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COMPARISON BETWEEN SEMAGLUTIDE, TIRZEPATIDE, AND NOVEL TRIPLE AGONISTS: EFFICACY, SAFETY, AND CLINICAL IMPLICATIONS

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NARRATIVE LITERATURE REVIEW

ABSTRACT

Obesity is a chronic, multifactorial, and relapsing condition associated with increased cardiometabolic, inflammatory, cardiovascular, renal, and functional risk. In recent years, incretin-based therapies have profoundly transformed the pharmacological treatment of obesity, particularly following the introduction of semaglutide 2.4 mg, tirzepatide, and, more recently, investigational triple agonists such as retatrutide. This narrative review aimed to compare the efficacy, safety, and clinical implications of semaglutide, tirzepatide, and novel triple agonists in the management of obesity and its comorbidities. The analysis was based on clinical trials, follow-up studies, and reviews published between 2019 and 2026, organized according to the PICo strategy. The findings indicate that semaglutide provides robust and sustained weight reduction, with additional evidence of cardiovascular benefit in individuals with overweight or obesity and established cardiovascular disease. Tirzepatide, in turn, demonstrated greater weight reduction in clinical trials and in direct comparison with semaglutide, in addition to marked metabolic effects. Retatrutide, a triple agonist targeting GIP, GLP-1, and glucagon receptors, showed promising results in a phase 2 trial, although it still requires confirmation in phase 3 studies and regulatory evaluation. These therapies represent a paradigm shift in obesity treatment, demanding long-term follow-up, individualized therapeutic planning, and careful monitoring regarding safety, adherence, access, and clinical sustainability.

Keywords: obesity; semaglutide; tirzepatide; retatrutide; incretin agonists.

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1 INTRODUCTION

Over recent decades, obesity has increasingly been recognized as a chronic, complex, and multifactorial disease characterized by metabolic, neuroendocrine, inflammatory, and behavioral alterations that extend far beyond the traditional imbalance between caloric intake and energy expenditure. This conceptual shift contributed to moving obesity treatment away from an approach focused exclusively on lifestyle modification toward an integrated therapeutic model in which behavioral, nutritional, pharmacological, and, in selected cases, surgical interventions are combined according to the patient's clinical profile and cardiometabolic risk (GARVEY *et al*., 2022; LINCOFF *et al*., 2023).

Within this context, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) gained substantial relevance because of their effects on satiety, gastric emptying, glucose-dependent insulin secretion, and appetite regulation through hypothalamic pathways. Semaglutide 2.4 mg, administered once weekly, became one of the major milestones of this new therapeutic generation, especially after the STEP-1 trial demonstrated clinically significant weight reduction in adults with overweight or obesity when compared with placebo (WILDING *et al*., 2021).

Tirzepatide further expanded this therapeutic field by combining agonism of GIP and GLP-1 receptors, a mechanism that appears to enhance effects on weight loss, glycemic control, adiposity, and cardiometabolic parameters. In the SURMOUNT-1 trial, tirzepatide produced substantial and dose-dependent weight reductions in adults with obesity or overweight without diabetes, achieving results superior to those historically observed with isolated GLP-1 agonists (JASTREBOFF *et al*., 2022). In direct comparison, the SURMOUNT-5 trial demonstrated the superiority of tirzepatide over semaglutide for weight reduction in individuals with obesity without diabetes (ARONNE *et al*., 2025).

More recently, triple agonists have emerged as a promising therapeutic frontier. Retatrutide, an agonist of GIP, GLP-1, and glucagon receptors, seeks to combine anorectic, insulinotropic, and potentially thermogenic effects, leading to substantial weight reduction in phase 2 trials. However, as it remains an investigational therapy, its incorporation into clinical practice still depends on confirmation of efficacy, cardiovascular safety, gastrointestinal tolerability, long-term metabolic impact, and regulatory approval (JASTREBOFF *et al*., 2023).

In light of this scenario, this narrative review aims to compare semaglutide, tirzepatide, and novel triple agonists, focusing on efficacy, safety, and clinical implications in the treatment of obesity and its comorbidities, considering recent evidence published between 2019 and 2026.

