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REVIEW ARTICLE

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Comparative clinical outcomes and metabolomic considerations of the use of tirzepatide and retatrutide in the treatment of obesity: a systematic and umbrella review

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Abstract

Introduction: According to the World Obesity Atlas, overweight and obesity could affect approximately 50% of the world's adult population by 2030. Obesity treatment is complex and multidisciplinary. Pharmacological treatment with tirzepatide and retatrutide begins in secondary prevention to stop disease progression. **Objective:** To highlight the main clinical outcomes of tirzepatide and retatrutide in the treatment of obesity and comorbidities. **Methods:** The systematic review guidelines of the PRISMA platform were followed. The search was conducted from September to November 2025 in the Scopus, Embase, PubMed, Science Direct, SciELO, and Google Scholar databases. The quality of the studies was based on the GRADE instrument, and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 92 articles were found. A total of 29 articles were evaluated, and 14 were included in this systematic review. Considering the Cochrane risk of bias tool, the overall assessment resulted in 18 studies with a high risk of bias and 20 studies that did not meet the GRADE and AMSTAR-2 criteria. Most studies showed homogeneity in their results, with X^2 = 86.5% > 50%. It was concluded that retatrutide offers superior efficacy in weight loss compared to tirzepatide and other GLP-1 analogs, but with a higher risk of adverse events. Dual agonists offer a favorable balance between efficacy and safety. Selecting personalized treatments based on patient characteristics is recommended. Available randomized clinical trials showed that, regarding weight loss, tirzepatide (15 mg) resulted in up to 17.8% weight loss at 72 weeks, semaglutide (2.4 mg) in up to 13.9% after 68 weeks, liraglutide (3.0 mg) in up to 5.8% after 26 weeks, and retatrutide (12 mg) produced the greatest weight loss, with 22.1% after 48 weeks. The main adverse effects of retatrutide were related to gastrointestinal events compared to tirzepatide.

Keywords: Obesity. Weight loss. Comorbidities. Tirzepatide. Retatrutide. GLP-1 analogs.

Introduction

According to the World Obesity Atlas, overweight and obesity could affect around 3 billion adults in the world's population by 2030 [1]. There are also worrying increases in the number of adults with obesity who are likely to need medical intervention during their lifetime, with serious implications for health systems. Obesity is a disease and one of the main drivers of NCDs, including some types of cancer, heart disease, stroke, and type II diabetes [1,2].

Overweight and obesity have significant implications for individual and societal health. Body mass index (BMI) values above normal are related to a higher risk of noncommunicable chronic diseases (NCDs), such as cardiovascular disease, diabetes, musculoskeletal diseases, and some types of cancer, as well as being associated with higher mortality rates [3].

The treatment of obesity is a complex and multidisciplinary process. In general terms, pharmacological treatment is an adjunct to targeted therapies focused on modifying lifestyle habits related to nutritional guidelines to reduce calorie consumption in the diet and exercise to increase calorie expenditure **[4]**. As with any chronic disease, pharmacological treatment begins in secondary prevention to prevent the progression of the disease to a more severe stage and to prevent complications and further deterioration, and should be maintained to avoid weight regain **[5,6]**.

There is no long-term pharmacological treatment that does not involve lifestyle changes. Lifestyle changes and cognitive-behavioral techniques are fundamental, and pharmacological treatment should not be used as treatment in the absence of other nonpharmacological measures. The choice of treatment should be based on the severity of the problem and the presence of associated complications **[7-10]**.

In this scenario, retatrudide is an innovative triple agonist that targets glucagon receptors, glucose-dependent insulinotropic polypeptide (GIP), and glucagon-like peptide-1 (GLP-1). The complex mechanism of action of retatrutide involves a synergistic interaction between these receptors, resulting in increased insulin secretion, improved glucose homeostasis, and refined appetite modulation. Phase 1 to 3 clinical trials have demonstrated significant efficacy, highlighted by significant reductions in body weight and favorable results in glycemic control **[8,9]**. In addition, retatrutide shows promise in mitigating cardiovascular risk factors and in treating steatotic liver disease associated with metabolic dysfunction. However, careful attention is needed to delineate its long-term safety profile and explore its potential in special populations **[11]**.

