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REVIEW ARTICLE

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Major clinical outcomes of the action of the co-agonist tirzepatide to liraglutide and semaglutide in the treatment of obesity and type 2 diabetes mellitus: a systematic review

Helena Ramalho Arvate[1*]

[1] Santa Marcelina Hospital, Itaquera, São Paulo, Brazil.

*Corresponding author: Helena Ramalho Arvate.
Santa Marcelina Hospital, Itaquera, São Paulo, Brazil.
E-mail: helena.arvate@gmail.com
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Abstract

Introduction: Obesity is a chronic disease that affects a significant portion of the population. In Brazil, in surveillance research on risk and protective factors for diseases, more than half of the Brazilian population, 56% are overweight. In this scenario, liraglutide and semaglutide are medication for the treatment of type 2 diabetes mellitus (T2DM) and obesity. Tirzepatide is the first dual GLP1/GIP receptor co-agonist that has been approved for the treatment of T2DM and obesity. **Objective:** It was to present the major clinical outcomes of the action of the co-agonist tirzepatide to liraglutide and semaglutide in the treatment of obesity and type 2 diabetes mellitus. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from September to October 2024 in the Scopus, 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:** A total of 84 articles were found, and 52 articles were evaluated and 23 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with a high risk of bias and 19 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X^2 =79.8% >50%. It was concluded that 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 some time. 72 weeks. Furthermore, liraglutide (3.0 mg) as a medication for the treatment of obesity, in association with lifestyle changes, in patients with and without diabetes proved to be a good therapeutic option with a response about weight loss and maintenance, in addition to benefits secondary to clinical comorbidities associated with obesity.

Keywords: Obesity. Type 2 diabetes mellitus. Tirzepatide. Semaglutide. Liraglutide. GLP-1. GIP.

Introduction

Obesity is a chronic disease that affects a significant portion of the population. For many years, this disease was underestimated and viewed only as a temporary weight status or aesthetically pleasing. Worldwide, overweight and obesity affect more than 2 billion adults and the prevalence has almost tripled in 40 years **[1]**. According to IBGE data between 2003 and 2019, the proportion of obese people in the population aged 20 or over in the country more than doubled, rising from 12.2% to 26.8%. In this same period, female obesity rose from 14.5% to 30.2% and remained above that of men, which rose from 9.6% to 22.8% **[2]**.

The problem becomes even greater when evaluating younger patients in global data, where more than 70% of people who are obese before puberty will also be obese in adulthood, which highlights the need for effective and durable interventions with adequate safety profiles early in life **[2,3]**. In Brazil, according to the 2018 telephone survey on risk and protective factors

for chronic diseases (VIGITEL), the prevalence of obesity in adults in Brazil increased by approximately 67.8% in the last thirteen years, rising from 11.8% in 2006 to 19.8% in 2018. According to VIGITEL, more than half of the Brazilian population, 55.7%, is overweight. This represents an increase of 30.8% compared to the percentage of 42.6% in 2006. The increase in prevalence was greater among the age groups of 18 to 24 years, at 55.7%. When stratified by sex, obesity among men increased by 21.7%, while in women, this rate was 40% **[3]**.

Overweight and obesity have significant implications for the health of the individual and society. Body mass index (BMI) values above the normal range are related to a higher risk of chronic non-communicable diseases (NCDs), such as cardiovascular diseases, diabetes, musculoskeletal diseases, and some types of cancer, in addition to being associated with higher mortality rates **[3]**.

The treatment of obesity is complex and multidisciplinary. In general, pharmacological treatment is an adjunct to targeted therapies focused on modifying lifestyle habits related to nutritional guidelines to reduce calorie intake and exercise to increase calorie expenditure **[4]**. As with all chronic diseases, pharmacological treatment begins with secondary prevention to prevent the progression of the disease to a more severe stage and prevent complications and subsequent deterioration and should be maintained to avoid weight regain. There is no long-term pharmacological treatment that does not involve lifestyle changes. Lifestyle changes and cognitive-behavioral techniques are essential and pharmacological treatment should not be used as treatment in the absence of other non-pharmacological measures.