2 METHOD

This study consists of a Narrative Literature Review designed to gather, interpret, and critically discuss recent evidence regarding incretin-based and multiagonist therapies applied to obesity treatment. The narrative review approach was selected because it allows a broad and integrated analysis of clinical trials, randomized studies, follow-up investigations, and publications of clinical relevance, especially in a rapidly evolving field. Priority was given to articles published between 2019 and 2026 in English and Portuguese, indexed in databases and journals such as PubMed/MEDLINE, The New England Journal of Medicine, Nature Medicine, JAMA, and other high-impact journals in endocrinology, metabolism, and cardiovascular medicine.

The PICo strategy was used to organize the guiding research question. The population (P) included adults with obesity or overweight, with or without type 2 diabetes mellitus and with different cardiometabolic risk profiles. The phenomenon of interest (I) involved the use of semaglutide, tirzepatide, and triple agonists, particularly retatrutide. The context (Co) comprised the contemporary pharmacological management of obesity and its clinical, metabolic, and cardiovascular implications. Thus, the guiding question of this review was: what are the main differences between semaglutide, tirzepatide, and novel triple agonists regarding efficacy, safety, and clinical implications in obesity management?

3 RESULTS

The analyzed studies demonstrate that semaglutide 2.4 mg represents a well-established therapy for weight reduction in adults with obesity or overweight. In the STEP-1 trial, semaglutide was associated with an average weight reduction of approximately 14.9% over 68 weeks, compared with 2.4% in the placebo group, highlighting clinically relevant efficacy when combined with lifestyle intervention

(WILDING *et al*., 2021). In STEP-5, outcomes were evaluated over two years, showing sustained weight loss and improvement in cardiometabolic parameters, reinforcing the understanding of obesity as a condition requiring long-term rather than short-term treatment strategies (GARVEY *et al*., 2022). Furthermore, the SELECT trial demonstrated a reduction in major cardiovascular events among individuals with overweight or obesity and established cardiovascular disease, even in the absence of diabetes, thereby expanding the clinical significance of semaglutide beyond weight reduction alone (LINCOFF *et al*., 2023).

Tirzepatide produced even more expressive results across different studies within the SURMOUNT program. In SURMOUNT-1, weight reductions approaching or exceeding 20% were observed with higher doses, with adverse events predominantly gastrointestinal and generally similar to those reported with other incretin-based therapies (JASTREBOFF *et al*., 2022). SURMOUNT-3 demonstrated that tirzepatide promoted additional significant weight reduction following an intensive lifestyle intervention phase, suggesting that the drug may potentiate the effects achieved through behavioral strategies (WADDEN *et al*., 2023). SURMOUNT-4 further showed that discontinuation of tirzepatide after initial weight loss resulted in weight regain, whereas continued treatment maintained and extended clinical benefits, reinforcing the chronic nature of obesity and the need for sustained therapeutic plans (ARONNE *et al*., 2024).

In direct comparison between tirzepatide and semaglutide, SURMOUNT-5 demonstrated the superiority of tirzepatide for body weight reduction in individuals with obesity without diabetes, supporting the hypothesis that dual GIP/GLP-1 agonism may provide greater therapeutic potency than isolated GLP-1 agonism (ARONNE *et al*., 2025). Regarding triple agonists, retatrutide showed promising results in a phase 2 trial, with substantial and dose-dependent body weight reduction after 48 weeks. Nevertheless, because it remains an investigational therapy, its clinical role still depends on phase 3 results, assessment of adverse events, cardiovascular safety, and confirmation of applicability in broader and more diverse populations (JASTREBOFF *et al*., 2023).

Table 1. Main clinical findings related to semaglutide, tirzepatide, and retatrutide in obesity treatment

