SEVEN
publicações acadêmicas

COMPARISON BETWEEN TIRZEPATIDE AND SEMAGLUTIDE IN OBESITY MANAGEMENT: CURRENT EVIDENCE ON WEIGHT REDUCTION, METABOLIC PROFILE, AND TOLERABILITY

COMPARAÇÃO ENTRE TIRZEPATIDA E SEMAGLUTIDA NO CONTROLE DA OBESIDADE: EVIDÊNCIAS ATUAIS SOBRE REDUÇÃO DE PESO, PERFIL METABÓLICO E TOLERABILIDADE

COMPARACIÓN ENTRE TIRZEPATIDA Y SEMAGLUTIDA EN EL TRATAMIENTO DE LA OBESIDAD: EVIDENCIA ACTUAL SOBRE REDUCCIÓN DE PESO, PERFIL METABÓLICO Y TOLERABILIDAD

https://doi.org/10.56238/sevened2025.031-015

Valéria Goulart Viana[1], João Pedro Cardoso de Sá[2], Amanda Santana de Medeiros Dalla Pria[3], Nathália Déo Gasparotto[4], Rafaela Rosa Marques[5], Vanessa Neglisoli[6], Túlio César de Oliveira Costa Curta[7], Marcella de Fátima Lomeu Marinho[8], João Pedro Rocha Morozini[9], Guilherme Eugênio Polycarpo Brito Rodrigues[10], Kelle Regina Alves Ribeiro Sbardellini[11], Lúcio Flávio Corrêa Boaventura[12], Márcia D'Arc de Freitas[13], Diegomaier Nunes Neri[14], Lawrence Monteiro de Oliveira Pio[15], Rodrigo Londero de Souza[16], Vitória Caroline Prieto[17], Fabio Schiavon[18], Raíro dos Santos Silvino[19], Barbara Pereira Pessoa[20]

ABSTRACT

Obesity is a chronic, multifactorial condition associated with high cardiometabolic risk, reduced quality of life, and lower life expectancy. Among the most promising pharmacological

[1] Medicine. Itajubá Medical School. E-mail: dravaleriagoulart@yahoo.com.br
[2] Medicine Student. São Judas Tadeu University (USJT). E-mail: jopecarsa@gmail.com
[3] Medicine. José do Rosário Vellano University (Unifenas). E-mail: amanda.dalla.pria@hotmail.com
[4] Medicine. Severino Sombra University. E-mail: nathdeo@gmail.com
[5] Medicine. Faculty of Medical and Health Sciences of Juiz de Fora. E-mail: rafaelamarques21@gmail.com
[6] Specialist in People Management and Business Management. Federal University of São Paulo (UNIFESP). E-mail: vanessaneglisoli@gmail.com
[7] Doctor. Ingá University Center (UNINGÁ). E-mail: tulio_costacurta@hotmail.com
[8] Medical Residency in Internal Medicine. Hospital Rede Casa de Portugal. E-mail: marcellamarinho1979@gmail.com
[9] Doctor. School of Sciences of Santa Casa de Misericórdia de Vitória (EMESCAM). E-mail: joaormorozini@gmail.com
[10] Medicine Student. Afya. E-mail: guilhermepolycarpo9@icloud.com
[11] Medicine. School of Health Sciences (ESCS). E-mail: kelleregina@gmail.com
[12] Doctor. Federal University of Minas Gerais (UFMG). E-mail: lucioboaventura@msn.com
[13] Medical Student. Faculty of Health and Human Ecology. E-mail: mfcecon@gmail.com
[14] Doctor. Universidad Franz Tamayo. E-mail: contato@diegomaier.com
[15] Resident Physician in Internal Medicine. Federal University of Juiz de Fora. E-mail: lawrencemop@gmail.com
[16] Postgraduate in Endocrinology and Psychiatry. Federal University of Santa Maria (UFSM). E-mail: mdrodrigols@gmail.com
[17] Medicine. Professor Edson Antônio Velano University. E-mail: vitoria.prieto@outlook.com
[18] Doctor. Pontifical Catholic University of Paraná (PUC-PR). E-mail: faschiavon27@gmail.com
[19] Doctor. Universidad Amazónica de Pando. E-mail: rairosilvino10@gmail.com
[20] Medical Student. Autonomous University of San Sebastian (UASS). E-mail: barbarapereirapessoa@hotmail.com

options for its treatment are glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, and tirzepatide, which combines activity on both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors. This study presents a comparative review of these two drugs, analyzing efficacy, safety, tolerability, and clinical applicability based on recent randomized clinical trials and meta-analyses. The findings indicate that tirzepatide tends to promote slightly greater weight loss than semaglutide, possibly due to its dual mechanism of action, while semaglutide remains relevant due to its well-established safety profile and broad clinical use. Both drugs show a positive impact on weight control and improvement in metabolic parameters, with gastrointestinal adverse events being the most frequent. Therapeutic choice should consider individual factors, availability, and cost, emphasizing the need to combine these pharmacological interventions with sustainable lifestyle modification strategies.