The choice of treatment should be based on the severity of the problem and the presence of associated complications **[5]**. In this scenario, liraglutide and semaglutide were developed for the treatment of type 2 diabetes mellitus and are glucagon-like peptide-1 (GLP-1) agonists that share 97% homology with native GLP-1, with the circulating half-life of GLP-1 increasing from 1-2 minutes to 13 hours at a dose of 3.0 mg liraglutide. These drugs have a hypothalamic action on neurons involved in energy balance, in centers linked to pleasure and reward, and a lesser action on the speed of gastric emptying. Liraglutide directly stimulates neurons that synthesize pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART) and indirectly inhibits neurotransmission in neurons that express neuropeptide Y (NPY) and agouti-related peptide (AgRP), GABA-dependent signaling pathways **[5]**. This molecule is one of the few options approved by the Brazilian Health Regulatory Agency (ANVISA) for the pharmacological treatment of obesity available in Brazil.

In addition, the combination of glucagon-like peptide-1 (GLP-1) with other gut hormones, including glucose-dependent insulinotropic polypeptide (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 **[6]**.

Therefore, the present study aimed to develop a systematic review to present the main clinical outcomes of the action of the co-agonist tirzepatide in relation to liraglutide and semaglutide in the treatment of obesity and type 2 diabetes mellitus.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 10/10/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 10/10/2024.

Data Sources and Search Strategy

The literature search process was carried out from September to October 2024 and developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS /MeSH Terms) were used: "Obesity. Type 2 diabetes mellitus. Tirzepatide. Semaglutide. Liraglutide. GLP-1. GIP", and using the Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

The 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 emphasis was on systematic review articles or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low quality of

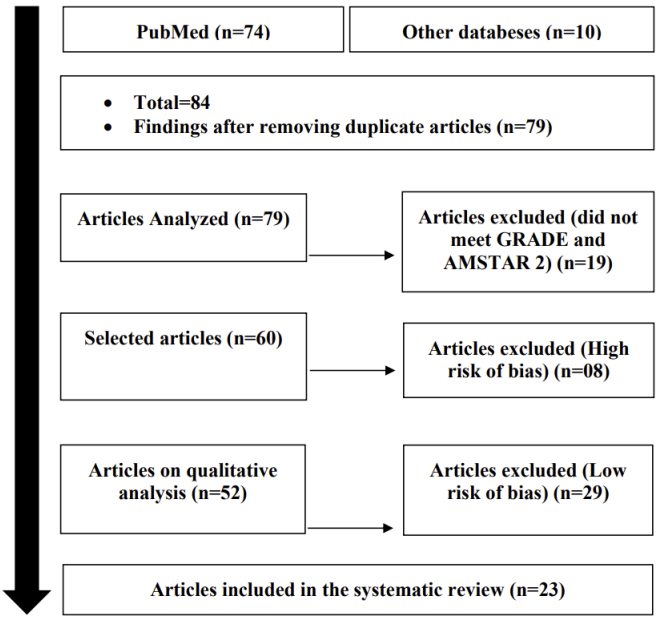
evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's d test.

Results

Summary of Findings

As a corollary of the literature search system, a total of 84 articles were found that were submitted to eligibility analysis and, subsequently, 23 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 presented homogeneity in their results, with X^2=79.8%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 8 studies with high risk of bias and 19 studies that did not meet GRADE.

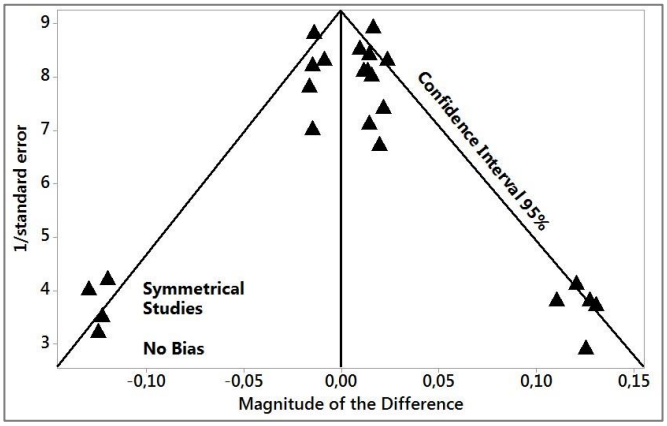
Figure 1. Article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). The precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, either among studies with small sample sizes (lower precision) that are shown at the base of the graph or in studies with large sample sizes that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph (n=23 studies).



Source: Own authorship.

Major Clinical Findings

According to the SURPASS trials evaluating the safety and efficacy of tirzepatide in people with T2DM, over 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 glucose-lowering 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 GLP-1 receptor analogs. In people without diabetes, tirzepatide 5 to 15 mg 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 gut hormone agonism **[6]**.

