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Comparative Efficacy of Tirzepatide and Semaglutide in the Treatment of Obesity: A Meta-analysis

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ABSTRACT

Obesity is a chronic and multifactorial disease that imposes a substantial burden of morbidity, mortality, and healthcare costs. Although lifestyle interventions are fundamental, they are often insufficient, highlighting the need for effective pharmacological therapies. This study aimed to technically and quantitatively compare the efficacy of semaglutide (a GLP-1 receptor agonist) and tirzepatide (a dual GIP/GLP-1 receptor agonist) in the treatment of obesity in adults without diabetes. A meta-analysis covering the period from 2021 to 2025 was conducted using the PubMed, Cochrane Library, Web of Science, and Scopus databases. Controlled descriptors and free-text terms related to "obesity," "semaglutide," "tirzepatide," and "clinical trial" were applied. Randomized controlled trials involving adults with overweight or obesity, with or without concomitant behavioral interventions, and reporting weight-loss efficacy outcomes (percentage change and proportions achieving ≥5%, ≥10%, ≥15%, and ≥20% weight loss) were included. Observational studies, case series, and studies involving predominantly diabetic populations were excluded, except when obesity-related outcomes were analyzed separately. Study selection followed PRISMA guidelines. Data were extracted using standardized forms and synthesized in tables and forest plots. The results demonstrated that both pharmacological agents promoted clinically meaningful weight loss when combined with lifestyle modifications. Semaglutide achieved mean weight reductions of approximately 15% in longer-term follow-up, whereas tirzepatide showed a greater average magnitude of weight loss (exceeding 20%) and a higher proportion of patients achieving more stringent weight-loss targets. Safety profiles were comparable between treatments and were predominantly characterized by mild to moderate gastrointestinal adverse events. In conclusion, semaglutide and tirzepatide represent significant advances in the pharmacological management of obesity. Based on the evaluated evidence, tirzepatide demonstrated superior average efficacy in weight reduction while maintaining a comparable safety profile, which may help guide therapeutic decision-making according to clinical goals and access considerations.

Keywords: Obesity; Tirzepatide; Semaglutide; Weight Loss; GLP-1 Receptor Agonists; Meta-analysis.

1. Introduction

Obesity is a chronic, multifactorial, and relapsing disease characterized by excessive accumulation of body fat with the potential to cause significant harm to health, leading to major clinical consequences, particularly metabolic disorders such as type 2 diabetes and cardiovascular abnormalities. At the population level, obesity prevalence has increased steadily over recent decades and now represents one of the major global public health challenges. Recent estimates indicate that by 2025, approximately 31% of the Brazilian population will be living with obesity. Globally, in 2022, more than 1 billion people were affected, meaning that nearly one in eight individuals worldwide lived with obesity. Adult obesity prevalence has more than doubled since 1990, accompanied by a marked increase among children and adolescents. These trends underscore the ongoing nutritional transition and lifestyle changes, reinforcing the urgent need for effective prevention strategies and longitudinal care[1,2].

The determinants of excess body weight result from complex interactions between obesogenic environments, social determinants of health, sedentary behavior, insufficient encouragement of healthy habits, easy access to ultra-processed foods, and biological susceptibility, including genetic and neurohormonal factors that regulate appetite, satiety, and energy expenditure. The clinical consequences of obesity are extensive and well documented, encompassing increased risks of type 2 diabetes, arterial hypertension, cardiovascular disease, nonalcoholic fatty liver disease, obstructive sleep apnea, and osteoarthritis, as well as impaired quality of life and increased all-cause mortality. Furthermore, overweight and obesity are associated with at least 13 types of cancer, accounting for a substantial proportion of incident cases, highlighting the systemic nature of obesity and its profound impact on life expectancy and quality of life. These data support the prioritization of integrated health promotion policies and timely therapeutic interventions[3,4].