Keywords: Obesity. Tirzepatide. Semaglutide. GLP-1 Receptor Agonists. Weight Loss. Pharmacotherapy.

RESUMO

A obesidade é uma condição crônica e multifatorial, associada a elevado risco cardiometabólico, redução da qualidade de vida e menor expectativa de vida. Entre as opções farmacológicas mais promissoras para seu tratamento, destacam-se os agonistas do receptor de peptídeo-1 semelhante ao glucagon (GLP-1), como a semaglutida, e a tirzepatida, que combina ação sobre os receptores de GLP-1 e do polipeptídeo inibidor gástrico (GIP). Este estudo apresenta uma revisão comparativa entre esses dois fármacos, analisando eficácia, segurança, tolerabilidade e aplicabilidade clínica com base em ensaios clínicos randomizados e meta-análises recentes. Os dados indicam que a tirzepatida tende a promover perda de peso ligeiramente superior à semaglutida, possivelmente em razão de seu mecanismo de ação duplo, enquanto a semaglutida mantém relevância pelo histórico consolidado de segurança e amplo uso clínico. Ambos os medicamentos demonstram impacto positivo no controle ponderal e na melhora de parâmetros metabólicos, sendo os eventos adversos gastrointestinais os mais frequentes. A escolha terapêutica deve considerar fatores individuais, disponibilidade e custo, reforçando a necessidade de associação com estratégias sustentáveis de modificação do estilo de vida.

Palavras-chave: Obesidade. Tirzepatida. Semaglutida. Agonistas do Receptor de GLP-1. Perda de Peso. Farmacoterapia.

RESUMEN

La obesidad es una enfermedad crónica multifactorial asociada a un elevado riesgo cardiometabólico, una menor calidad de vida y una esperanza de vida más corta. Entre las opciones farmacológicas más prometedoras para su tratamiento se encuentran los agonistas de los receptores del péptido similar al glucagón-1 (GLP-1), como la semaglutida, y la tirzepatida, que combina la acción sobre los receptores del GLP-1 y del polipéptido inhibidor gástrico (GIP). Este estudio presenta una revisión comparativa de estos dos fármacos, analizando su eficacia, seguridad, tolerabilidad y aplicabilidad clínica a partir de ensayos clínicos aleatorizados y metaanálisis recientes. Los datos indican que la tirzepatida tiende a promover una pérdida de peso ligeramente mayor que la semaglutida, posiblemente debido a su doble mecanismo de acción, mientras que la semaglutida sigue siendo relevante por su consolidado historial de seguridad y su amplio uso clínico. Ambos fármacos tienen un impacto positivo en el control del peso y en la mejora de los parámetros metabólicos, siendo

los acontecimientos adversos gastrointestinales los más frecuentes. La elección del tratamiento debe tener en cuenta factores individuales, la disponibilidad y el coste, lo que refuerza la necesidad de combinarlo con estrategias sostenibles de modificación del estilo de vida.

Palabras clave: Obesidad. Tirzepatida. Semaglutida. Agonistas del Receptor GLP-1. Pérdida de Peso. Farmacoterapia.

1 INTRODUCTION

Obesity is currently recognized as one of the main global public health challenges, characterized as a multifactorial condition resulting from the excessive accumulation of adipose tissue, which compromises health and increases the risk of several comorbidities, including type 2 diabetes mellitus (DM2), cardiovascular diseases, obstructive sleep apnea, and certain types of cancer (Martins et al., 2024; Migowski et al., 2024). Data from Vigitel indicate that the prevalence of obesity and overweight in Brazil has increased significantly in recent decades, reflecting changes in lifestyle, eating patterns, and the reduction in physical activity (Brasil, 2020; Migowski et al., 2024). It is estimated that more than 20% of the Brazilian adult population is obese, configuring it as a silent and progressive epidemic.

The economic and social impact of obesity is also significant. In addition to overloading health systems due to the treatment of associated diseases, there are losses related to quality of life, productivity, and life expectancy (Kosmalski et al., 2023). This scenario reinforces the need for effective, safe, and sustainable therapeutic approaches. Traditionally, obesity control is based on lifestyle changes, including dietary re-education, regular physical exercise, and psychological and educational support (Fernandes Nascimento et al., 2023). However, for a significant portion of patients, such isolated measures do not result in clinically relevant or long-term sustained weight loss, making it necessary to introduce pharmacological interventions (Guo et al., 2022; Oliveira et al., 2023).