In this sense, the drug tirzepatide is intended as an adjunctive treatment to diet and exercise to improve glycemic control in adults with T2DM. Tirzepatide is the first dual glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist. The starting dose: is 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 individual, 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 **[7-9]**. Furthermore, 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, mean body weight was 104.8 kg, mean BMI was 38.0, and 94.5% of participants had a BMI of 30 or greater. The mean percent change in weight at week 72 was -15.0% (95% confidence interval [CI], -15.9 to -14.2) with weekly tirzepatide 5 mg doses, -19.5% (95% CI, -20.4 to -18.5) with 10 mg doses, -20.9% (95% CI, -21.8 to -19.9) with 15 mg doses, 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 had a weight reduction of 5% or greater was 85% (95% CI, 82 to 89), 89% (95% CI, 86 to 92), and 91% (95% CI, 88 to 94) with tirzepatide 5 mg, 10 mg, and 15 mg, 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 had a reduction in body weight of 20% or greater, compared with 3% (95% CI, 1 to 5) in the placebo group (P<0.001 for all comparisons with placebo). Improvements in all prespecified cardiometabolic measures were observed with tirzepatide. The most common adverse events with tirzepatide were gastrointestinal, and most were mild to moderate in severity, occurring primarily during dose escalation. Adverse events led to treatment discontinuation in 4.3%, 7.1%, 6.2%, and 2.6% of participants receiving 5 mg, 10 mg, and 15 mg doses of tirzepatide and placebo, respectively **[8]**.

In addition, the main study to demonstrate the efficacy of liraglutide was the Xavier Pi-Sunyer et al Scale Obesity and Prediabetes study **[10]**, a 56-week, double-blind, randomized clinical trial involving 3,731 patients who did not have type 2 diabetes and who had a BMI of at least 30 or a BMI of at least 27 if they had dyslipidemia or hypertension. Patients received a 2:1 ratio of once-daily subcutaneous injections of liraglutide at a dose of 3.0 mg (2,487 patients) or placebo (1,244 patients); both groups received lifestyle modification counseling. The outcomes assessed were changes in body weight and the proportions of patients who lost at least 5% and more than 10% of their initial body weight. At the end of the study, a greater proportion of patients in the liraglutide group than in the placebo group had lost at least 5% of their body weight (63.2% vs. 27.1%), more than 10% of their body weight (33.1% vs. 10.6%), and more than 15% of their body weight (14.4% vs. 3.5%). A subanalysis of the SCALE study by Careal W Le Roux et. al **[11]** aimed to assess the proportion of individuals with prediabetes who were diagnosed with type 2 diabetes throughout the study, taking into account the different frequencies of diagnosis between the treatment groups. The time to onset of diabetes over 160 weeks among all randomized individuals was 2.7 times greater with liraglutide than with placebo.

As liraglutide was a priori designed for the treatment of diabetes, Melanie J. Davies et. Al. (The Scale Diabetes Randomized Clinical Trial) **[12]**, conducted a randomized clinical trial with a follow-up of fifty-six weeks, 846 patients with diabetes were randomized. Inclusion criteria were a BMI of 27.0 or higher, and an age equal to or greater than 18 years. Once daily, subcutaneous liraglutide (3.0 mg) (n=423), liraglutide (1.8 mg) (n=211) or placebo (n = 212) and all groups with diet and physical activity. Weight loss of 5% or more occurred in 54.3% with liraglutide (3.0 mg) and 40.4% with liraglutide (1.8 mg) vs 21.4% with placebo. Weight loss greater than 10% occurred in 25.2% with liraglutide (3.0 mg) and 15.9% with liraglutide (1.8 mg) vs. 6.7% with placebo.

In the evaluation of the articles, 2 studies focusing on behavioral therapy were analyzed, for lifestyle changes. Thomas A. Wadden et al. **[13]**, evaluated intensive behavioral therapy (IBT) associated with liraglutide, 150 adults with obesity were randomized to: IBT alone; IBT combined with liraglutide; or IBT combined with liraglutide associated with a low-calorie diet. Respectively, 44.0%, 70.0%, and 74.0% of these participants lost ≥5% of their weight. The groups treated with liraglutide were superior to IBT alone in both outcomes.