Clinical management of obesity is based on structured lifestyle interventions, including a hypocaloric diet with adequate nutritional quality, increased physical activity, and behavioral support. Recommended goals align with guidelines advocating at least 150 to 300 minutes per week of moderate aerobic physical activity, or an equivalent amount of vigorous activity for adults, while recognizing that any increase in physical movement confers health benefits[5]. When lifestyle interventions alone are insufficient or when specific indications are present, clinical guidelines recommend adjunct pharmacotherapy with approved medications and, in selected cases, metabolic–bariatric surgery, whose effectiveness and favorable impact on metabolic outcomes and mortality are supported by long-term evidence[6,7].

Within the current pharmacological armamentarium, incretin-based therapies have emerged as a major advancement, particularly semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, and tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor co-agonist, both administered once weekly. Mechanistically, these agents modulate central appetite pathways, enhance satiety, and delay gastric emptying, thereby complementing behavioral interventions as part of a contemporary strategy for weight management[8,5,6,7].

In light of this epidemiological and therapeutic context, the objective of this study is to conduct a comparative meta-analysis of the efficacy of tirzepatide versus semaglutide in the treatment of obesity in adults without diabetes. The analysis synthesizes percentage body weight change and the proportion of participants achieving predefined weight-loss targets (≥5%, ≥10%, ≥15%, and ≥20%), as well as describing the reported safety profile, in order to provide clear and clinically applicable evidence to support informed therapeutic decision-making.

2. Theoretical framework

2.1 FUNDAMENTAL CONCEPTS AND PATHOPHYSIOLOGICAL MECHANISMS

Obesity is a condition characterized by excessive accumulation of body fat capable of significantly impairing health. Beyond a simple imbalance between energy intake and expenditure, obesity is currently recognized as a chronic, multifactorial disease with slow progression, influenced by environmental, behavioral, genetic, and metabolic factors. The continuous rise in its prevalence has made obesity one of the greatest public health challenges worldwide, affecting not only individual

quality of life but also health systems due to the high demand for treatment of associated comorbidities[1].

From a pathophysiological perspective, obesity results from dysregulation of energy balance, a process governed by complex circuits involving the central nervous system, hormones, and peripheral tissues. The hypothalamus—responsible for integrating hunger and satiety signals—receives inputs from gastrointestinal hormones, adipokines, and neurotransmitters. Among these, leptin, produced by adipose tissue, physiologically signals satiety to the hypothalamus. When dysregulation occurs, leptin resistance develops, leading to increased caloric intake, progressive fat accumulation, and worsening insulin resistance. Environmental changes, such as widespread availability of ultra-processed foods and reduced physical activity, further exacerbate this condition[2].

Another critical aspect is the role of adipose tissue as an active endocrine organ, rather than merely an energy reservoir. Adipose tissue secretes inflammatory cytokines and hormones that directly influence metabolic processes. Excessive expansion of adipose tissue promotes a state of chronic low-grade inflammation, contributing to impaired insulin sensitivity and disturbances in glucose and lipid metabolism. This inflammatory milieu is closely associated with the development of obesity-related conditions such as type 2 diabetes, arterial hypertension, obstructive sleep apnea, and certain types of cancer.

Thus, obesity should be understood not merely as excess body weight, but as a complex metabolic syndrome involving interactions between the brain, gastrointestinal tract, adipose tissue, and immune system[3].

2.2 EPIDEMIOLOGY OF OBESITY IN THE BRAZILIAN CONTEXT

In Brazil, obesity has increased progressively and has become one of the country's most pressing public health problems. Data from Vigitel (Surveillance of Risk and Protective Factors for Chronic Diseases), conducted by the Ministry of Health, indicate that the prevalence of obesity among adults rose from 15.1% in 2010 to 22.4% in 2021. This means that more than one in five Brazilian adults is currently living with obesity, a scenario associated with increased risks of cardiovascular disease, diabetes, and cancer. Furthermore, the same surveillance system reports that premature deaths attributable to obesity nearly doubled during this period, underscoring the growing burden of obesity-related chronic diseases[4].