In this context, glucagon-like peptide-1 receptor agonists (GLP-1RAs) emerge as an innovative and promising therapeutic class, acting not only to improve glycemic control in individuals with diabetes, but also to promote significant weight loss in patients without the disease (Alkhezi et al., 2023; Hu et al., 2024). The mechanism of action of GLP-1RAs includes stimulation of glucose-dependent insulin secretion, reduction of glucagon secretion, delay of gastric emptying, and increased satiety, resulting in lower caloric intake (Tsapas et al., 2021).

Semaglutide, a potent GLP-1 agonist, has gained prominence due to the significant results of phase 3 clinical trials, which showed significant reductions in body weight and additional improvements in cardiometabolic parameters (Rubino et al., 2022; Tan et al., 2022). Available in weekly and oral subcutaneous formulations, semaglutide has been approved for the treatment of obesity in several countries, including Brazil, under the trade name Wegovy® (Wegovy, 2024; Oliveira et al., 2023). Studies such as STEP 8 have shown that semaglutide promotes weight loss greater than that observed with liraglutide, another

GLP-1RA, presenting an acceptable safety profile, with gastrointestinal adverse effects being the most frequent (Rubino et al., 2022; Stretton et al., 2023).

Tirzepatide, in turn, is a double agonist of GLP-1 and GIP (gastric inhibitory polypeptide) receptors, representing a new generation of therapies for glycemic control and weight loss. The combined incretinal action seems to potentiate the effects on energy metabolism and appetite, resulting in even more significant weight reductions than those obtained with traditional GLP-1RAs (Alkhezi et al., 2023). Initially developed for the treatment of T2DM, tirzepatide has been investigated for the management of obesity in patients without diabetes, with promising results that have boosted its off-label use and fostered discussions about future formal indications (Guo et al., 2022).

The choice between semaglutide and tirzepatide in the management of obesity should consider multiple factors, including efficacy in weight loss, impact on metabolic parameters, safety profile, tolerability, cost, and adherence to treatment (Kim et al., 2022; Seijas-Amigo et al., 2022). Although they share pharmacological similarities, their differences in mechanisms of action and clinical response profiles warrant direct comparisons based on the latest evidence. Systematic reviews and meta-analyses suggest that tirzepatide may promote greater weight reduction than semaglutide; however, long-term data, especially on weight loss safety and maintenance, are still limited (Alkhezi et al., 2023; Hu et al., 2024).

Regarding tolerability, the most common adverse effects of GLP-1RAs include nausea, vomiting, diarrhea, and constipation, which are generally more intense at the beginning of therapy and tend to attenuate over time (Bald; Raber, 2023; Hu et al., 2024). Measures such as gradual dose titration and guidance on eating habits can minimize such events. Questions about long-term safety, especially regarding pancreatic, biliary, and cardiovascular risk, remain under investigation, requiring rigorous clinical follow-up (Verma et al., 2020; Hu et al., 2024).

In Brazil, the incorporation of agents such as semaglutide and, in the future, tirzepatide, represents an advance in the therapeutic arsenal against obesity, but also a challenge, considering its high costs and restricted access in the public health system (Kim et al., 2022; Oliveira et al., 2023). In this scenario, comparative analyses of efficacy, safety, and cost-effectiveness are essential to support clinical decisions and public policies.

Thus, the present review aims to compare the most recent evidence on the efficacy of tirzepatide and semaglutide in the management of obesity, considering three main dimensions: (1) weight reduction, (2) impact on the metabolic profile, and (3) tolerability. The

analysis will be based on randomized controlled trials, systematic reviews, and meta-analyses published in recent years, allowing for a comprehensive and critical assessment of the role of these therapies in contemporary clinical practice. This comparison is relevant not only because of the potential difference in absolute efficacy, but also because of the implications for treatment adherence, management of adverse effects, and cost-effectiveness, which are determining factors for therapeutic success and for the feasibility of strategies to combat obesity on a large scale.

2 METHODOLOGY

This study was developed in the form of an integrative-based narrative literature review, with the objective of synthesizing the current evidence available in the scientific literature on the comparison between tirzepatide and semaglutide in the management of obesity, with emphasis on three dimensions: weight reduction, metabolic profile, and tolerability. The choice of the integrative review format was motivated by its ability to gather and critically analyze studies with different designs and methodological approaches, providing a comprehensive and multifaceted view of the phenomenon investigated (Mendes et al., 2008).

The integrative literature review is a research method that allows the inclusion of experimental and non-experimental studies, favoring a broader understanding of a given topic. It ranges from randomized controlled trials (RCTs) to systematic reviews, meta-analyses, and observational studies (Mendes et al., 2008). This methodology was chosen considering that pharmacological therapies for obesity, especially GLP-1 agonists and double incretinal therapies, have been evaluated under different research designs, making it necessary to integrate multiple evidence formats to allow a consistent comparison between tirzepatide and semaglutide.

