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GLP-1 therapies for obesity: mechanisms, outcomes, and regulatory challenges

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Abstract

Obesity is a global epidemic and a complex chronic condition associated with various noncommunicable chronic diseases (NCDs) and has a substantial economic impact. In this context, glucagon-like peptide-1 (GLP-1) analogues and polyagonists, such as liraglutide, semaglutide, and tirzepatide, emerge as pharmacological innovations. This study conducted a descriptive literature analysis focusing on the mechanisms of action and clinical impacts of these drugs in obesity management, alongside the regulatory landscape and their challenges regarding implementation, market access, and policy implications. The review demonstrated that these medications modulate the incretin axis, delay gastric emptying, and act on neural appetite centers, resulting in significant weight loss and improved cardiometabolic parameters. However, the analysis identified that treatment discontinuation is associated with substantial weight regain, highlighting that weight loss is maintained long-term only with continuous therapy and integration with lifestyle changes. Furthermore, the study emphasized that access is severely limited by high costs and by patent barriers, regulatory and policy frameworks that hinder generic competition and health system coverage. In summary, while GLP-1 analogues represent a major therapeutic advance, their broader impact on public health depends on overcoming challenges related to treatment sustainability and equity of access.

Keywords: *obesity, GLP-1 receptor agonists, weight loss, health economics, regulatory frameworks, drug access*

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1. Introduction

Obesity is a severe global public health crisis affecting populations worldwide. Its classification is based on the body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. An adult is considered to have obesity when presenting a BMI equal to or greater than 30, according to the criteria of the World Health Organization (WHO) [1]. Obesity is a multifactorial disease, strongly influenced by genetic factors, an obesogenic environment, and psychosocial aspects [1].

The global prevalence of obesity among adults doubled between 1990 and 2022. In 2022, this increase resulted in 2.5 billion adults living with overweight, of whom 890 million had obesity [1]. What was once regarded as a concern mainly of high-income countries has become an epidemic affecting middle- and low-income nations. Regionally, the trend is most pronounced in the Americas, which recorded the highest prevalence of overweight, affecting 67% of adults, followed by the African and South-East Asian regions, where 31% of adults were overweight [1].

The situation in the United States is particularly severe, with an average obesity prevalence more than twice that observed in other G7 countries. The crisis also affects younger populations, one in five children older than 6 years in the United States has obesity. This is especially alarming because approximately 80% of adolescents with obesity are likely to remain obese in adulthood [2].

Several noncommunicable chronic diseases (NCDs) are associated with obesity. In children and adults, obesity increases the risk of type 2 diabetes mellitus (T2DM), respiratory disorders, joint problems, gallstones, and gallbladder dysfunction, as well as elevated cholesterol levels and blood pressure [3]. Overweight and obesity are among the four key metabolic abnormalities that increase the risk of NCDs, including cardiovascular diseases, which account for the largest share of premature deaths [4].

Worldwide, obesity also imposes a substantial economic burden. In England, for example, the National Health Service (NHS) spends 11.4 billion pounds annually on obesity, in addition to the costs of related comorbidities. When indirect costs such as unemployment, loss of productivity, and social care are included, this figure rises to 74.3 billion pounds per year [5]. In the United States, medical expenditures attributable to obesity reached 173 billion dollars in 2019 [6]. An adult with obesity incurs 1861 US dollars in additional annual medical costs compared with a person of normal weight, and for severe obesity, this excess cost can reach 3097 US dollars per person [6].

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Given this challenging scenario, pharmacotherapy with glucagon-like peptide-1 (GLP-1) analogues has emerged as a transformative innovation in obesity management. These drugs offer a new option for patients who previously failed to achieve clinically meaningful weight loss or to maintain weight loss through behavioral and lifestyle changes alone [5]. In this context, these agents elicit a much more potent activation of GLP-1 receptors than the endogenous hormone. The main drugs in this class include semaglutide, liraglutide, exenatide, and orforglipron [7].

The primary mechanism of action of these medications is the activation of pancreatic GLP-1 receptors, leading to increased insulin secretion and reduced glucagon secretion, two hormones that are glucose-dependent [7]. Weight loss and the sensation of satiety are likely induced through multiple central and peripheral mechanisms which, in addition to hormonal changes, include activation of the ileal brake, delayed gastric emptying, increased satiety and resting energy expenditure, and effects on the parietal and orbitofrontal cortex, the hypothalamus, and the brainstem [8].

In the United States, exenatide became the first GLP-1 receptor agonist approved for the treatment of diabetes in 2005 [9], and only later, in 2014, was liraglutide approved for obesity [10]. The choice of therapy for T2DM should be based on a patient-centered, shared-decision approach that takes into account efficacy, safety, comorbidities, and individual preferences [11]. For type 1 diabetes mellitus, these agents may be used as adjunctive treatments to insulin [11]. The use of GLP-1 analogues has expanded owing to their proven long-term efficacy in weight control, as demonstrated in clinical trials [12]. However, this clinical success contrasts with the increasing misuse of these drugs. The growing and uncontrolled demand for these medications to achieve rapid weight loss, driven mainly by influencers and social media, has led to a dangerous rise in off-label use, beyond approved indications, for purely aesthetic purposes. This popularity is reinforced by an increasingly favorable public perception, directly shaped by the aesthetics industry [13]. The accelerated demand and subsequent shortages have fostered the proliferation of compounded and counterfeit products which, together with aggressive marketing, raise serious safety and regulatory concerns for health care systems [14].

Complementary studies are therefore needed to assess the long-term impacts of GLP-1 analogues, as they represent a relatively new class of medications [15]. This also underscores the urgent need to establish guidelines to govern aesthetic use and promote responsible prescribing [13]. Moreover, choosing the most appropriate treatment remains a highly individualized decision [15]. Given the rapidly expanding literature, there is a clear need for an up-to-date narrative review. This study aims to provide a concise overview of the mechanisms of action and clinical effects of these medications, while discussing the regulatory and policy frameworks implications of their use.

1.1. Search strategy and data sources

This study is a narrative review of the literature concerning the mechanisms of action, clinical impacts, and regulatory landscape of GLP-1 receptor agonists in obesity management. The primary search was conducted in PubMed/MEDLINE, focusing on studies published between 2005 (the date of the first GLP-1 analog approval) and 2025; the final search was completed in October 2025. Additionally, official reports from international health organizations such as the WHO, the Centers for Disease Control and Prevention (CDC), and the NHS, as well as regulatory documents from the U.S. Food and Drug Administration (FDA) and Brazil's National Health Surveillance Agency (ANVISA), were consulted.

The search process utilized combinations of the following terms and Boolean operators:

-GLP-1 receptor agonists AND obesity;

-GLP-1 receptor agonists AND obesity AND (body composition OR eating habits OR dietary habits OR food intake);

-Obesity AND (chronic disease OR type 2 diabetes OR cardiovascular disease OR hypertension);

-Obesity AND chronic disease AND Brazil.

1.2. Eligibility criteria

To ensure the inclusion of high-quality evidence, specific filters were applied during the database search, where eligible study types included randomized controlled trials (RCTs), adaptive clinical trials, multicenter studies, comparative studies, observational studies, systematic reviews, meta-analyses, and clinical practice guidelines. Furthermore, official consensus protocols and reports from governmental health agencies were included to address the regulatory and economic scope, while exclusion criteria were applied to studies that were not original research (unless official guidelines or reports), articles with poorly defined methodologies, and works that did not align with the dual focus on physiological mechanisms and socio-economic barriers to treatment.