In addition, the combination of GLP-1 with other gut hormones, including GIP, has been explored to complement and further enhance the effects of GLP-1 on glycemia and weight loss. Tirzepatide is the first dual GLP-1/GIP receptor co-agonist that has been approved for the treatment of type 2 diabetes mellitus (T2DM) and obesity based on the results of the SURPASS program. The SURPASS trials evaluated the safety and efficacy of tirzepatide in people with T2DM, from monotherapy to the addition of insulin in global populations, with two other trials dedicated to the Japanese population **[12]**.

Therefore, this study aimed to highlight the main clinical outcomes of tirzepatide and retatrutide in the treatment of obesity and comorbidities.

Methods

Study Design

This study followed an international model for systematic review, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: October 25, 2025. The methodological quality standards of AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews) were also followed. Available at: https://amstar.ca/. Accessed on: October 25, 2025.

Data Sources and Search Strategy

The literature search process was conducted from September to November 2025 and developed using Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, encompassing scientific articles from various periods to the present day. The following descriptors were used (DeCS/MeSH Terms): "Obesity. Weight loss. Comorbidities. Tirzepatide. Retatrutide. GLP-1 analogs", and the Boolean operator "and" was used between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot (Sample size versus Effect size), using Cohen's d test.

Results

Summary of Findings

As a corollary to the literature search system, a total of 92 articles were found, which were submitted to eligibility analysis, and subsequently, 14 studies were selected to compose the results of this systematic review. The listed studies presented medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in study types such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with

X^2=86.5%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 18 studies with a high risk of bias and 20 studies that did not meet the GRADE and AMSTAR-2 criteria.

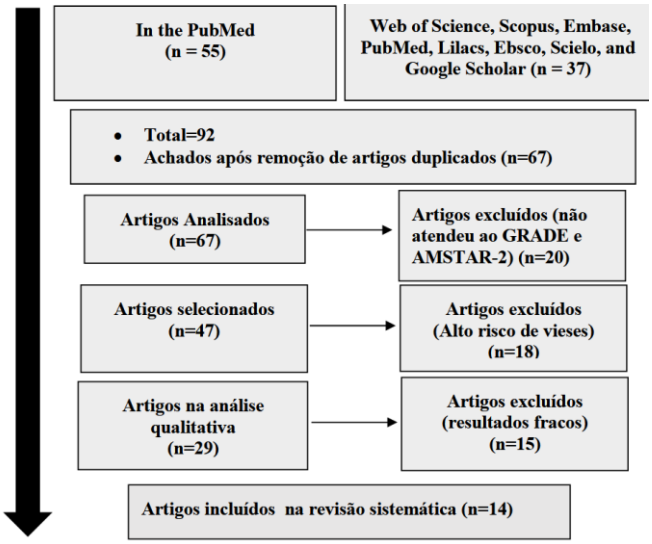

Figure 1. Flowchart showing the article selection process. Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) shown at the bottom of the graph and in studies with large sample sizes shown at the top.

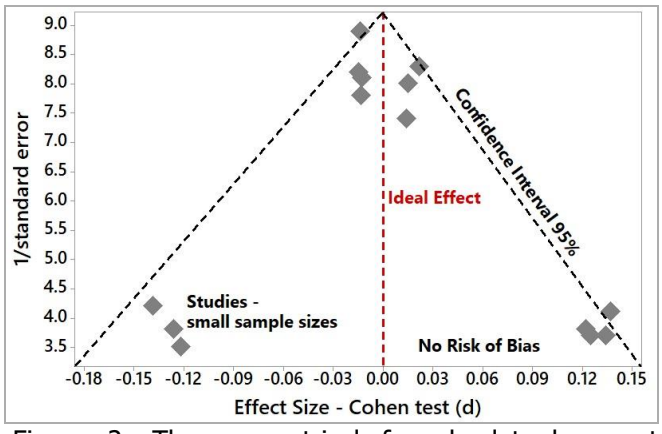

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=14 studies). Source: Own authorship.