2.1 FORMULATION OF THE RESEARCH QUESTION

The first stage consisted of the formulation of the guiding question, based on the **PICO strategy** (Population, Intervention, Comparison, Outcome/Outcome).

- **Population (P):** overweight or obese adults, with or without type 2 diabetes;
- **Intervention (I):** treatment with tirzepatide or semaglutide;
- **Comparison (C):** direct or indirect comparison between the two drugs;

- **Outcome (O):** efficacy in weight reduction, impact on metabolic profile (blood glucose, lipids, blood pressure) and safety/tolerability profile.

Thus, the central question was, *"What is the current evidence on the efficacy and safety of tirzepatide compared to semaglutide in the treatment of obesity, considering weight loss, metabolic changes, and tolerability?"*

2.2 SEARCH STRATEGY

The bibliographic search was carried out in national and international databases recognized for their relevance in the health area, including: **PubMed/MEDLINE, Scopus**, **Web of Science**, **SciELO, LILACS** and **Cochrane Library**.

To maximize the sensitivity of the search, controlled descriptors from **MeSH (Medical Subject Headings)** and free terms in Portuguese and English were used, combined with Boolean operators "AND" and "OR". The main terms were:

- *Tirzepatide* OR LY3298176;
- *Semaglutide* OR *NN9535* OR *Wegovy* OR *Ozempic*;
- *Obesity* OR *Overweight* OR *Weight loss*;
- *GLP-1 receptor agonists* OR *GIP receptor agonists*;
- *Metabolic profile* OR *Safety* OR *Tolerability*.

The search included articles published up to August 2025, including studies from 2016, the year in which liraglutide was approved as an adjunct therapy for weight control (Liraglutide, 2016), a milestone that represents the beginning of the clinical popularization of GLP-1RAs in the management of obesity.

2.3 INCLUSION AND EXCLUSION CRITERIA

2.3.1 Inclusion criteria

- Studies published in peer-reviewed journals;
- Languages: Portuguese, English or Spanish;
- Adult population (≥ 18 years) overweight or obese;
- Studies evaluating directly or by indirect analysis the efficacy and/or safety of tirzepatide and semaglutide;

- Designs: randomized clinical trials, observational studies, systematic reviews, meta-analyses, and clinical guidelines.

2.3.2 Exclusion criteria

- Studies with pediatric sample;
- Opinion articles, editorials, letters to the editor and isolated case reports;
- Studies with duplicate data from previous publications;
- Research that exclusively addresses T2D without focusing on the impact on obesity or overweight.

2.4 SELECTION OF STUDIES AND DATA EXTRACTION

The selection took place in two stages:

1. **Screening of titles and abstracts**, to exclude studies that did not meet the basic criteria;
2. **Read the pre-selected articles in full** , to confirm eligibility.

The extracted data included: year and country of publication, study design, sample characteristics (number of participants, gender, mean age, presence or absence of T2DM), interventions used (dose, route, duration), main outcomes (absolute and percentage weight loss, changes in metabolic parameters), adverse effects, and authors' conclusions.

2.5 EVALUATION OF METHODOLOGICAL QUALITY

The evaluation of the quality of the studies was made according to the type of design:

- **Randomized controlled trials**: **Jadad scale**;
- **Systematic reviews and meta-analyses:** AMSTAR 2 **checklist**;
- **Observational studies**: **Newcastle-Ottawa Scale (NOS) tool**.

Only studies classified as of moderate to high quality were included in the comparative analysis, in line with the methodological recommendations for integrative reviews (Mendes et al., 2008).

2.6 SYNTHESIS AND ANALYSIS OF RESULTS

The synthesis of the data followed a descriptive and comparative approach. Initially, a general characterization of the scientific production on the subject was carried out, evidencing the recent growth of studies on GLP-1 agonists and tirzepatide (Guo et al., 2022; Hu et al., 2024). Then, the evidence was organized into three analytical axes:

1. **Effectiveness in weight loss** – including magnitude of weight reduction and response rates ≥ 5%, ≥ 10%, and ≥ 15% body weight loss (Rubino et al., 2022; Alkhezi et al., 2023; Tan et al., 2022);
2. **Impact on metabolic profile** – changes in fasting blood glucose, HbA1c, lipid profile, and blood pressure (Tsapas et al., 2021; Verma et al., 2020);
3. **Safety and tolerability** – incidence of gastrointestinal adverse effects, serious adverse events, discontinuation rate, and specific events (Bald; Raber, 2023; Hu et al., 2024).

2.7 ETHICAL CONSIDERATIONS

Results from indirect comparison studies and network meta-analysis were also incorporated, considering that there are not always *head-to-head clinical trials* between tirzepatide and semaglutide (Alkhezi et al., 2023; Xia et al., 2021).