1.3. Selection and data synthesis

The selection process involved an initial screening of titles and abstracts, followed by a full-text analysis of the remaining documents to ensure thematic alignment. Since the search was primarily centered on the PubMed database using comprehensive filters, formal software-based duplicate removal was not required.

The initial database search yielded 904 records, which were screened based on title relevance and abstract alignment to identify the core literature. Following the exclusion of articles that did not meet the thematic scope or presented poorly defined methodologies, a final subset of 12 primary studies was selected for full-text analysis and descriptive synthesis. Given the nature of this study as a narrative literature review, the selection and evaluation of the included literature were conducted qualitatively by a single reviewer without formal blinding. The authors acknowledge that this approach inherently introduces selection bias. Furthermore, standard quality assessment tools or risk-of-bias evaluations (such as Cochrane RoB or AMSTAR 2) were not applied, as they are tailored for systematic reviews and meta-analyses, which falls outside the scope of this descriptive overview. This review aims to summarize the current landscape of obesity treatments rather than to perform a quantitative or comparative evaluation of clinical trials.

2. Review findings and discussion

2.1. Pathophysiological mechanisms of obesity

Obesity is a complex condition directly linked to the dysregulation of several physiological, hormonal, and satiety mechanisms, which serve as the primary targets for weight-loss medications [16]. These pathophysiological impacts are closely interconnected with other metabolic disorders, including T2DM, hyperlipidemia, hypertension, and cardiovascular diseases [17]. A central element in this network is the pathogenesis of insulin resistance (IR), which is intrinsically linked to fat accumulation and characterized by reduced tissue responsiveness to insulin [18]. Because the skeletal muscle is the principal site of postprandial glucose uptake [18], any reduction in skeletal muscle mass directly impairs glucose metabolism and intensifies IR [19].

In parallel, body-weight homeostasis involves systemic neuroendocrine dysregulation, such as alterations in the hypothalamic–pituitary–adrenal (HPA) axis and cortisol activity. Cortisol plays a key role in fat accumulation and weight gain by promoting the conversion of pre-adipocytes into mature adipocytes; consequently, hypotheses suggest that obesity may lead to prolonged increases in cortisol concentrations, further intensifying adipose tissue accumulation [20]. Beyond this central regulation, body-weight homeostasis is modulated daily by gastrointestinal hormones that influence long-term food intake through the vagus nerve and peripheral hormonal pathways [21].

In individuals with obesity, however, the postprandial response to these gastrointestinal hormones tends to be significantly blunted [21]. This is particularly evident with ghrelin, an orexigenic hormone produced in the stomach that stimulates appetite around mealtimes, and peptide YY (PYY), an anorexigenic hormone that suppresses appetite [21]. Paradoxically, studies indicate that individuals with obesity may exhibit higher caloric intake than those without obesity, despite reporting lower perceived hunger in the postprandial period [21]. This phenomenon is supported by evidence showing that both basal and postprandial ghrelin concentrations are lower in individuals with obesity compared to controls [21].

Ultimately, these observations demonstrate that gastrointestinal hormones like ghrelin and PYY do not show a straightforward correlation with satiety signals in this population as seen in non-obese individuals [21]. These alterations in appetite perception are largely mediated by impaired vagal sensitivity and other central mechanisms, as illustrated in **Figure 1** [21]. Furthermore, food intake in individuals with obesity is heavily driven beyond pure physiological mechanisms, being strongly influenced by the hedonic system—especially within an obesogenic environment characterized by the widespread availability of highly palatable foods [21].

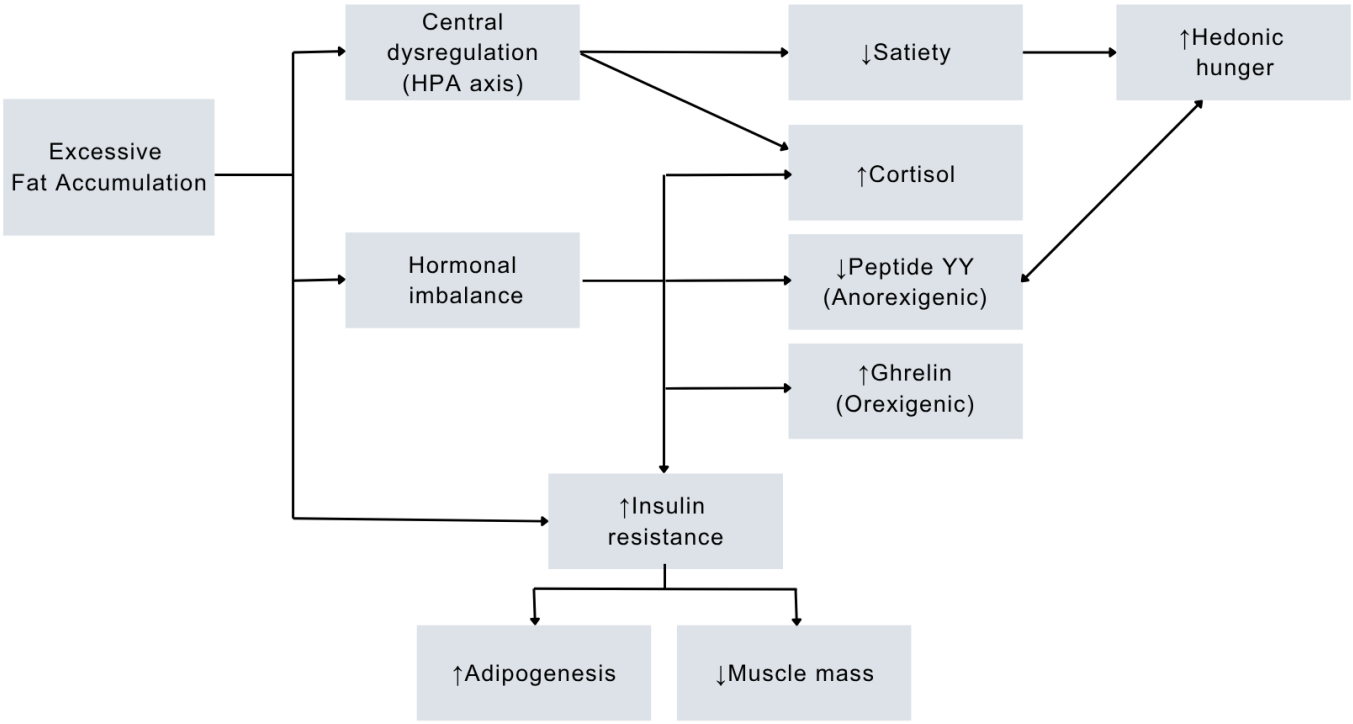

Figure 1 • Overview of the primary pathophysiological mechanisms of obesity, including hormonal dysregulation and hypothalamic signaling. The flowchart illustrates how excessive fat accumulation triggers systemic pathways involving central dysregulation of the HPA axis, hormonal imbalances, and insulin resistance. The connecting arrows denote the directional flow of causal relationships and pathophysiological progression. Within the text boxes, downward arrows (↓) indicate a downregulation, reduction, or inhibition of physiological outcomes (e.g., decreased satiety, peptide YY levels, and muscle mass). Conversely, upward arrows (↑) represent an upregulation, elevation, or stimulation of specific metabolic and behavioral processes (e.g., increased hedonic hunger, cortisol secretion, ghrelin levels, insulin resistance, and adipogenesis). HPA: hypothalamic–pituitary–adrenal.