In a real-world cohort study conducted in Canada, Sean Wharton et al. **[14]** had 311 participants, divided into 2 cohorts of 4 and 6 months of follow-up. The percentage change in body weight from baseline was -7.1% in the 6-month follow-up group and 6.3% in the 4-month group. Of the participants in the 6-month group, 64.10% and 34.5% lost more than 5% and more than 10% of body weight, respectively.

In a comparative analysis with other medications, 2 studies comparing liraglutide with orlistat were found. In a randomized clinical trial conducted with the participation of 19 European countries, Arne Astrup et al. **[15]** compared 564 participants, who were randomized to liraglutide (escalated doses 1.2, 1.8, 2.4,

and 3.0) with orlistat and placebo, with a follow-up time of 20 weeks. Mean weight loss with liraglutide 1.2, 1.8, 2.4, and 3 mg was, respectively, 4.8 kg, 5.5 kg, 6.3 kg, and 7.2 kg compared with 2.8 kg with placebo and 4.1 kg with orlistat. Of the participants in the intervention group with liraglutide 3.0 mg (76%) lost more than 5% of the weight than with placebo (30%) or orlistat (44%). In another Juan J. Gorgojo-Martínez et al. (The Xensor Study) **[16]** performed a retrospective and observational cohort study comparing the clinical outcomes of orlistat and liraglutide. Five hundred patients, 400 in the orlistat group and 100 in the liraglutide group were included in the study. Weight loss with liraglutide (−7.7 kg) was significantly greater than that seen with orlistat (−3.3 kg), and more individuals lost at least 5% of their baseline weight with liraglutide (64.7%) than with orlistat (27.4%). In both studies, liraglutide was superior to orlistat in terms of weight loss.

The study by Wadden et al. (SCALE Maintenance Study) **[17]** focused on weight maintenance. Overweight and obese participants who had lost 5% of their initial weight were randomly assigned to liraglutide 3.0 mg daily or placebo for 56 weeks. From randomization to week 56, weight decreased by an additional mean of 6.2% with liraglutide and 0.2% with placebo. More participants receiving liraglutide (81.4%) maintained the 5% loss of their initial weight compared with those receiving placebo (48.9%), and 50.5% versus 21.8% of participants lost more than 5% of their weight after randomization.

As shown in the above studies, the most effective dose for weight loss of liraglutide is 3.0 mg, a finding corroborated by the study by J. P. H. Wilding et al. **[18]** which found that there was a clear response to exposure to weight loss. Weight loss increased with increasing exposure and appeared to plateau at higher exposures associated with liraglutide 3.0 mg in most subjects. Another important aspect assessed in this study was that serious gastrointestinal adverse events (acute pancreatitis or benign breast/colorectal/malignant neoplasms) did not occur with increased exposure to liraglutide compared to the general population.

To complement the analysis of primary studies, 2 reviews were analyzed to corroborate and solidify the above data. A 2016 systematic review conducted in the United States by A. Mehta et al. **[19]** evaluated five randomized, placebo-controlled clinical trials of liraglutide for weight management. In addition to the recommended diet and physical activity, liraglutide consistently resulted in a weight loss of 4 to 6 kg, with a greater proportion of patients achieving at least 5 and 10% weight loss compared to placebo. Comparative data suggest that weight loss with liraglutide is greater than that seen with orlistat or lorcaserin, but slightly less than that seen with phentermine/topiramate. This did not have as its main objective the comparison of weight loss medications, however a 2019 systematic review with the meta-analysis by Awadhesh Kumar Singh & Ritu Singh **[20]**, in the process of publication, evaluated pharmacotherapy in obesity, a meta-analysis found a significant reduction in body weight with orlistat (N = 10,435; Δ -3.07 kg, 95% CI, -3.76 to -2.37), phentermine plus topiramate (N=2985; Δ -9.77 kg; 95% CI, -11.73 to -7.81), lorcaserin (N = 16,856; Δ - 3.8 kg; 95% CI, -3.49 to -2.66), naltrexone plus bupropion (N = 3239; Δ -4.39 kg; 95% CI, -5.05 to -3.72) and liraglutide (N = 4978; Δ -5.25 kg; 95% CI, -6.17 to -4.32), compared with placebo (all $p<0.0001$).