As this is a literature review based exclusively on data in the public domain, there was no need to submit to a research ethics committee, in accordance with the Brazilian and international guidelines applicable to this type of study.

2.8 METHODOLOGICAL LIMITATIONS

Among the limitations inherent to the present method, the heterogeneity among the included studies stands out, especially with regard to the dose and duration of the interventions, the characteristics of the populations analyzed, and the operational definitions of obesity and overweight. In addition, part of the comparative evidence between tirzepatide and semaglutide comes from indirect comparisons or network analyses, which may introduce biases related to methodological differences between studies (Alkhezi et al., 2023; Guo et al., 2022).

Even so, the use of an integrative methodology allowed us to gather a robust body of evidence from different contexts and designs, enabling a comprehensive analysis of the current therapeutic scenario for obesity.

3 RESULTS

3.1 WEIGHT REDUCTION

The results of different clinical trials and meta-analyses indicate that both tirzepatide and semaglutide have robust efficacy in inducing significant weight loss in individuals with obesity or overweight, with or without the presence of type 2 diabetes. However, the magnitude of the effect tends to be greater with tirzepatide in several scenarios.

In a network meta-analysis conducted by Alkhezi et al. (2023), which compared the efficacy of several glucagon-like peptide-1 receptor agonists (GLP-1RAs) in adults without diabetes, tirzepatide demonstrated a mean body weight reduction of up to −15.6% at doses of 15 mg, while semaglutide 2.4 mg showed an average loss of −12, 0% in the same period (72 weeks). These findings reinforce the superiority of tirzepatide in terms of the absolute magnitude of weight loss, although both molecules are clinically relevant.

The STEP 8 study, conducted by Rubino et al. (2022), showed that semaglutide 2.4 mg in overweight or obese individuals without diabetes led to average losses of 9.4% to 14.9% of body weight, varying according to adherence and population characteristics. These values are consistent with previous systematic reviews (Tan et al., 2022; Guo et al., 2022), who demonstrate solid weight reduction results with semaglutide, including compared to other GLP-1RAs, such as liraglutide and dulaglutide.

In the case of tirzepatide, although there is a smaller volume of studies published in exclusively non-diabetic populations, phase 3 trials, such as SURMOUNT-1, indicate that the effect on weight loss may be approximately 20% greater than that obtained with semaglutide, especially at higher doses (Kosmalski et al., 2023). This advantage seems to be associated with its dual mechanism of action, as a simultaneous agonist of GLP-1 and GIP receptors, increasing appetite suppression and energy expenditure.

Integrative reviews (Souza et al., 2023; Oliveira et al., 2023) also point out that, although semaglutide is highly effective, patients who use tirzepatide tend to achieve weight reductions closer to those observed in less invasive bariatric interventions, which supports its potential as a non-surgical alternative in selected cases.

3.2 METABOLIC PROFILE

Improvement of the metabolic profile, including blood glucose, insulin sensitivity, lipid profile, and blood pressure, was observed with both drugs, although the magnitude of the changes tends to favor tirzepatide.

According to Tsapas et al. (2021), GLP-1 agonists, including semaglutide, are able to significantly reduce HbA1c and improve cardiometabolic markers, even in non-diabetic individuals, due to modulation of gastric emptying, glucagon suppression, and increased satiety. Specific studies, such as SUSTAIN-10 (Capehorn et al., 2020), showed that semaglutide promoted significantly higher HbA1c reductions than those obtained with liraglutide (−1.7% vs −1.0%), an effect that also extends to overweight and obese patients without diabetes.

On the other hand, data from network meta-analysis presented by Xia et al. (2021) indicate that tirzepatide can reduce HbA1c by up to −2.3% in diabetics, with a similar impact in pre-diabetics and individuals with insulin resistance, in addition to showing more pronounced reductions in triglyceride and LDL cholesterol levels. These additional metabolic effects may represent an advantage for patients with metabolic syndrome associated with obesity.

Another relevant point is the impact on blood pressure. Hu et al. (2024) and Alkhezi et al. (2023) report mean systolic pressure reductions of between −5 and −7 mmHg with semaglutide, while tirzepatide has slightly larger drops (−6 to −9 mmHg). Improved blood pressure profile is associated with weight loss, but also with direct effects on the autonomic nervous system and endothelial function.

3.3 TOLERABILITY AND SAFETY

The tolerability of both drugs is similar, presenting an adverse event profile predominantly characterized by gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and constipation, which tend to occur more frequently in the first weeks of treatment and to reduce over time (Bald; Raber, 2023; Niman et al., 2021).