Main Clinical Results

Moiz et al. (2025) **[13]** evaluated the efficacy and safety of GLP-1 RAs and coagonists for the treatment of obesity in adults without diabetes. Safety outcomes included death, serious adverse events (SAEs), any adverse events (AEs), and gastrointestinal AEs. Twenty-six randomized clinical trials were included with 15,491 participants (72% women; mean body mass index 30 to 41 kg/m²; mean age 34 to 57 years) and 12 agents (3 commercially available agents, liraglutide, semaglutide, and tirzepatide, and 9 agents in premarketing for long-term weight management). Treatment ranged from 16 to 104 weeks (median 43 weeks). Compared to placebo, tirzepatide (15 mg once weekly) resulted in weight loss of up to 17.8% (95% CI, 16.3% to 19.3%) after 72 weeks of therapy; semaglutide (2.4 mg once weekly), up to 13.9% (95% CI, 11.0% to 16.7%) after 68 weeks; and liraglutide (3.0 mg once daily), up to 5.8% (CI, 3.6% to 8.0%) after 26 weeks. Retatrutide (12 mg once weekly) produced greater weight loss, up to 22.1% (CI, 19.3% to 24.9%) after 48 weeks; other novel GLP-1 agents, alone or in combination, were also effective to varying degrees. Although adverse events (AEs) were frequent (GLP-1 receptor agonists vs. placebo: 80% to 97% vs. 63% to 100%), most were related to the gastrointestinal tract (47% to 84% vs. 13% to 63%, respectively), the most common being nausea, vomiting, diarrhea, and constipation.

The authors Sinha and Ghosal (2025) **[14]** analyzed through a meta-analysis study the efficacy and safety of GLP-1 receptor agonists (GLP-1RAs), dual agonists (GLP1RAs/GIP or GCGR), and retatrudide (GLP-1/GIP/glucagon) for weight loss in overweight or obese adults. This study was conducted in a Bayesian network with 19 randomized clinical trials and 29,506 adults (BMI ≥ 25 kg/m²), evaluating liraglutide, semaglutide, survodutide, tirrizepatide, retatrutide, and placebo. Outcomes included mean weight loss, achievement of weight loss ≥ 5%, ≥ 10%, and ≥ 15%, waist circumference (WC), BMI, and adverse events (AEs) at ≥ 36 weeks. Retatrutide and dual agonists achieved equivalent mean weight loss (-11.0 kg), outperforming GLP-1 receptor agonists (GLP-1RAs) (-9.0 kg), with retatrutide standing out in achieving weight loss ≥ 15% (OR 54.6). Dual agonists and GLP1RAs showed similar results (OR=16.4 and 9.0, respectively). Retatrutide had the highest risk of adverse events.

A systematic review and meta-analysis study conducted by the authors Xie et al. (2024) **[15]** presented the efficacy and safety of seven glucagon-like peptide-1 (GLP-1) receptor agonists and polyagonists for weight loss in patients with obesity or

overweight. Relevant randomized clinical trials with an intervention duration of at least 16 weeks evaluating seven GLP-1 receptor agonists and polyagonists (mazdutide, 6 or 4.5 mg; retatrutide, 12 or 8 mg; tirzepatide, 15 or 10 mg; liraglutide, 3.0 mg; semaglutide, 2.4 mg; orforglipron, 45 or 36 mg; and beinaglutide, 0.2 mg) were selected. The primary outcome was the percent change in body weight from baseline. Secondary outcomes included changes in waist circumference, hemoglobin A1c, and fasting glucose level from baseline; adverse events, serious adverse events, adverse event withdrawal, and hypoglycemic events. A total of 27 randomized clinical trials with seven GLP-1 receptor agonists and polyagonists and 15,584 patients were included in the network meta-analysis. In terms of efficacy, compared to placebo, retatrutide 12 mg (-22.10% in body weight and -17.00 cm in waist circumference), retatrutide 8 mg (-20.70% and -15.90 cm), and tirzepatide 15 mg (-16.53% and -13.23 cm) were the three most effective treatments for reducing body weight and waist circumference. However, these treatments were less effective in patients with T2DM. In terms of safety, patients without T2DM had a higher incidence of adverse events than those with T2DM. None of the interventions increased the incidence of serious or hypoglycemic adverse events (<54 mg/dL).

