improvement in MAFLD/NASH markers
Wilson *et al*. (2020) [45]	Clinical Trial	Tirzepatide	Type 2 diabetes	Improved lipid profile and glycemic control	Reduced cardiovascular risk factors

Conclusion

GLP-1 receptor agonists and dual incretin agonists represent a major breakthrough in modern obesity management. These therapies have transformed obesity treatment from modest weight reduction toward comprehensive metabolic disease management. Beyond their remarkable effects on body weight, these agents improve cardiovascular health, glycemic control, fatty liver disease, renal outcomes, inflammation, and quality of life. Dual agonists such as tirzepatide demonstrate superior efficacy and signal the beginning of a new era in obesity pharmacotherapy.

Despite these advances, obesity remains a chronic and complex disease requiring multidisciplinary care. Lifestyle modification, nutritional counselling, behavioural therapy, and physical activity continue to play critical roles alongside pharmacotherapy. Future research should focus on long-term safety, affordability, personalized treatment approaches, and combination therapies. As newer triple

agonists and oral agents emerge, incretin-based therapies are likely to become central components of precision obesity medicine in the coming decades.

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