2.2. Mechanisms and pharmacokinetics of GLP-1 receptor agonists

Glucagon and glucagon-like peptide-1 (GLP-1) are both derived from the same precursor gene but exert opposite effects on glucose metabolism. Glucagon is released by pancreatic alpha cells in response to hypoglycemia to raise blood glucose levels through hepatic glycogenolysis and gluconeogenesis, whereas GLP-1 acts to lower it [22]. In patients with diabetes, this glucagon-secretion response is impaired, contributing to poorly regulated hypoglycemic episodes; understanding this context is fundamental to comprehending how GLP-1 analogues modulate glycemia and support metabolic control [22].

Physiologically, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted by intestinal L and K cells, respectively, during the postprandial period [23]. They stimulate insulin secretion by pancreatic beta cells through their specific receptors, thereby reducing plasma glucose concentrations primarily by increasing glucose uptake in skeletal muscle and adipose tissue, where GIP further enhances insulin sensitivity and potentiates glucose uptake [23].

The activation of the GIP receptor acts on the central nervous system to reduce appetite, caloric intake, and body weight, while also attenuating treatment-induced nausea, thereby expanding therapeutic tolerance [24]. In the pancreas, GIP functions as an essential incretin hormone, stimulating glucose-dependent insulin secretion, increasing gene transcription, and promoting beta-cell survival and proliferation while reducing apoptosis [24, 25]. Finally, GIP optimizes peripheral metabolism by increasing blood flow and nutrient delivery to adipose tissue, which maximizes triglyceride clearance and safe lipid storage; this healthy expansion of adipose tissue prevents lipid spillover into organs like skeletal muscle, which directly and indirectly improves insulin sensitivity and whole-body glucose uptake (**Figure 2**, [24, 25]).

For patients with T2DM who require intensified injectable therapy, GLP-1 analogues offer good cost-effectiveness, as their high efficacy in preventing clinical events may reduce other healthcare expenditures [26]. Most of these medications are peptide agonists administered subcutaneously, which can be inconvenient and compromise treatment adherence, especially among patients who prefer oral formulations [12]. However, a recent meta-analysis suggests that the efficacy of GLP-1 analogues remains similar regardless of whether they are administered orally or subcutaneously [27].

Among the specific agents in this class, liraglutide possesses a 97% compatibility with native GLP-1 and is marketed under the brand names Victoza®, Saxenda®, and Olire® [28]. This analogue has a prolonged half-life of approximately 13 hours compared with the 1–2 minutes of native GLP-1, and it acts on hypothalamic neurons involved in energy metabolism, brain reward and pleasure centers, gastric emptying, and the pancreas, where it stimulates insulin secretion while inhibiting glucagon and somatostatin [28].

Semaglutide, available commercially as Ozempic® and Wegovy® (manufactured by Novo Nordisk), also mimics the effects of native GLP-1 [28, 29]. It acts at multiple sites, including the hypothalamus and the mesolimbic reward system, to promote weight loss by reducing caloric intake, decreasing hunger, and increasing satiety [28]. Semaglutide features an elimination half-life of approximately one week and remains in the body for 5–7 weeks after the last dose [30]. Although oral semaglutide was long established as the primary oral option available for T2DM management, its clinical utility is often limited by the requirement of strict fasting conditions to prevent peptic degradation [12].

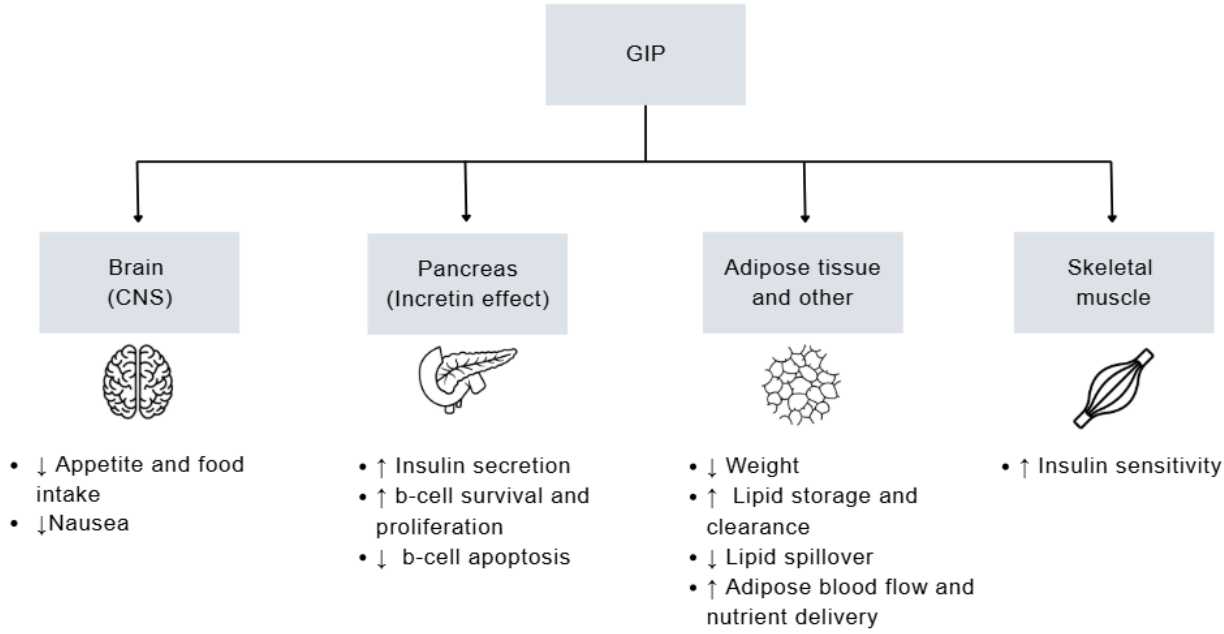

Figure 2 • Main mechanisms of action of GIP and their effects on metabolic and central nervous system pathways. GIP acts multi-organically to regulate energy homeostasis. Downward arrows (↓) represent a downregulation or reduction in specific functions (e.g., decreased appetite, food intake, nausea, beta-cell apoptosis, overall body weight, and lipid spillover). Upward arrows (↑) indicate an upregulation or enhancement of biological processes, including stimulated insulin secretion, improved beta-cell survival and proliferation, enhanced adipose tissue lipid storage, clearance, and blood flow, as well as increased skeletal muscle insulin sensitivity. GIP: glucose-dependent insulinotropic polypeptide; CNS: central nervous system.

Tirzepatide, marketed as Mounjaro® and Zepbound® by Eli Lilly®, represents a dual agonist of both the GLP-1 and GIP receptors [29]. While the GLP-1 component acts on pancreatic cells to control glycemia and on the central nervous system to regulate appetite, the GIP component exerts an incretin effect on the pancreas and promotes a catabolic effect on adipose tissue postprandially [28, 30]. In Brazil, the regulatory agency ANVISA has approved tirzepatide for T2DM treatment as well as for weight control in combination with a low-calorie diet and increased physical activity [31].

To minimize side effects, these medications require careful administration through gradual dose escalation [28]. Liraglutide treatment should start at 0.6 mg/day and be increased by 0.6 mg every week up to a maximum dose of 3.0 mg/day [28]. Semaglutide is initiated at 0.25 mg weekly, with dose escalation every 4 weeks until the effective maximum dose for weight loss is achieved [28]. Similarly, tirzepatide is initiated at 2.5 mg weekly, with increments of 2.5 mg at 4-week intervals up to a maximum weekly dose of 15 mg [28]. For tirzepatide specifically, gastrointestinal adverse events, particularly nausea and vomiting, are dose-dependent; therefore, starting with lower doses and increasing them gradually—with the option of using antiemetics when necessary—is highly recommended to prevent treatment discontinuation [17].