The National Health Survey (PNS 2020) complements these findings by showing that approximately 60.3% of Brazilian adults have excess body weight, including overweight and obesity, corresponding to more than 96 million individuals. Obesity alone affects more than one quarter of the adult population, a striking figure given the rapid growth observed over the past two decades. Higher prevalence has been reported among women, individuals with lower educational attainment, and urban residents, reflecting social inequalities and disparities in access to healthy food. These findings confirm obesity as a silent epidemic with increasing impact across different population strata in Brazil[5].

Data released by SISVAN (Food and Nutrition Surveillance System) indicate that 34.66% of the monitored population presented some degree of obesity in 2024, based on the assessment of more than 26 million individuals. These figures further emphasize the magnitude of the problem and the importance of continuous nutritional surveillance.

Projections by Fiocruz Brasília reinforce the severity of the situation, estimating that if current trends persist, by 2044 nearly 48% of Brazilian adults will be living with obesity, and an additional 27% will be overweight, totaling approximately 75% of the adult population with excess body weight. Such projections point to a highly challenging future for the Brazilian healthcare system, which will face large-scale complications related to obesity, including heart failure, obstructive sleep apnea, and osteoarthritis. These estimates highlight the urgent need for more effective public policies focused on prevention, promotion of healthy lifestyles, and access to evidence-based treatments[6].

2.3 DIAGNOSIS AND RISK FACTORS

Since January 2025, body mass index (BMI) has no longer been considered the sole metric for defining clinical obesity, following the consensus work of a global commission of experts. This updated approach proposes revised diagnostic guidelines that formally recognize obesity as a chronic and continuous disease, rather than merely a risk factor, when excess body fat is accompanied

by evidence of organ or functional impairment. The Lancet Diabetes & Endocrinology Commission introduced a distinction between "clinical obesity" and "preclinical obesity", based on the presence or absence of objective tissue or organ dysfunction.

The commission—comprising 58 experts from multiple disciplines and countries—used the Delphi method to reach consensus on diagnostic criteria, emphasizing that excess adiposity should be confirmed beyond BMI through assessment of body fat distribution and functional limitations in daily activities. Although BMI (calculated as weight in kilograms divided by height in meters squared) has historically served as a standard indicator—defining obesity as class I (30–34.9 kg/m²), class II (35–39.9 kg/m²), and class III (≥40 kg/m²)—this isolated metric presents significant limitations for individual diagnosis[1].

Complementary assessments, such as waist circumference, waist-to-height ratio, and waist-to-hip ratio, are now recommended to better estimate central adiposity and associated metabolic risk. In particular, individualized waist-to-height ratio assessment has been emphasized, with the recommendation that waist circumference should not exceed half of an individual's height.

Beyond anthropometric measures, obesity is increasingly recognized through clinical signs and symptoms reflecting target-organ damage or overload, affecting respiratory, cardiovascular, renal, hormonal, musculoskeletal, and lymphatic systems. This perspective stems from a growing body of evidence conceptualizing obesity as a systemic condition, rather than simply excess weight. The distinction between preclinical and clinical obesity lies primarily in the presence of measurable organ dysfunction or functional limitation, which defines when excess adiposity becomes a disease requiring personalized medical intervention.

In this context, clinical obesity requires identification of at least one criterion beyond excess adiposity to support diagnosis and justify intensive treatment. Reliance solely on BMI fails to capture patient heterogeneity: some individuals with high BMI remain free of organ dysfunction, whereas others with lower BMI already exhibit metabolic or functional impairment. This conceptual evolution redefines obesity as a chronic disease with direct implications for clinical care, risk stratification, and therapeutic decision-making, encouraging individualized, stigma-free management focused on reversing or mitigating obesity-related organ damage.

3. Methods

This study was designed as a descriptive and comparative meta-analysis aimed at identifying, selecting, and analyzing the available scientific evidence regarding the efficacy of semaglutide and tirzepatide in the treatment of obesity in adults, with and without type 2 diabetes. The review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure methodological rigor and transparency throughout the stages of study identification, screening, eligibility, and inclusion.