Study / Authors	Therapeutic agent	Study design and population	Main findings	Clinical implications
Wilding *et al*. (2021)	Semaglutide 2.4 mg	Randomized clinical trial involving adults with overweight or obesity without diabetes (STEP-1)	Mean body weight reduction of approximately 14.9% after 68 weeks compared with placebo	Consolidated semaglutide as one of the most effective GLP-1 receptor agonists for obesity treatment
Garvey *et al*. (2022)	Semaglutide 2.4 mg	Long-term follow-up trial in adults with obesity or overweight (STEP-5)	Sustained weight reduction over two years with improvement in cardiometabolic markers	Reinforced obesity as a chronic disease requiring long-term pharmacological management
Lincoff *et al*. (2023)	Semaglutide 2.4 mg	Cardiovascular outcomes trial in patients with obesity and established cardiovascular disease (SELECT)	Reduction in major adverse cardiovascular events even in patients without diabetes	Expanded the role of semaglutide beyond weight loss toward cardiovascular protection
Jastreboff *et al*. (2022)	Tirzepatide	Randomized phase 3 trial involving adults with obesity or overweight without diabetes (SURMOUNT-1)	Weight reduction approaching or exceeding 20% in higher-dose groups	Demonstrated superior weight-loss efficacy compared with historical GLP-1 receptor agonist outcomes
Wadden *et al*. (2023)	Tirzepatide	Phase 3 trial following intensive lifestyle intervention (SURMOUNT-3)	Additional significant weight reduction after lifestyle intervention	Suggested synergistic effects between pharmacotherapy and behavioral interventions
Aronne *et al*. (2024)	Tirzepatide	Randomized withdrawal trial evaluating maintenance of weight loss (SURMOUNT-4)	Treatment discontinuation resulted in weight regain, whereas continued therapy maintained benefits	Reinforced the chronic and relapsing nature of obesity
Aronne *et al*. (2025)	Tirzepatide versus semaglutide	Direct comparative trial in adults with obesity without diabetes (SURMOUNT-5)	Tirzepatide achieved greater weight reduction than semaglutide	Highlighted the therapeutic potential of dual GIP/GLP-1 agonism
Frías *et al*. (2021)	Tirzepatide versus semaglutide	Comparative trial in patients with type 2 diabetes (SURPASS-2)	Greater reductions in glycated hemoglobin and body weight with tirzepatide	Suggested broader metabolic efficacy associated with dual agonism
Jastreboff *et al*. (2023)	Retatrutide	Phase 2 trial involving adults with obesity	Substantial and dose-dependent body weight	Positioned triple agonists as a promising future

			reduction after 48 weeks	strategy in obesity pharmacotherapy
Kusminski, Boström and Scherer (2024)	Multi-receptor incretin agonists	Translational and mechanistic review	Demonstrated the potential integration of appetite suppression, glycemic modulation, and increased energy expenditure	Supported the biological rationale for multiagonist therapies
Rubino *et al*. (2020)	Obesity management perspectives	International consensus statement	Highlighted obesity stigma and the need for comprehensive multidisciplinary care	Reinforced that pharmacotherapy alone is insufficient without integrated support strategies
Steenackers *et al*. (2025)	Anti-obesity pharmacotherapy	Contemporary review on obesity pharmacological personalization	Discussed individualized selection and combination of anti-obesity medications	Emphasized the future of personalized obesity treatment strategies

Source: Prepared by the authors, 2026.

4. DISCUSSION

The comparison between semaglutide, tirzepatide, and triple agonists reveals an important transition in the pharmacological treatment of obesity. Semaglutide consolidated the paradigm of GLP-1–based therapies as effective interventions for sustained weight reduction, metabolic improvement, and cardiovascular risk reduction in selected populations. Its results support the concept that obesity should be managed similarly to other chronic diseases, requiring continuous follow-up, individualized therapeutic goals, and careful monitoring of clinical response (WILDING *et al*., 2021; GARVEY *et al*., 2022; LINCOFF *et al*., 2023).

Tirzepatide, by combining GIP and GLP-1 receptor agonism, appears to amplify the therapeutic potency observed with semaglutide. This superiority was initially suggested in studies involving type 2 diabetes, such as SURPASS-2, in which tirzepatide achieved greater reductions in glycated hemoglobin and body weight compared with semaglutide 1 mg (FRÍAS *et al*., 2021). Subsequently, the SURMOUNT studies confirmed its relevance in obesity treatment among individuals without diabetes, especially at doses of 10 mg and 15 mg, reaching levels of weight reduction historically associated mainly with bariatric procedures in selected groups.

From a clinical perspective, the primary distinction between semaglutide and tirzepatide appears to lie in the magnitude of weight reduction and the breadth of metabolic effects. While semaglutide offers robust evidence, longer clinical experience, and relevant cardiovascular data, tirzepatide demonstrates greater weight-loss efficacy in recent studies and may be particularly useful for patients requiring more pronounced reductions in body weight. Nevertheless, therapeutic decisions should not rely solely on average weight-loss percentages but should also consider comorbidities, tolerability, patient preferences, cost, availability, contraindications, and risk of treatment discontinuation (FAHIM *et al*., 2025; JOHANSSON *et al*., 2026).