All drugs in this class are associated with gastrointestinal adverse effects such as nausea, vomiting, diarrhea, and constipation, without presenting an increased risk of hypoglycemia [7]. Patients without T2DM may experience a higher incidence of these adverse effects than those with T2DM [32]. In general, these symptoms are more frequent at the beginning of treatment and tend to diminish over time, suggesting a favorable long-term safety profile, and none of the analogues have been associated with severe adverse events such as serious gastrointestinal reactions, major cardiovascular events, and severe hypoglycemia [32, 33]. Nonetheless, the occurrence of these transient adverse effects can lead to lower adherence, which predisposes patients to treatment discontinuation, subsequent weight regain, and the development of multiple comorbidities [7]. Furthermore, dosing frequency impacts tolerance, as weekly regimens are associated with fewer adverse effects than daily administration [34].

2.3. Evidence of GLP-1 analogues on the eating regulatory system

In individuals with obesity, the infusion of gastrointestinal hormones directly affects eating behavior; however, hunger and appetite perception remain complex phenomena, and their precise correlation with physiological hormone levels is not yet fully established [21]. The mechanisms of action of GLP-1 receptor agonists are strongly related to appetite regulation. Although not entirely understood, these mechanisms involve the inhibition of gastric emptying and direct actions on the central nervous system—as summarized in **Figure 3**—leading to decreased hunger, increased satiety, and a subsequent reduction in overall energy and *ad libitum* food intake [34].

To evaluate these effects clinically, Blundell et al. conducted a randomized, double-blind, placebo-controlled study examining how semaglutide affects appetite, energy intake, eating control, and food preferences in patients with obesity [35]. The trial demonstrated that semaglutide substantially reduced energy intake, causing a 24% decrease in caloric consumption from *ad libitum* meals throughout the day compared with the placebo [35]. Additionally, the pharmacological treatment resulted in significant appetite suppression, less self-reported hunger, reduced overall food cravings, and a lower preference for high-fat foods [35].

These clinical outcomes are supported by the fact that GLP-1 analogues act on specific regions of the central nervous system involved in appetite regulation, promoting weight loss through the direct activation of the hypothalamus [35]. This localized central mechanism helps explain the comprehensive behavioral effects observed with semaglutide, particularly the robust reduction in appetite and the decreased desire for food [35].

Specifically, this neuroendocrine modulation occurs predominantly within the arcuate nucleus (ARC) of the hypothalamus, which acts as a central mediator of eating behavior by integrating hormonal and nutritional signals. The ARC contains two distinct neuronal populations: those synthesizing the orexigenic neuropeptides neuropeptide Y (NPY) and agouti-related protein (AgRP), and those producing the anorectic neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The signaling pathway is fundamentally driven by adenosine monophosphate-activated protein kinase (AMPK), a cellular energy sensor heavily expressed in these hypothalamic circuits. Hormonal responses that inhibit hypothalamic AMPK phosphorylation downstream promote an anorexigenic signaling cascade, directly stimulating the POMC/CART neurons while simultaneously suppressing NPY/AgRP expression. This intricate reciprocal modulation shifts the metabolic balance toward appetite suppression and increased energy expenditure, providing the exact neurobiological framework that underpins the therapeutic efficacy of GLP-1 receptor agonists in weight management [36].

2.4. Evidence of GLP-1 analogues on weight loss

2.4.1. Comparative efficacy in weight loss and adiposity reduction

Robust clinical evidence demonstrates that GLP-1 receptor agonists and associated polyagonists promote significant reductions in body weight and BMI in overweight or obese populations [7, 27, 32, 34] (**Table 1**). Within the scope of this narrative review, it is important to emphasize that direct cross-trial comparisons cannot be statistically established, as the included studies present heterogeneous populations and clinical designs. However, a descriptive observation of the isolated data reported by different trials suggests distinct ranges of weight reduction across these agents. For instance, within their respective studies, the triple agonist retatrutide (acting on GLP-1, GIP, and glucagon receptors) at doses of 8 mg and 12 mg showed reported reductions in body weight (up to −20.70% and −22.10%, respectively) and waist circumference (up to −15.9 cm and −17.0 cm) [32]. In separate evaluations, the dual incretin agonist tirzepatide achieves average weight reductions of up to 16.53% at 15 mg doses in some meta-analyses [32] and up to 20% in long-term assessments [33]. Among pure GLP-1 receptor agonists, semaglutide consistently shows pronounced weight-loss effects in the literature compared to classic analogues like liraglutide and exenatide [7, 27, 34], as well as newer small-molecule formulations [12]. Furthermore, a dose-dependent relationship has been described across this class, where higher therapeutic doses of semaglutide, liraglutide, and other novel agonists consistently yield greater reductions in weight and waist circumference than lower or intermediate regimens within the same clinical trials [7, 32]. The authors reiterate that these metrics serve a purely contextual purpose in this qualitative overview, and no definitive meta-analytical hierarchy or statistical superiority is implied.