The literature search was conducted in internationally recognized databases, including PubMed, the Cochrane Library, and ScienceDirect, as well as high-impact indexed journals. Controlled descriptors and free-text terms were combined using Boolean operators and included *"tirzepatide," "semaglutide," "obesity," "clinical trial," "weight loss,"* and *"meta-analysis."* Studies published between 2021 and 2025 were considered eligible, corresponding to the period during which the principal randomized clinical trials evaluating both therapies were conducted and reported.

Only randomized controlled trials (RCTs) assessing the efficacy of tirzepatide or semaglutide in individuals with overweight or obesity were included, regardless of concomitant lifestyle modification programs, provided that they reported quantitative weight-loss outcomes, expressed as mean percentage change or as the proportion of participants achieving predefined weight-loss targets (≥5%, ≥10%, ≥15%, and ≥20%). Observational studies, narrative reviews, case reports, case series, and trials conducted predominantly in diabetic populations were excluded, except when obesity-related outcomes were analyzed separately.

After initial screening of titles and abstracts, the selected articles underwent full-text review for data extraction. Extracted variables included year of publication, study objectives, methodological design, sample characteristics, interventions, study duration, primary and secondary outcomes,

magnitude of weight loss, adverse events, and limitations reported by the authors.

The extracted data were organized into comparative tables and subsequently used to generate forest plots, enabling visual representation of effect sizes and their respective confidence intervals. The final body of evidence consisted primarily of the STEP trials, evaluating semaglutide, and the SURMOUNT trials, evaluating tirzepatide, which together represent the most relevant clinical investigations on pharmacological obesity treatment to date.

Within the STEP program, the following trials were included: STEP 1, which assessed semaglutide in individuals with obesity without diabetes; STEP 2, which evaluated its effects in patients with type 2 diabetes, demonstrating benefits in both weight loss and glycemic control; STEP 3, which combined semaglutide with intensive behavioral therapy; STEP 4, which investigated weight-loss maintenance after treatment discontinuation; and STEP 5, which assessed the durability of semaglutide's effects over a two-year follow-up period.

Within the SURMOUNT program, the analysis included SURMOUNT-1, which compared tirzepatide with placebo in adults with obesity and demonstrated substantial weight reductions; SURMOUNT-2, conducted in patients with type 2 diabetes and obesity, showing improvements in both weight loss and metabolic parameters such as glycated hemoglobin and lipid profile; SURMOUNT-3, which evaluated tirzepatide as a maintenance therapy following an intensive lifestyle intervention; SURMOUNT-4, which assessed treatment continuation and showed sustained weight loss among participants who remained on tirzepatide compared with significant weight regain in the placebo group; and SURMOUNT-5, the first direct head-to-head comparison between tirzepatide and semaglutide in adults with obesity and comorbidities without diabetes, in which tirzepatide demonstrated superior reductions in body weight and waist circumference.

Additionally, emerging evidence from exploratory and ongoing studies—such as SURMOUNT-OSA, which evaluates the effects of tirzepatide on obstructive sleep apnea severity, and SURMOUNT-MMO, an ongoing phase 3 trial investigating multiple metabolic manifestations of obesity—was considered contextually to inform interpretation, without inclusion in quantitative synthesis.

All included studies were critically and integratively assessed to examine methodological similarities and differences, effect sizes, and consistency of findings across diverse populations and clinical contexts. This approach enabled a comprehensive evaluation of the efficacy, safety, and durability of both pharmacological interventions. Ultimately, results were synthesized to construct a comparative perspective on outcomes observed in the STEP and SURMOUNT programs, considering not only the magnitude of weight loss but also metabolic effects and tolerability profiles. This methodology ensured robustness, clarity, and reproducibility, while contributing to the consolidation of evidence regarding incretin-based therapies as promising options for obesity treatment.