Studies such as SEVERAL (Seijas-Amigo et al., 2022) indicate that semaglutide has discontinuation rates for adverse events between 7% and 12%, while reviews on tirzepatide report slightly higher rates, ranging from 8% to 15%, depending on the dose used (Guo et al., 2022). This difference may be related to the greater anorectic potency of tirzepatide, which potentiates initial gastrointestinal symptoms.

Both drugs have a low risk of hypoglycemia in non-diabetic patients, as long as they are not used in combination with insulin or secretagogues (Hu et al., 2024). Rare adverse events such as acute pancreatitis and cholelithiasis have also been described, but with a low and comparable incidence between the two drugs (Kosmalski et al., 2023).

3.4 HEAD TO HEAD COMPARISON: TIRZEPATIDE VS SEMAGLUTIDE

The direct comparisons available are still limited, but indirect evidence and network data point out that:

- **Weight reduction**: Tirzepatide > Semaglutide (mean difference of 2% to 4% body weight in favor of tirzepatide) (Alkhezi et al., 2023; Guo et al., 2022).
- **Metabolic profile improvement**: Both effective, but tirzepatide with a greater impact on HbA1c, triglycerides, and LDL (Xia et al., 2021; Tsapas et al., 2021).
- **Tolerability**: Similar profiles, but tirzepatide may have slightly more gastrointestinal events (Hu et al., 2024; Seijas-Amigo et al., 2022).

From a clinical perspective, the choice between the two agents should consider not only absolute efficacy, but also cost, availability, expected compliance, and the patient's comorbidity profile (Kim et al., 2022).

3.5 INTERPRETATIVE SYNTHESIS OF THE FINDINGS

The integrated analysis of the data shows that both drugs represent significant advances in the pharmacological treatment of obesity. Semaglutide has consolidated efficacy, with a well-established safety profile and extensive clinical experience. Tirzepatide, in turn, emerges as a potentially more potent option in promoting weight loss and improving the metabolic profile, especially at higher doses, although the accumulated long-term experience is still limited.

In the current context, semaglutide remains a safe and widely available choice, while tirzepatide is positioned as an alternative for therapeutic replacement or escalation in refractory cases or those that require greater weight loss, as long as it is well tolerated and accessible to the patient.

4 DISCUSSION

The comparison between tirzepatide and semaglutide in the management of obesity has become a central theme in the endocrinology and pharmacotherapy of this condition, due to the significant increase in its prevalence at the global and national levels (Migowski et al., 2024; Brazil, 2020). Both molecules act as glucagon-like peptide-1 receptor (GLP-1RA) agonists, but tirzepatide has an additional mechanism in that it also acts as a glucose-dependent insulinotropic polypeptide (GIP) agonist, giving it a potentially superior

pharmacodynamic profile in weight reduction and metabolic control (Alkhezi et al., 2023; Hu et al., 2024).

Recent network meta-analysis studies indicate that, among GLP-1 agonists, tirzepatide promotes greater mean body weight reductions compared to semaglutide, especially at higher doses (Alkhezi et al., 2023; Guo et al., 2022). While semaglutide, at a dose of 2.4 mg/week, provides an average loss of approximately 14% to 15% of body weight in individuals without diabetes (Rubino et al., 2022; Tan et al., 2022), tirzepatide, at doses of 15 mg/week, achieves reductions of more than 20% in some studies, approaching the results obtained by bariatric procedures (Alkhezi et al., 2023). This difference is clinically relevant and may influence the therapeutic decision, especially in patients with severe obesity or refractory to previous therapies.

Despite this, semaglutide maintains a consolidated and widely studied role, with robust evidence of efficacy and safety not only in weight control, but also in reducing cardiovascular risk in patients with type 2 diabetes and high risk (Verma et al., 2020; Seijas-Amigo et al., 2022). Its use was expanded by ANVISA for the treatment of obesity even without a diagnosis of diabetes, reinforcing its role in the multifactorial approach to the disease (Wegovy, 2024; Oliveira et al., 2023). In addition, direct comparative studies with other GLP-1RAs, such as liraglutide, demonstrate advantages of semaglutide in both the magnitude of weight loss and dosage convenience (Capehorn et al., 2020; Rubino et al., 2022).

Regarding the metabolic profile, both drugs promote significant improvement in parameters such as fasting glucose, glycated hemoglobin, lipid profile, and blood pressure (Tsapas et al., 2021; Hu et al., 2024). There is, however, evidence that tirzepatide may provide additional reductions in HbA1c and greater improvement in the HOMA-IR index, possibly due to its dual GIP/GLP-1 agonism (Alkhezi et al., 2023). This effect may be particularly relevant in patients with prediabetes or metabolic syndrome, conditions that are highly prevalent among individuals with obesity (Martins et al., 2024).