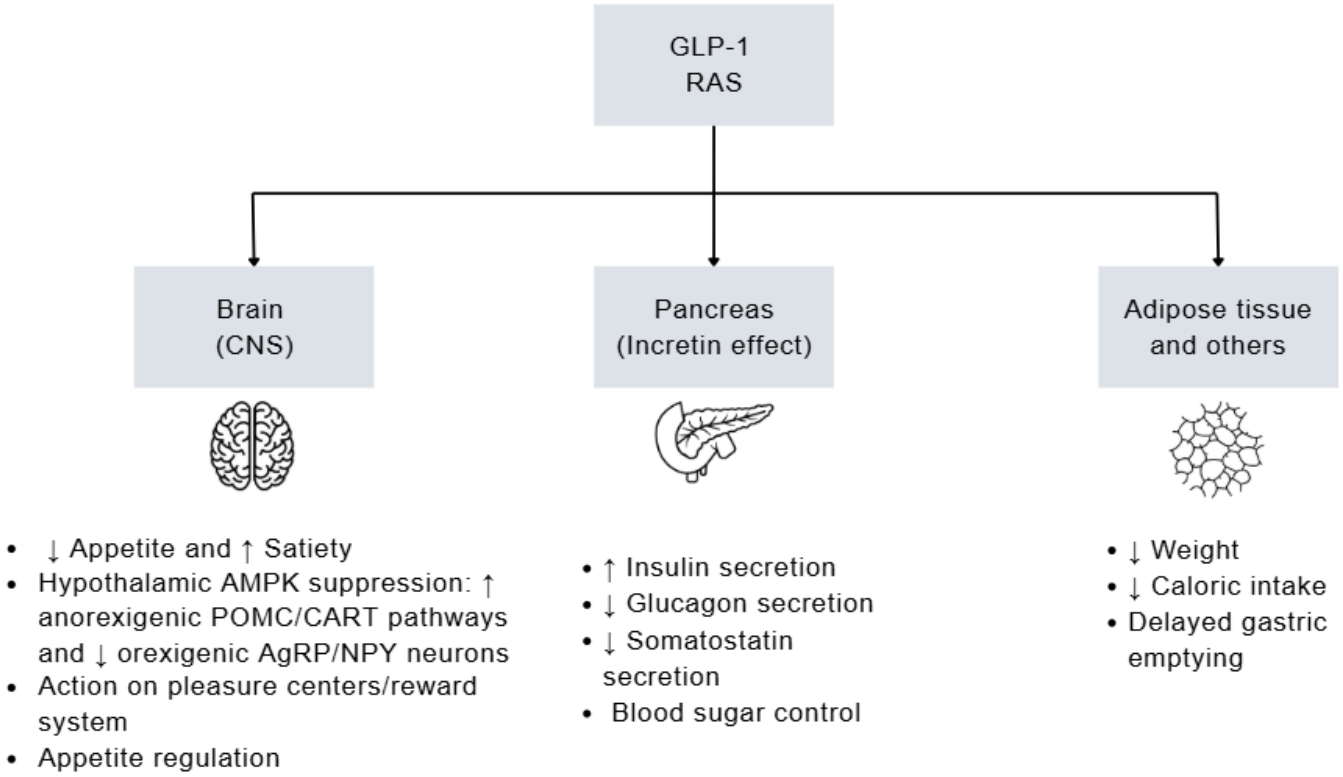

Figure 3 • Main mechanisms of action of GLP-1 analogues and their effects on metabolic and central nervous system pathways. The diagram illustrates the multi-organ physiological effects mediated by GLP-1 receptor agonists (GLP-1 RAs). Downward arrows (↓) indicate a downregulation, suppression, or reduction in the respective physiological pathways (e.g., decreased appetite, caloric intake, overall body weight, glucagon and somatostatin secretion, and a reduction in orexigenic AgRP/NPY neurons). Conversely, upward arrows (↑) denote an upregulation, stimulation, or enhancement of specific target mechanisms (e.g., increased satiety, insulin secretion, and stimulation of anorexigenic POMC/CART pathways). GLP-1: glucagon-like peptide-1; GLP-1 RAs: GLP-1 receptor agonists; CNS: central nervous system; AMPK: AMP-activated protein kinase; POMC: pro-opiomelanocortin; CART: cocaine- and amphetamine-regulated transcript; AgRP: agouti-related peptide; NPY: neuropeptide Y.

2.4.2. Predictors of clinical response, muscle preservation mechanisms and pediatric application

The therapeutic response to these medications is modulated by demographic, clinical, physiological, and genetic factors. Systematic reviews indicate that weight-loss outcomes are significantly more pronounced in women, younger individuals, patients with higher baseline weight and BMI, and those presenting a lower baseline glycated hemoglobin (HbA1c) [27]. Conversely, patients with T2DM exhibit a smaller weight-loss effect, a phenomenon potentially linked to impaired stomach and small intestine motility that attenuates GLP-1-mediated gastrointestinal modulation [27]. On a physiological level, liraglutide (3 mg) has been shown to induce weight loss by delaying the gastric emptying of solids for up to 16 weeks and modulating appetite [8]. A direct correlation exists between the magnitude of this gastric emptying delay and overall weight loss—particularly in individuals with a faster baseline gastric motor phenotype [8]. Additionally, genetic variability may dictate treatment efficacy, specifically through polymorphisms identified in the GLP-1R and TCF7L2 genes [8].

Crucially, the rapid and substantial weight loss induced pharmacologically by GLP-1 receptor agonists and dual incretin therapies carries a significant clinical risk of muscle wasting and sarcopenic effects. Recent meta-analytical evidence demonstrates that lean mass loss accounts for a reported range of 25% to 39% of the total weight reduction achieved with these agents, specifically compiled as 35.2% with semaglutide, 25.4% with tirzepatide, and 26.8% with liraglutide in specific studies. According to the literature [37], such depletion is highlighted as a factor that may lower basal metabolic rate and compound the risk of sarcopenic obesity, with authors suggesting it could parallel the relative muscle loss observed in intensive lifestyle interventions or post-bariatric states [37]. To counteract these adverse changes in body composition, integrating clinical exercise physiology protocols is vital [38]. The prescription of concurrent training, combining functional strength interventions with high-intensity interval training (HIIT), acts as a powerful therapeutic strategy. While progressive resistance training serves as a primary modifier to stimulate muscle protein synthesis (MPS) and directly minimize lean mass loss to its lowest proportional levels (17.5%), implementing HIIT further drives skeletal muscle tissue remodeling [38]. Systematic data establishes that HIIT effectively stimulates post-exercise rates of mixed and myofibrillar protein synthesis, facilitating the power-generating capacity and architecture of working skeletal muscle. Furthermore, when combined with proper therapeutic compliance, these dual training modalities induce essential skeletal muscle adaptations—such as mitochondrial biogenesis and enhanced metabolic flexibility—ensuring that rapid weight reduction is derived predominantly from adipose tissue expansion while successfully preserving functional muscle quantity and quality [38].

Beyond adult populations, these agonists show comparable efficacy in pediatric patients for treating obesity and T2DM, leading to reductions in fasting glucose, HbA1c, body weight, and body composition [39]. However, regulatory frameworks differ: while the FDA authorizes use for T2DM in pediatric patients aged 10 and older, pediatric use for obesity remains restricted to children aged 12 and older in the United States and European Union, facing limitations due to a scarcity of pediatric randomized trials, heterogeneous dosing, and a lack of post-treatment data [39].

2.4.3. Cardiometabolic outcomes beyond weight reduction

The clinical benefits of these therapies extend far beyond weight reduction, encompassing broad improvements in systemic metabolic and cardiovascular health. GLP-1 receptor agonists and polyagonists consistently lower systolic blood pressure and improve metabolic profiles, as shown in **Tables 1** and **2** [7, 12, 40, 41]. The blood pressure-lowering effect is hypothetically driven by a combination of direct vasodilatory effects, central nervous system interactions, and renal diuretic mechanisms [7]. Regarding lipid parameters, tirzepatide and the novel agonist orforglipron demonstrate significant, modest improvements across all fractions (LDL, VLDL, triacylglycerols, total cholesterol, and HDL) [7], while liraglutide and semaglutide also show marked multi-parameter cardiometabolic and anti-inflammatory enhancements [34, 40]. Long-term tirzepatide therapy significantly reduces the risk of progression to T2DM, successfully restoring normoglycemia in 92% of individuals with prediabetes [33] (**Table 2**), which is complemented by its ability to improve pancreatic cell function, insulin sensitivity, glucagon secretion, and liver enzyme profiles [30, 33]. Similarly, liraglutide at doses from 1.8 mg to 3.0 mg reduces the prevalence of prediabetes by 84–96% [41]. Crucially, semaglutide (2.4 mg once weekly) provides robust secondary prevention of cardiovascular events, effectively reducing major adverse cardiovascular events (MACE)—such as non-fatal stroke and myocardial infarction—in patients with overweight or obesity and established cardiovascular disease, even in the absence of diabetes [40].

2.4.4. Novel oral formulations and the challenge of discontinuation

Recent pharmaceutical developments have introduced non-peptidic, small-molecule GLP-1 receptor agonists, such as orforglipron and danuglipron [12, 32]. These agents significantly reduce HbA1c, fasting plasma glucose, body weight, and systolic blood pressure, yielding results comparable to the classical oral semaglutide doses of 7 mg and 14 mg [12]. Because of their non-peptidic structure, orforglipron and danuglipron possess pharmacokinetic profiles that favor oral administration; they are completely resistant to degradation by intestinal peptidases and do not require the strict fasting conditions mandated by oral semaglutide [12, 42].

Despite these therapeutic advances, maintaining weight loss after treatment cessation remains a critical challenge. Discontinuation of these medications triggers substantial weight regain that typically starts around 8 weeks post-cessation and persists through 20 weeks [43]. This weight trajectory is clinically significant and directly proportional to the initial weight lost [44]. For instance, patients withdrawing from semaglutide and tirzepatide experience an average weight regain of 7% over 17 weeks [33] or a substantial mean regain of 9.69 kg [44]. Conversely, the liraglutide group exhibits a more modest, less clinically significant regain of approximately 2.2 kg [44]. These combined findings strongly reinforce that weight loss is only sustainable in the long term when accompanied by permanent lifestyle changes, meaning that GLP-1 analogue therapy must be conceptualized as a chronic, ongoing treatment to successfully mitigate obesity-related comorbidities and prevent unfavorable weight rebound [33, 44].