Furthermore, another systematic review study evaluated the safety and efficacy of retatrutide for the treatment of obesity using data from available clinical trials. Three articles were included, screening a total of 1,082 patients, with 691 randomly allocated to the groups. The mean age of the participants was 54.26 ± 9.9 years, with 335 men (48%) and 356 women (52%). Retatrutide was administered to 510 participants, while 130 received a placebo. The 12 mg dosage of retatrutide showed the most significant reductions in body weight, body mass index, and waist circumference. It also led to a higher percentage of patients achieving weight losses of≥ 5, 10, 15, and 20%. Gastrointestinal adverse effects were the most commonly reported. Weekly subcutaneous injections of retatrutide in obese patients resulted in significant weight loss and metabolic improvements compared to a placebo **[16]**.

A recent meta-analysis study developed by the authors Abdrabou Abouelmagd et al. (2025) **[17]** that evaluated the efficacy and safety of retatrudide in obese patients with or without diabetes was also observed. It was used for analysis, with subgroup evaluation by dose (4 mg, 8 mg, 12 mg). Three randomized clinical trials, encompassing 878 patients, met our inclusion criteria. Retatrudide significantly reduced body weight (mean difference **[MD]**: -14.33%), body mass index (MD: -5.38), waist circumference (MD: -10.51 cm), fasting blood glucose (MD: -23.51 mg/dL), hemoglobin A1c (MD: -0.91%), and systolic and diastolic blood pressure (MD: -9.88 mmHg and -3.88 mmHg, respectively), all with pvalues<0.00001. No significant difference in adverse events was observed between the groups (relative risk: 1.11, p=0.24).

The authors Coskun et al. (2025) **[18]** designed a randomized, double-blind, phase 2, parallel-group, placebo-controlled clinical trial, conducted at 42 medical centers in the USA. Retatrutide, a glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon receptor agonist, demonstrated robust reductions in glucose and body weight in participants with type 2 diabetes. A total of 534 participants were selected for inclusion in the main study. 253 were excluded, and 281 participants were enrolled and randomly assigned to the main study. Of the main study participants, 189 participants were enrolled in the body composition substudy (29 in the placebo group, 32 in the retatrutide 0.5 mg group, 31 in the retatrutide 4 mg [pooled] groups, 33 in the retatrutide 8 mg [pooled] group, 30 in the retatrutide 12 mg group, and 34 in the dulaglutide 1.5 mg group). Of these, 155 had a baseline DXA scan and 103 completed treatment and both baseline and week 36 DXA scans. 105 (56%) of the 189 participants were women, and 84 (44%) were men. Of the 189 participants, 160 (85%) were white, 24 (13%) were black, and five (3%) were Asian. The percent reduction from baseline in total fat mass was 4.9% (SE 1.4%) with retatrutide 0.5 mg, 15.2% (3.2%) with retatrutide 4 mg (pooled), 26.1% (2.5%) with retatrutide 8 mg (pooled), 23.2% (3.0%) with retatrutide 12 mg, 2.6% (1.6%) with dulaglutide, and 4.5% (1.2%) with placebo. Serious adverse events occurred in two (7%) of the 29 participants in the placebo group, two (6%) of the 32 participants in the retatrutide 0.5 mg group, zero of the 31 participants in the retatrutide 4 mg group, three (9%) of the 33 participants in the retatrutide 8 mg group, one (3%) of the 30 participants in the retatrutide 12 mg group, and zero of the 34 participants in the dulaglutide group. Gastrointestinal events were the most frequently reported adverse events, and no deaths were reported.