4. Results

During the literature search and selection process on the treatment of obesity with incretin-based therapies, five studies stood out for their relevance and methodological quality, forming the basis of this comparative analysis between semaglutide and tirzepatide. These studies span publications from 2021 to 2025 and include randomized controlled trials and one network meta-analysis.

The initial studies (STEP 1 and STEP 5) evaluated semaglutide in adults with overweight or obesity, consistently in combination with lifestyle interventions. Subsequently, the SURMOUNT trials evaluated tirzepatide, including its effects following intensive lifestyle intervention (SURMOUNT-3) and its direct comparison with semaglutide (SURMOUNT-5).

Table 1 summarizes the objectives, methodologies, and main results of each study.

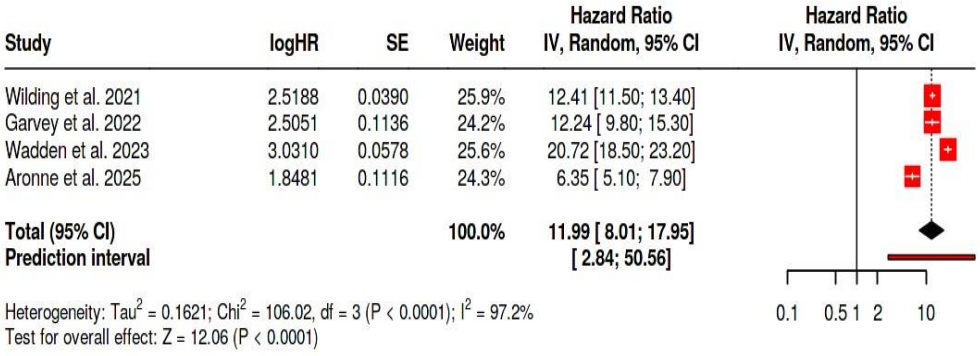
Table 1. Studies evaluating tirzepatide and semaglutide in obesity

Study (Author, Year)	Objective	Design	Sample	Duration	Main Results
Wilding et al.[12] (STEP 1)	Evaluate semaglutide 2.4 mg in adults with obesity without diabetes	Randomized, double-blind, placebo-controlled trial	n = 1,961	68 weeks	Weight change: −14.9% vs −2.4% (placebo); ≥5% weight loss: 86.4% vs 31.5%; GI adverse events common
Garvey et al.[13] (STEP 5)	Assess long-term efficacy of semaglutide	Randomized, double-blind, placebo-controlled trial	n = 304	104 weeks	Weight change: −15.2% vs −2.6%; ≥5% weight loss: 77.1% vs 34.4%; sustained effect over 2 years
Wadden et al.[14] (SURMOUNT-3)	Evaluate tirzepatide after lifestyle intervention	Randomized, double-blind, placebo-controlled trial	n = 579	72 weeks	Additional weight change: −18.4% vs +2.5%; ≥5% weight loss: 87.5% vs 16.5%
Aronne et al.[18] (SURMOUNT-5)	Compare tirzepatide vs semaglutide	Randomized, open-label trial	n = 751	72 weeks	Weight change: −20.2% vs −13.7%; greater waist reduction; higher ≥10–25% weight loss
Karagiannis et al.[15]	Compare tirzepatide vs semaglutide (T2DM)	Systematic review and network meta-analysis	n = 23,622	—	Weight reduction greater with tirzepatide (−5.27 to −9.57 kg) vs semaglutide (−2.52 to −4.97 kg)

Source: Author.

In addition to the tabular presentation, the results were plotted in a forest plot (Figure 1), illustrating the magnitude of weight loss and corresponding confidence intervals across studies.

Figure 1. Forest plot



Source: Author.