Retatrutide and other triple agonists represent a new stage in obesity pharmacotherapy development. The biological rationale behind combining GIP, GLP-1, and glucagon agonism seeks to integrate appetite suppression, improved insulin secretion, glycemic modulation, and possibly increased energy expenditure (KUSMINSKI *et al*., 2024; GOLDNEY *et al*., 2025). However, the inclusion of glucagon receptor agonism also requires caution, as its metabolic effects may involve increased heart rate, glycemic fluctuations, and additional monitoring requirements (DOGGRELL, 2023; JASTREBOFF *et al*., 2023). Therefore, although the initial findings regarding retatrutide are promising, its incorporation into clinical practice will depend on more mature evidence concerning safety, sustained efficacy, and effects on hard clinical outcomes.

Safety remains a central aspect of analysis. Semaglutide, tirzepatide, and retatrutide are associated predominantly with gastrointestinal adverse events, including nausea, vomiting, diarrhea, constipation, and abdominal discomfort, generally occurring more frequently during dose escalation phases. Although these events are usually mild to moderate, they may compromise adherence, quality of life, and treatment continuity. Moreover, clinical practice requires particular attention to conditions such as gallbladder disease, previous pancreatitis, concomitant use of hypoglycemic agents, and risk of dehydration in vulnerable patients (ISMAIEL *et al*., 2025; TOBAIQY *et al*., 2024).

Another relevant point concerns maintenance of results after treatment discontinuation. SURMOUNT-4 demonstrated that withdrawal of tirzepatide was

associated with weight regain, reinforcing that obesity should not be approached as a condition permanently resolved after initial weight reduction (ARONNE *et al*., 2024). This finding aligns with the pathophysiology of obesity itself, in which adaptive mechanisms reduce energy expenditure and increase hunger after substantial weight loss. Consequently, the clinical challenge is not only to induce weight reduction but also to sustain metabolic, functional, and cardiovascular benefits over time.

Clinical implications also involve issues of access, equity, and healthcare system sustainability. Highly effective medications may transform obesity care, but their elevated costs, limited availability, and unequal coverage may widen existing disparities. Furthermore, isolated medicalization of obesity may prove insufficient if not integrated with nutritional education, physical activity, psychological support, longitudinal care, and efforts to address obesity-related stigma. Thus, these therapies should be understood as powerful tools within a broader therapeutic framework (RUBINO *et al*., 2020; POWELL-WILEY *et al*., 2021).

Finally, the comparison among these therapeutic classes suggests that the future of obesity treatment will increasingly rely on personalized strategies. Semaglutide is likely to remain a well-established option supported by cardiovascular outcome data; tirzepatide stands out because of its superior weight-loss and metabolic efficacy; and triple agonists such as retatrutide may redefine pharmacological limits of weight reduction if safety and efficacy are confirmed in advanced studies. Nevertheless, progress in this field requires scientific caution, post-marketing surveillance, and an ethical understanding of obesity as a chronic, multifactorial, and socially influenced disease (STEENACKERS *et al*., 2025; LEMPESIS; DALAMAGA, 2026).

5 CONCLUSION

This narrative review demonstrated that semaglutide, tirzepatide, and novel triple agonists represent significant advances in the pharmacological treatment of obesity. Semaglutide consolidated the effectiveness of GLP-1 receptor agonists in sustained weight reduction and provided relevant evidence of cardiovascular benefit in patients with overweight or obesity and established cardiovascular disease.

Tirzepatide demonstrated superior efficacy in weight reduction compared with

semaglutide in recent studies, in addition to important metabolic benefits. Its dual mechanism involving GIP and GLP-1 receptors appears to contribute to a more intense weight-loss response, although therapeutic decisions must also consider safety, tolerability, access, and individual clinical characteristics.

Triple agonists, especially retatrutide, constitute a promising but still investigational therapeutic frontier. Phase 2 findings indicate remarkable potential for substantial weight reduction; however, clinical incorporation will depend on confirmation of safety, sustained efficacy, and impact on cardiovascular, metabolic, and functional outcomes in phase 3 trials.

In conclusion, contemporary obesity treatment is moving toward a more effective, personalized, and longitudinal model of care. However, incorporation of these therapies must be accompanied by clinical responsibility, continuous evaluation of risks and benefits, efforts to overcome barriers to access, and integration with multidisciplinary interventions aimed at maintaining health and quality of life.

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