2.5. Evidence of different therapies on weight loss

2.5.1. Surgical versus pharmacological interventions

When comparing therapeutic approaches for obesity, a systematic review and meta-analysis by Pipek et al. evaluated the clinical outcomes of surgical treatment against various pharmacological options, including GLP-1 analogues, the dual incretin agonist tirzepatide, and other traditional medications such as orlistat, phentermine, and sibutramine [15]. The analysis demonstrated that both surgical and pharmacological approaches are effective in mitigating overall cardiovascular risk, showing that weight loss from either modality leads to substantial improvements in lipid profiles, IR, and blood pressure [15]. However, within the findings evaluated by Pipek et al., bariatric surgery yielded statistically superior results across several metabolic and clinical parameters in the analyzed cohort [15]. Specifically, their data indicated that the surgical approach proved superior to isolated pharmacotherapy under those specific trial conditions in reducing body weight, BMI, waist circumference, blood pressure, IR, and glycated hemoglobin (HbA1c), while achieving significantly higher rates of T2DM remission [15]. Furthermore, surgery showed enhanced outcomes for long-term glycemic control, comprehensive lipid profiles, and the management of associated comorbidities such as asthma, bone turnover, and non-alcoholic steatohepatitis (NASH) [15].

Table 1 • Summary of systematic reviews and meta-analyses on the efficacy of glucagon-like peptide-1 (GLP-1) RAs for weight management.

Authors	Study design	Population	Intervention/ comparator	Duration	Main weight outcome (absolute or %) *	Key metabolic outcome	Major limitations
Ansari et al. [7]	Systematic review and meta-analysis	-10,638 individuals -With obesity (BMI >30 kg/m²) -Without diabetes -Mean age 48.3 ± 3.67 years	Semaglutide, Liraglutide, Tirzepatide, Exenatide, Orforglipron	Semaglutide: 68 wks. Liraglutide: 20 to 68 wks. Tirzepatide: 68 wks. Orforglipron: 26 wks. Exenatide: 16 and 24 wks.	Tirzepatide: ↓17% Semaglutide: ↓12% Orforglipron: ↓10% Liraglutide: ↓5% Exenatide: ↓3.3%	Systolic BP: ↓4.13 mm Hg Diastolic BP: ↓1.39 mm Hg Modest magnitude effect on the lipid profile	High statistical heterogeneity among the studies and the inclusion of only one clinical trial for tirzepatide and orforglipron, which may overestimate the effects of these medications.
Wong et al. [27]	Systematic review and meta-analysis	-23,244 patients -Adults -Overweight or obese -With or without diabetes	Liraglutide, Semaglutide, Exenatide, Dulaglutide, Danuglipron, Orforglipron, Efpeglenatide -Similar efficacy across administration routes	4 to 104 weeks	Mean body weight: ↓4.57 kg Mean BMI: ↓2.07 kg/m² Semaglutide: ↓7.18 kg, ↓2.86 kg/m² and WC ↓6.39 cm	-For each ↑1% in baseline HbA1c, weight loss ↓2.40 kg -Mean WC: 4.55 cm	Substantial statistical heterogeneity (attributed to broad inclusion criteria and diverse populations) and a disproportionately small number of studies on oral GLP-1 RAs compared to injectable ones.
Xie et al. [32]	Network meta-analysis	-15,584 patients -63.7% women -66.4% White; 21.9% Asian -With or without T2DM -With obesity or overweight	Retatrutide, Tirzepatide, Mazdutide, Liraglutide, Semaglutide, Orforglipron, Beinaglutide	16 to 72 weeks	Body weight: Retatrutide 12 mg: ↓22.10% Retatrutide 8 mg: ↓20.70% Tirzepatide 15 mg: ↓16.53% -Retatrutide 12 mg: ↓17.00 cm WC -Retatrutide 8 mg: ↓15.90 cm WC -Tirzepatide 15 mg: ↓13.23 cm WC -↑Doses = ↑Weight loss and waist circumference reduction	Tirzepatide (15 mg): HbA1c: ↓2.06% Fasting glycemia: ↓57.66 mg/dl	Absence of 10% or 20% weight loss proportional analysis. Limited safety data, focusing primarily on severe hypoglycemic events. Inclusion of studies with ongoing phase 2 trials for agents like retatrutide and orforglipron.

Table 1 • *Cont.*

Authors	Study design	Population	Intervention/ comparator	Duration	Main weight outcome (absolute or %) *	Key metabolic outcome	Major limitations
Liu et al. [34]	Systematic review and meta-analysis	-15,135 participants -75.6% female -Overweight or obese -Without diabetes	Semaglutide, Liraglutide, Exenatide, Efpeglenatide	4 to 160 weeks	Body weight: ↓5.319 kg BMI: ↓2.373 kg/m^2 WC: ↓4.302 cm Waist-to-hip ratio: ↓0.011 The weight loss effect is dose-dependent and non-linear	-	Significant statistical heterogeneity in some outcomes and a lack of long-term data beyond the trial durations.
Wu et al. [43]	Systematic review (focus on discontinuation)	-1573 participants -Adults -With obesity or overweight -With or without T2DM	Liraglutide, Semaglutide, Beinaglutide, Exenatide, AMG133	Minimum 4 weeks	Body weight (Regain): After 8 weeks: ↑1.50 kg After 12 weeks: ↑1.76 kg After 20 weeks: ↑2.50 kg	-	The follow-up period after drug discontinuation was relatively short in most included studies, and there was a limited number of trials evaluating newer agents.
Berg et al. [44]	Systematic review (focus on weight regain)	-Adults and children -Overweight or obese (BMI $\geq$ 27) -With/without T2DM and pre-diabetes -Obesity and NAFLD	Liraglutide, Semaglutide, Tirzepatide	20 to 160 weeks	Body weight (Regain): Semaglutide and Tirzepatide: ↑9.69 kg Liraglutide: ↑2.2 kg	The interruption resulted in the reversal of the metabolic benefits obtained, such as improvements in HbA1c and lipid levels.	High variability in follow-up duration post-discontinuation and limited data on weight maintenance strategies after stopping GLP-1 RAs.

Orforglipron (Foundayo) was approved by the FDA for obesity in April 2026. Efpeglenatide, mazdutide, beinaglutide, retatrutide, and AMG133 are currently not FDA-approved for weight management, with some agents approved only in China. Dulaglutide and exenatide are approved only for T2DM. * Metrics are reported as either absolute weight change (kg) or percentage reduction (%) adhering strictly to the primary outcome presentation of each respective source study to preserve original meta-analytical data integrity. Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease in the respective outcomes or baseline values. BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; HbA1c: glycated hemoglobin (hemoglobin A1c); NAFLD: non-alcoholic fatty liver disease; RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus; WC: waist circumference.

Table 2 • Characteristics and outcomes of landmark randomized clinical trials on glucagon-like peptide-1 (GLP-1) receptor agonists.