According to the SURPASS trials that evaluated the safety and efficacy of tirzepatide in people with T2DM, during treatment periods of up to 104 weeks, tirzepatide 5 to 15 mg once weekly reduced glycosylated hemoglobin (1.87% to 3.02%), body weight (5.4 to 12.9 kg), and improved multiple cardiometabolic risk factors (including reductions in liver fat, new-onset macroalbuminuria, blood pressure,

and lipids) across the spectrum of T2DM. Tirzepatide provided better efficacy than placebo and other commonly used glucoselowering medications such as semaglutide 1 mg, dulaglutide, insulin degludec, and glargine. All doses of tirzepatide were well tolerated, with a side effect profile similar to that of GLP1 receptor analogs. In people without diabetes, 5 to 15 mg of tirzepatide once weekly for the treatment of obesity (SURMOUNT-1) resulted in substantial reductions in body weight (16.5% to 22.4%) over 72 weeks. Overall, the SURPASS program and the SURMOUNT-1 study suggest that tirzepatide is marking a new era in the treatment of T2DM and/or obesity through dual agonism of gut hormones **[12]**.

In this sense, tirzepatide is intended to be an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Tirzepatide is the first dual GIP receptor and GLP-1 receptor agonist. Starting dose: 2.5 mg once weekly. After 4 weeks, the dose should be increased to 15 mg/week. It can lead to nausea, vomiting, gastrointestinal changes, even constipation, diarrhea, depending on the person, and very rarely even hypoglycemia. However, clinical studies have accumulated evidence of the off-label action of this drug for weight loss in patients with obesity **[4-7, 19-21]**.

Also, a double-blind, randomized, controlled phase 3 study assigned 2,539 adults with a body mass index (BMI; weight in kilograms divided by the square of height in meters) of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes, in a 1:1:1:1 ratio to receive subcutaneous tirzepatide (5 mg, 10 mg, or 15 mg) once weekly or placebo for 72 weeks, including a 20-week dose escalation period. At baseline, the mean body weight was 104.8 kg, the mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or higher. The mean percent change in weight at week 72 was -15.0% (95% confidence interval [CI], -15.9 to -14.2) with weekly doses of 5 mg of tirzepatide, -19.5% (95% CI, -20.4 to -18.5) with doses of 10 mg, -20.9% (95% CI, -21.8 to -19.9) with doses of 15 mg, and -3.1% (95% CI, -4.3 to -1.9) with placebo ($p<0.001$ for all comparisons with placebo). The percentage of participants who experienced a weight reduction of 5% or more was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with 5 mg, 10 mg, and 15 mg of tirzepatide, respectively, and 35% (95% CI, 30 to 39) with placebo; 50% (95% CI, 46 to 54) and 57% (95% CI, 53 to 61) of participants in the 10 mg and 15 mg groups experienced a reduction in body weight of 20% or more, compared with 3% (95% CI, 1 to 5) in the placebo group ($p<0.001$ for all comparisons with placebo). Improvements were observed in all pre-specified cardiometabolic measures with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were of mild to moderate severity, occurring mainly during dose escalation. Adverse events caused treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants who received 5 mg, 10 mg, and 15 mg doses of tirzepatide and placebo, respectively **[20]**.

Limitations

Significant gaps remain in the research, including limited data on long-term effects, requiring more robust clinical trials.

Conclusion

It was concluded that retatrutide offers superior efficacy in weight loss compared to tirzepatide and other GLP-1 analogs, but with a higher risk of adverse events. Dual agonists offer a favorable balance between efficacy and safety. Selecting personalized treatments based on patient characteristics is recommended. Available randomized clinical trials showed that, regarding weight loss, tirzepatide (15 mg) resulted in up to 17.8% weight loss at 72 weeks, semaglutide (2.4 mg) in up to 13.9% after 68 weeks, liraglutide (3.0 mg) in up to 5.8% after 26 weeks, and retatrutide (12 mg) produced the greatest weight loss, with 22.1% after 48 weeks. The main adverse effects of retatrutide were related to gastrointestinal events compared to tirzepatide.

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Author contributions: Flávio Henrique Figueiredo de Macêdo Andrade carried out this study alone.

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Ethical Approval

Not applicable.

Informed Consent

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Data Sharing Statement

No additional data are available

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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