Regarding tolerability, semaglutide has a well-characterized profile, with predominantly gastrointestinal adverse events, such as nausea, vomiting, and diarrhea, more common in the first weeks of treatment, which can be minimized by gradual dose titration (Bald; Raber, 2023; Pires Weber et al., 2023). Tirzepatide shows a similar pattern, although some studies indicate a slightly higher incidence of nausea at the highest doses (Alkhezi et al., 2023). Discontinuation rates for adverse effects are between 6% and 10% for both drugs in major clinical trials (Hu et al., 2024).

Cost-effectiveness is also worth mentioning. Semaglutide, although cost-effective, can be considered cost-effective in certain scenarios, especially when considering benefits in reducing cardiovascular events and improving quality of life (Kim et al., 2022). For tirzepatide, there are still fewer studies from this perspective, but preliminary data suggest that its incremental cost per unit of weight lost may be competitive against semaglutide, especially if the market price is similar (Alkhezi et al., 2023).

In terms of adherence and persistence, weekly medications, such as tirzepatide and semaglutide, represent an advance over daily use options, such as liraglutide, due to greater convenience and lower therapeutic burden (Stretton et al., 2023; Liraglutide, 2016). Observational studies indicate that persistence tends to be higher with weekly formulations, although persistent adverse effects may impact long-term adherence (Jensen et al., 2023).

In the Brazilian context, the choice between tirzepatide and semaglutide must consider not only efficacy and tolerability, but also regulatory factors, availability in the Unified Health System (SUS), cost to the patient, and eventual coverage by health plans. Semaglutide already has broad approval and consolidated use, while tirzepatide is in the process of expanding indications in the country, which may limit its immediate access (Wegovy, 2024; Oliveira et al., 2023).

The impact of these therapies on the quality of life and mental health of patients with obesity is also relevant. Significant reductions in body weight, when sustained, can improve self-esteem, reduce depressive symptoms, and facilitate physical activity (Guo et al., 2022; Hu et al., 2024). Both semaglutide and tirzepatide have the potential to positively influence these outcomes, although studies focused on quality of life are more numerous for semaglutide (Seijas-Amigo et al., 2022).

It is important to recognize that therapeutic response can vary substantially between individuals. Factors such as genetics, gut microbiota, degree of systemic inflammation, dietary pattern, and adherence to treatment influence the results (Kosmalski et al., 2023). Thus, the choice of therapy should be personalized, considering not only population averages from clinical trials, but also the specific patient profile.

From a public health perspective, the incorporation of potent pharmacological therapies in the management of obesity can contribute to reducing the burden of associated chronic diseases, such as type 2 diabetes, hypertension, and dyslipidemia, and even reduce the need for surgical interventions (Gomes; Trevisan, 2021; Souza et al., 2023). However,

the financial and logistical feasibility of offering these medications on a large scale still represents a challenge for health systems in middle-income countries, such as Brazil.

In summary, the current literature indicates that tirzepatide tends to promote weight reductions greater than those obtained with semaglutide, possibly with additional benefits in glycemic control due to its dual mechanism of action. However, semaglutide maintains advantages in the robustness of the evidence, the history of use, the well-established safety profile, and regulatory approvals for multiple indications. The therapeutic decision must be individualized, weighing efficacy, tolerability, cost, availability, and patient preferences. Long-term studies and real-world analyses are still needed to confirm whether the initial benefits observed with tirzepatide are maintained and translate into a significant reduction in morbidity and mortality.

5 CONCLUSION

The comparative analysis between tirzepatide and semaglutide in the management of obesity shows that both represent significant advances in the pharmacotherapy of this condition, contributing significantly to weight reduction, improvement of the metabolic profile, and potential benefit in cardiometabolic outcomes. Tirzepatide tends to have superior results in weight loss, possibly due to its dual mechanism of action, while semaglutide stands out for its extensive clinical experience, proven safety, and consistent efficacy in different patient profiles.

In the field of tolerability, both share a predictable and generally manageable adverse event profile, with mild to moderate gastrointestinal symptoms predominating. However, there are still gaps regarding cardiovascular safety and long-term impact on obese patients without comorbidities, reinforcing the need for prolonged follow-up.

The therapeutic choice should be individualized, considering not only the magnitude of weight loss, but also clinical characteristics, presence of comorbidities, cost, availability, adherence, and patient preferences. Integrating these therapies with sustainable lifestyle interventions is critical to optimizing outcomes and ensuring long-term benefit maintenance.

Thus, tirzepatide presents itself as an innovative and promising option, while semaglutide maintains a consolidated position in the therapeutic arsenal. The most precise definition of the role of each one will depend on the evolution of research and the expansion of direct comparative studies, capable of guiding clinical decisions based on robust evidence.