Wilding et al.[12] demonstrated that once-weekly semaglutide 2.4 mg led to a mean weight reduction of −14.9% at 68 weeks, compared with −2.4% in the placebo group (difference −12.4 percentage points; 95% CI, −13.4 to −11.5). Weight-loss targets of ≥5%, ≥10%, and ≥15% were achieved by 86.4%, 69.1%, and 50.5% of participants receiving semaglutide, versus 31.5%,

12.0%, and 4.9% in the placebo group. Adverse events were predominantly gastrointestinal, with discontinuation occurring in 4.5% of the active group versus 0.8% of the placebo group.

Garvey et al.[13] reported a mean weight reduction of −15.2% with semaglutide versus −2.6% with placebo at 104 weeks (difference −12.6 percentage points; 95% CI, −15.3 to −9.8). A total of 77.1% of participants achieved ≥5% weight loss compared with 34.4% in the placebo group. Gastrointestinal adverse events were reported in 82.2% of participants receiving semaglutide and 53.9% receiving placebo.

Wadden et al.[14] showed that tirzepatide produced an additional mean weight loss of −18.4% compared with +2.5% in the placebo group (difference −20.8 percentage points; 95% CI, −23.2 to −18.5). A total of 87.5% of participants achieved an additional ≥5% reduction compared with 16.5% in the placebo group.

Aronne et al.[18] reported a mean weight reduction of −20.2% with tirzepatide versus −13.7% with semaglutide (95% CI, −21.4 to −19.1 vs −14.9 to −12.6). Waist circumference decreased by −18.4 cm with tirzepatide and −13.0 cm with semaglutide. The proportion of participants achieving ≥10%, ≥15%, ≥20%, and ≥25% weight loss was higher with tirzepatide.

Karagiannis et al.[15] reported that tirzepatide produced greater weight reductions than semaglutide in patients with type 2 diabetes. Weight reduction ranged from −5.27 kg to −9.57 kg with tirzepatide and from −2.52 kg to −4.97 kg with semaglutide. Gastrointestinal adverse events were more frequent with both treatments compared with placebo.

5. Discussion

This meta-analysis demonstrates that incretin-based therapies are highly effective in promoting clinically meaningful weight loss in adults with obesity.

Semaglutide established a consistent and durable efficacy profile, with mean weight reductions of approximately 15% sustained over periods of up to 104 weeks. These findings support its role as a reliable pharmacological option for long-term obesity management.

Tirzepatide demonstrated greater efficacy across studies, particularly in achieving higher weight-loss thresholds such as ≥15% and ≥20%. This additional effect may be explained by its dual mechanism of action involving both GIP and GLP-1 receptors.

The SURMOUNT-3 trial highlights the potential benefit of using tirzepatide following initial lifestyle intervention, suggesting a stepwise therapeutic approach to obesity treatment.

Direct comparison in the SURMOUNT-5 trial showed a difference of approximately 6–7 percentage points in mean weight loss favoring tirzepatide, along with greater reductions in waist circumference, indicating a potentially stronger effect on central adiposity.

Despite differences in study design, including placebo-controlled and open-label trials, the consistency of findings across studies strengthens the validity of the results.

Safety profiles were similar between semaglutide and tirzepatide, with adverse events predominantly gastrointestinal and generally mild to moderate in severity.

The network meta-analysis by Karagiannis et al. further supports these findings by demonstrating superior weight reduction with tirzepatide in a different population (patients with type 2 diabetes), reinforcing the consistency of its effect.

However, heterogeneity in study populations, designs, and outcome measures should be considered when interpreting these findings. Differences such as duration of follow-up, presence of lifestyle interventions, and inclusion criteria may partially explain variability in reported outcomes.

6. Conclusion

In conclusion, both semaglutide and tirzepatide are highly effective pharmacological options for the treatment of obesity in adults without diabetes, promoting clinically significant weight loss when combined with lifestyle interventions.

Tirzepatide demonstrated superior average efficacy in terms of weight reduction and likelihood of achieving higher weight-loss thresholds, while maintaining a safety profile comparable to semaglutide.

These findings support the use of incretin-based therapies within a stepwise treatment approach, with therapeutic choice guided by individual clinical goals, tolerability, and access considerations.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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