Authors	Study design	Population	Intervention/ comparator	Duration	Main weight outcome (absolute or %) *	Key metabolic outcome	Major limitations
Maselli et al. [8]	Short-term clinical trial (focus on pharmacogenetics)	-136 adults -With obesity (BMI > 30 kg/m²) -Ages between 18 and 65 years (average age 42)	Liraglutide	Up to 16 weeks	After 5 weeks: ↓3.8 kg After 16 weeks: ↓5.8 kg	Significant delay in gastric emptying of solids and increased postprandial fullness (satiety).	Short-term follow-up; relatively small sample size for a pharmacogenetic study, which may lack power to detect small genetic effects; focus on physiological mechanisms rather than long-term clinical outcomes.
Chadda et al. [39]	Systematic review of pediatric clinical trials	-286 children -Age: 9.9 to 15.2 years -With or without T2DM, pre-diabetes and obesity	Liraglutide, Exenatide	Liraglutide: 5 to 56 weeks Exenatide: 13 to 24 weeks	Body weight: ↓1.86 kg and BMI ↓1.26 kg/m². In children with obesity: ↓2.74 kg. In children with T2DM: ↓0.97 kg (not significant)	HbA1c: ↓0.30% (Pre-diabetes: ↓0.72% and Obesity ↓0.08%) Fasting Glycemia: ↓4.0 mg/dl (Pre-diabetes ↓19.4 mg/dl and Obesity ↓1.9 mg/dl)	Small number of available pediatric trials and limited sample sizes; high heterogeneity in study designs and baseline metabolic conditions; lack of long-term safety and efficacy data in the pediatric population.
Karakasis et al. [12]	Randomized clinical trial (RCT)—phase 2	-1037 patients -Majority men -Age: 54.2 to 59 years -793 with T2DM -244 with obesity without T2DM	Orforglipron, Danuglipron	Median duration of 16 weeks	Mean BMI: ↓2.87 kg/m² With T2DM: ↓3.26 kg With obesity without T2DM: ↓7.52 kg	With T2DM: Mean HbA1c: ↓1.03% Mean fasting glycemia: ↓28.53 mg/dl With obesity without T2DM: ↓0.46% Systolic BP: ↓3.48 mm Hg	Limited number of included RCTs and relatively small total sample size; short intervention duration (up to 16 weeks); high heterogeneity in weight-loss outcomes among the studied agents.
Lincoff et al. [40]	Large-scale randomized clinical trial (RCT)	-17,604 patients -Age: ≥45 years -BMI ≥ 27 -Pre-existing cardiovascular disease -Without diabetes	Semaglutide	39.8 months	Body weight: ↓9.39% WC: ↓7.56 cm	-Systolic BP: ↓3.82 mm Hg -Diastolic BP: ↓1.02 mm Hg -hs-CRP: ↓39.12% -Total cholesterol: ↓4.63% -LDL: ↓5.25%; HDL: ↑4.86% -Triglycerides: ↓18.34%	Strict inclusion of patients with pre-existing CVD, limiting generalizability of primary prevention; low female representation (27.7%).

Table 2 • *Cont.*

Authors	Study design	Population	Intervention/ comparator	Duration	Main weight outcome (absolute or %) *	Key metabolic outcome	Major limitations
Jastreboff et al. [33]	Randomized clinical trial (RCT)—Phase 3 (SURMOUNT-1)	-1032 participants -Mean age: 48.2 years -63.9% female -Obesity or pre-diabetes	Tirzepatide	176 weeks	Tirzepatide 5 mg: ↓12.3% Tirzepatide 10 mg: ↓18.7% Tirzepatide 15 mg: ↓19.7% Mean weight regain of 7% after discontinuation	T2DM Diagnosis: 1.3% of participants Reversal to normoglycemia: 89.9% (5 mg), 91.2% (10 mg), 93.3% (15 mg) HbA1c: ↓0.51% (15 mg) -Improvement in BP -↑Lipid profile and liver enzymes	Significant weight regain (approx. 7%) within 17 weeks of treatment discontinuation, highlighting the need for long-term therapy; limited generalizability to individuals without pre-diabetes.
Astrup et al. [41]	Randomized clinical trial (RCT)—Dose-ranging	-564 participants -Age: 18 to 65 years -With obesity: BMI: 30 to 40 kg/m^2 -Without diabetes	Liraglutide Orlistat as comparator	20 weeks	Body weight: ↓4.8 kg (1.2 mg), ↓5.5 kg (1.8 mg), ↓6.3 kg (2.4 mg) and ↓7.2 kg (3.0 mg)	Pre-diabetes: ↓84–96% (1.8 to 3.0 mg/day) Systolic BP: ↓5.7 to 8.8 mmHg Diastolic BP: ↓1.2 to 2.9 mmHg	Relatively short initial treatment duration to assess long-term sustainability; dose-ranging focus rather than definitive cardiovascular outcomes; results focused on a specific BMI range (30–40 kg/m^2).

Orforglipron (Foundayo) was approved by the FDA for obesity in April 2026. Efpeglenatide, mazdutide, beinaglutide, retatrutide, and AMG133 are currently not FDA-approved for weight management, with some agents approved only in China. Dulaglutide and exenatide are approved only for T2DM. * Metrics are reported as either absolute weight change (kg) or percentage reduction (%) adhering strictly to the primary outcome presentation of each respective source study to preserve original meta-analytical data integrity. Upward arrows (↑) indicate an increase, and downward arrows (↓) indicate a decrease in the respective outcomes or baseline values. BMI: body mass index; BP: blood pressure; CVD: cardiovascular disease; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; LDL: low-density lipoprotein; NAFLD: non-alcoholic fatty liver disease; RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus; WC: waist circumference.

2.5.2. Synergistic and combined therapeutic approaches

It is essential to recognize that available obesity treatments are not mutually exclusive and can be strategically combined to achieve optimized clinical outcomes [15]. For instance, pharmacological tools can act as an effective secondary intervention, where GLP-1 receptor agonists have been shown to successfully reverse and promote a reduction of up to two-thirds of the weight regained by patients after bariatric surgery [15]. Another critical factor influencing both long-term adherence and metabolic success is the integration of pharmacological therapy with structured physical exercise [27]. While the isolated use of GLP-1 analogues leaves patients highly susceptible to significant weight regain following treatment discontinuation, the addition of exercise helps sustain the achieved weight loss [27]. This combined approach is further reinforced by a randomized controlled trial conducted by Sandsdal et al., which demonstrated that combining liraglutide with physical exercise resulted in a significantly greater reduction in android fat compared to a placebo [45]. Furthermore, this specific lifestyle-pharmacological synergy led to a significant decrease in high-sensitivity C-reactive protein (hsCRP) after one year of continuous treatment, underscoring its systemic anti-inflammatory benefits [45].

2.5.3. Multidisciplinary management, public policy, and treatment sustainability

Despite the excellent therapeutic efficacy of GLP-1 analogues in driving weight loss and reducing NCDs, authoritative bodies such as the Scientific Committee of the British Nutrition Foundation and the specialist obesity and diabetes groups of the British Dietetic Association (BDA) emphasize that these medications are not a stand-alone solution to the rising global prevalence of obesity [46]. Managing this epidemic effectively requires a broad, systemic approach and robust public policies designed to reduce treatment costs, improve widespread access to healthy foods, decrease prevailing health inequalities, and fundamentally upgrade the food environment [46].

Consequently, patient care must be anchored in a multidisciplinary follow-up framework involving physicians, specialized dietitians, and psychologists who can collectively provide the necessary behavioral support for dietary changes and lifestyle modification [46]. Within this framework, a comprehensive mental health assessment is fundamental to identify potential clinical contraindications, such as underlying eating disorders [46]. Finally, because obesity is recognized as a chronic, complex, and recurrent disease, therapeutic support must not be conceptualized as a temporary intervention; thus, anti-obesity medications should not be discontinued as long as they remain clinically effective, safe, and well-tolerated by the patient [46].