Another randomized controlled clinical trial study, with similar analysis and main outcomes, conducted by Thomas A. Wadden (The Scale IBT) **[21]** evaluated the benefit of ICT in primary care associated with liraglutide 3.0 mg, performed a 56-week follow-up in individuals with obesity who received 3.0 mg of liraglutide (n = 142) or placebo (n = 140) as an adjunct to intensive behavioral therapy. The mean weight loss with liraglutide plus ICT was 7.5% and 4.0% with placebo combined with ICT. Significantly more individuals on liraglutide than placebo achieved ≥5% weight loss (61.5% vs. 38.8%).

A medication in the same class as GLP-1 is semaglutide. Patrick M. O`Neil et al. **[22]** conducted a multicenter randomized controlled clinical trial in 957 obese (BMI greater than 30) patients over 18 years of age without diabetes. Patients were divided into 7 groups: semaglutide (0.05 mg; 0.1 mg; 0.2 mg; 0.3 mg and 0.4 mg), liraglutide 3.0 mg and placebo, with a follow-up time of 52 weeks. Weight loss was (-2.3%) in the placebo group, (-7.8%) liraglutide 3.0 mg, (-6%) semaglutide 0.05 mg, (-8.6%) 0.1 mg, (-11.6%) 0.2 mg, (-11.6%) 0.3 mg and (-13.8%) semaglutide 0.4 mg. Doses greater than or equal to 0.2 mg semaglutide demonstrated statistically significant weight loss relative to liraglutide.

Another clinical trial that compared the medications was the study by Richard Pratley et al. (PIONEER 4) **[23]**, however in different populations, oral semaglutide and with different outcomes, in this multicenter, double-blind, randomized clinical trial, patients with type 2 diabetes were selected from 100 sites in 12 countries. The 771 patients were randomized to oral semaglutide once daily (dose increased to 14 mg), subcutaneous liraglutide once daily (dose increased to 1.8 mg) or placebo for 52 weeks. The primary outcome was the change from baseline to week 26 in glycated hemoglobin and the confirmatory secondary outcome was the change from baseline in body weight. Oral

semaglutide showed non-inferiority to liraglutide in reducing glycated hemoglobin, however, it showed weight loss compared to liraglutide at the end of 26 weeks (-4.4 kg vs -3.1 kg). As described in the introduction, obesity has unfortunately been increasing significantly in adolescents.

Finally, a clinical trial published in 2020 by Aaron S. Kelly et al. **[4]** evaluated the efficacy and safety of liraglutide in adolescents (aged 12 years and younger than 18) with obesity and a poor response to lifestyle therapy. Participants were randomly assigned to receive liraglutide (3.0 mg) or placebo in addition to lifestyle therapy. A total of 125 participants were assigned to the liraglutide group and 126 to the placebo group. Liraglutide was superior to placebo to the change from baseline in BMI standard deviation score at week 56 (estimated difference, −0.22). A reduction in BMI of at least 5% was observed in 51 of 113 participants in the liraglutide group and 20 of 105 participants in the placebo group (estimated percentage, 43.3% vs. 18.7%), and a reduction in BMI of at least 10% was observed in 33 and 9, respectively (estimated percentage, 26.1% vs. 8.1%).

Conclusion

It was concluded that in people with type 2 diabetes mellitus, doses of 5 to 15 mg of tirzepatide once weekly significantly reduced cardiovascular risks, and in patients without type 2 diabetes mellitus, tirzepatide for the treatment of obesity (SURMOUNT-1) resulted in substantial reductions in body weight (16.5% to 22.4%) over 72 weeks. Furthermore, liraglutide (3.0 mg) as a medication for the treatment of obesity, in association with lifestyle changes, in patients with and without diabetes, proved to be a good therapeutic option with a response concerning weight loss and maintenance, in addition to secondary benefits to clinical comorbidities associated with obesity. However, doses greater than or equal to 0.2 mg of semaglutide demonstrated statistically significant weight loss to liraglutide. Oral semaglutide showed non-inferiority to liraglutide in reducing glycated hemoglobin, however, it showed weight loss concerning liraglutide at the end of 26 weeks. Despite this, treatment with tirzepatide showed the best results in weight reduction and reduction of cardiovascular risks to semaglutide and liraglutide.

CRediT

Author contributions: Conceptualization; Data curation; Formal Analysis; Investigation; Methodology; Project administration; Supervision; Writing- original draft; and Writing-review & editing by Helena Ramalho Arvate.

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Ethical Approval

Not applicable.

Informed Consent

It was applicable.

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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®.

Peer Review Process

It was performed.

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