2.6. Main challenges for implementation

Given the major challenges in obesity treatment, the WHO issued its global guideline in December 2025, providing clear recommendations on the use of GLP-1 and GIP analogues for the treatment of adults [47]. This document establishes conditional recommendations for the use of these medications in adults with obesity or overweight accompanied by comorbidities, emphasizing that pharmacotherapy should be integrated with lifestyle guidelines, such as diet and physical activity. Furthermore, the guideline highlights the importance of a patient-centered approach and the need for continuous monitoring to mitigate adverse gastrointestinal effects and ensure long-term treatment adherence [47]. This initiative by the leading global health authority underscores the established necessity for a well-defined regulatory and policy framework to ensure the safe, ethical, and equitable use of this therapeutic class worldwide [1].

The implementation model for this drug class in England's public health system is widely cited as an example, reflecting both the guidelines of its regulatory body, the National Institute for Health and Care Excellence (NICE), and the logistical capacity of the NHS. NHS Chief Executive Amanda Pritchard has recognized that these drugs are a "game changer" in obesity treatment but warned that without reorganization of care pathways, they could overburden public services that are already operating at capacity [48].

The Obesity Health Alliance reinforces that ensuring access to these medications is essential to mitigate rising health inequalities, highlighting access barriers imposed by the health system itself. The new NHS model for tirzepatide, based on a prioritization protocol according to BMI and comorbidities, establishes a three-step treatment pathway (assessment/counselling, dose titration and maintenance), aiming to guarantee adherence and multidisciplinary follow-up [48].

Another legal aspect that directly influences global access to GLP-1 analogues is patent protection. Although the first agonist was approved almost two decades ago, there are currently no generic competitors, and companies have achieved an expected exclusivity period of more than 18 years. This extended protection is supported by a "patent thicket" strategy, whereby manufacturers file numerous patents, more than half of which cover delivery devices (e.g., injection pens) rather than the active ingredient, methods of use or formulations. This focus on device patents makes it difficult for generic manufacturers to obtain FDA approval, providing grounds for litigation and delaying market competition [49].

The coverage landscape for anti-obesity medications (AOMs) in the United States is complex and divided between public and private sectors, heavily influenced by historical statutory and financial barriers [50]. In the public sector, the United States Medicare Part D program is governed by an explicit exclusion that bars coverage for medications used for weight loss or obesity [51]. This restriction was established because, at the time the benefit was constructed, the limited effectiveness and unfavorable safety profile of available treatments failed to generate justification for drugs perceived to be used primarily for cosmetic purposes [51]. To circumvent these legal-structural barriers and expand access, legislative measures like the Treat and Reduce Obesity Act have been proposed to reform the statute, alongside administrative alternatives such as testing regional coverage policies under the waiver authority of the Center for Medicare and Medicaid Innovation [51]. However, permanent legislative expansion and broader model implementation continue to face significant friction, driven primarily by high projected fiscal costs and substantial reluctance from major insurance plan sponsors to absorb the financial risks associated with widespread utilization [50, 51].

Opponents of expanding coverage argue that treating the large eligible population—which could encompass more than half of the US population based on clinical criteria—would impact prescription drug affordability and crowd out other high-value treatments

in public budgets [51]. It is estimated that expanding Medicare coverage to include GLP-1 analogues would result in a net fiscal cost of US$8 billion over ten years, even under a moderate-uptake scenario [52]. This impact underscores the importance of further price reductions and low-cost strategies for weight management, including de-implementation of low-value care [52]. Conversely, long-term economic modeling suggests that a public health investment in obesity reduction, allowing for broad utilization of AOMs, could significantly decrease cumulative government expenditures for Medicare and Medicaid over an extended time horizon [50]. These projected savings are driven by the reduction in chronic comorbidities, expanded workforce participation, and a subsequent increase in state and federal tax revenues [50].

Rising demand and shortages of GLP-1 analogues have created a serious public safety and legal issue: the proliferation of compounded and counterfeit versions. These products are not subject to the FDA's rigorous safety and efficacy review, exposing consumers to significant risks, such as dosing errors and the use of active ingredients of questionable quality [14]. Furthermore, current Canadian clinical guidance recommends against the use of compounded medications, or drugs not approved for weight loss, in individuals with excess adiposity due to safety and efficacy concerns [53]. In addition, aggressive marketing often delivered via online weight-loss programs exploits drug shortages, contributing to unbalanced communication that downplays potential risks and facilitates the entry of falsified and adulterated products into the U.S. supply chain [1]. This risk is further emphasized by recent clinical updates which warn that compounded GLP-1 and GIP receptor agonists, often emerging due to cost and supply issues, lack necessary regulation. Due to critical uncertainties regarding their content, safety, and quality, there is a strong recommendation against using any compounded or non-approved medications for weight management to ensure patient safety [53].

2.7. Limitations

GLP-1 analogues such as liraglutide, semaglutide and tirzepatide have demonstrated significant impact on weight loss and on improving metabolic and cardiovascular parameters in patients with obesity. However, it is crucial to address the limitations of the available studies, which often include small samples and short follow-up periods, as well as practical challenges such as adverse effects and high cost.

In addition to the constraints identified in the primary literature, several methodological limitations of the present review must be acknowledged. First, the literature screening and data extraction processes were conducted by a single reviewer without formal blinding, which inherently introduces a risk of selection bias. Second, while this work heavily synthesizes quantitative trial endpoints through a narrative approach, it initially lacked a systematic study quality appraisal. Nevertheless, the lack of an independent dual-reviewer framework means that the comparative efficacy observations outlined herein should be interpreted with appropriate caution.

Weight regain after treatment discontinuation reinforces that these drugs are not a stand-alone solution but rather part of a chronic, multifactorial treatment strategy. The sustainability of outcomes depends intrinsically on the adoption of a new lifestyle, with healthy eating and regular physical activity, highlighting the importance of multidisciplinary management to maintain long-term benefits. Pharmacotherapy for obesity should therefore be framed as a long-term strategy, since treatment interruption tends to be followed by weight regain and a loss of health benefits [53].

Although GLP-1 analogues represent a revolution in obesity treatment, optimal implementation still requires further research. Future studies should focus not only on efficacy but also on interactions between these medications and genetic factors, inter-individual variability in response, and their combination with nutritional and psychological interventions. Moreover, for a larger number of patients to benefit from this drug class, costs must be reduced to expand access. It is essential that legislators and regulatory authorities develop solutions to address the current patent system and facilitate access to the drug–device combination [49].

3. Conclusions

The class of GLP-1 receptor agonists and polyagonists represents a significant therapeutic breakthrough in the treatment of obesity and T2DM. Their mechanism of action, which modulates the incretin axis and acts on central neural circuits of appetite and satiety, has shown superior efficacy for weight loss and for improving cardiometabolic parameters such as blood pressure and glycemic control.

It is important to emphasize that obesity is a chronic, recurrent disease, and the efficacy of these drugs is not sustainable in isolation. The substantial weight regain observed after treatment discontinuation underscores the need to consider therapy as chronic and to integrate it into robust multidisciplinary care, focused on long-lasting lifestyle change.

The widespread use of GLP-1 analogues faces two major obstacles: gastrointestinal adverse effects and access barriers. These barriers arise at multiple levels, including high fiscal cost, legal and regulatory constraints, and patent strategies that limit competition. Therefore, for the transformative potential of GLP-1 analogues to be realized in public health, it is essential that legislators and regulatory agencies develop solutions that facilitate generic competition, reduce acquisition costs and ensure more equitable patient access, while broader public health policies address obesity as a systemic problem.

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Author contributions

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Conflict of interest

The authors declare that they have no competing interests. The funding sponsors played no role in the study's conception, execution, or interpretation, or in the preparation of this article.

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