REFERENCES

Alkhezi, O. S., et al. (2023). Comparative effectiveness of glucagon-like peptide-1 receptor agonists for the management of obesity in adults without diabetes: A network meta-analysis of randomized clinical trials. Obesity Reviews, 24(3), e13543. https://doi.org/10.1111/obr.13543

Bald, E., & Raber, H. (2023). Semaglutide (Wegovy) for the treatment of obesity. American Family Physician, 107(1), 90. https://pubmed.ncbi.nlm.nih.gov/36689981/

Capehorn, M. S., et al. (2020). Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes & Metabolism, 46(2), 100–109. https://doi.org/10.1016/j.diabet.2019.101117

Fernandes Nascimento, M. H., et al. (2023). Eficácia e segurança da semaglutida comparada à terapia padrão de mudanças no estilo de vida para tratamento do sobrepeso e obesidade em adultos: Revisão rápida de evidências. Revista Científica da Escola Estadual de Saúde Pública de Goiás, 9(9j2), 1–16.

Gomes, H. K. B., & Trevisan, M. (2021). O uso do Ozempic (semaglutida) como medicamento off label no tratamento da obesidade e como auxiliar na perda de peso. Revista Artigos.com, 29, e7498.

Guo, X., et al. (2022). The antiobesity effect and safety of GLP-1 receptor agonist in overweight/obese patients without diabetes: A systematic review and meta-analysis. Hormone and Metabolic Research, 54(7), 458–471. https://doi.org/10.1055/a-1843-9177

Hu, E.-H., et al. (2024). A review and meta-analysis of the safety and efficacy of using glucagon-like peptide-1 receptor agonists. Medicina (Kaunas, Lithuania), 60(3), 357. https://doi.org/10.3390/medicina60030357

Jensen, A. B., et al. (2023). Efficacy of the glucagon-like peptide-1 receptor agonists liraglutide and semaglutide for the treatment of weight regain after bariatric surgery: A retrospective observational study. Obesity Surgery, 33(4), 1017–1025. https://doi.org/10.1007/s11695-023-06492-2

Kim, N., et al. (2022). Cost-effectiveness analysis of semaglutide 2.4 mg for the treatment of adult patients with overweight and obesity in the United States. Journal of Managed Care & Specialty Pharmacy, 28(7), 740–752. https://doi.org/10.18553/jmcp.2022.28.7.740

Kosmalski, M., et al. (2023). Pharmacological support for the treatment of obesity—Present and future. Healthcare (Basel, Switzerland), 11(3), 433. https://doi.org/10.3390/healthcare11030433

Liraglutida é aprovada como tratamento auxiliar para o controle do peso em adultos. (2016). https://www.gov.br/anvisa/pt-br/assuntos/noticias-anvisa/2016/liraglutida-e-aprovada-como-tratamento-auxiliar-para-o-controle-do-peso-em-adultos

Martins, R. B. M., et al. (2024). Características sociodemográficas associadas ao baixo peso e ao excesso de peso em adultos com 50 anos ou mais (ELSI-Brasil): Diferenças entre sexos. Cadernos de Saúde Pública, 40(1). https://doi.org/10.1590/0102-311XPT093323

Mendes, K. D. S., et al. (2008). Revisão integrativa: Método de pesquisa para a incorporação de evidências na saúde e na enfermagem. Texto & Contexto Enfermagem, 17(4), 758–764. https://doi.org/10.1590/S0104-07072008000400018

Migowski, A., et al. (2024). Análise temporal da prevalência da obesidade e do sobrepeso no Brasil entre 2006 e 2023: Evidências a partir dos dados do Vigitel. OnScience, 2(1), e00104.

Brasil. Ministério da Saúde. (2020). Vigitel Brasil 2019: Vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: Estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados e no Distrito Federal em 2019. Brasília, Brazil: Ministério da Saúde.

Niman, S., et al. (2021). A review on the efficacy and safety of oral semaglutide. Drugs in R&D, 21(2), 133–148. https://doi.org/10.1007/s40268-021-00341-6

Oliveira, I. P. D., et al. (2023). Semaglutida no tratamento de obesidade e sobrepeso. Research, Society and Development, 12(3), e29812340656. https://doi.org/10.33448/rsd-v12i3.40656

Pires Weber, T., et al. (2023). Uso do medicamento semaglutida como aliado no tratamento da obesidade. RECIMA21 - Revista Científica Multidisciplinar, 4(2), e422731. https://doi.org/10.47820/recima21.v4i2.2731

Rubino, D. M., et al. (2022). Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 randomized clinical trial. JAMA: The Journal of the American Medical Association, 327(2), 138. https://doi.org/10.1001/jama.2021.23619

Seijas-Amigo, J., et al. (2022). Semaglutide versus GLP-1 agonists. Effectiveness, safety, and quality of life in patients with diabetes mellitus 2. The SEVERAL study. Farmacia Hospitalaria, 46(6), 372–379. https://doi.org/10.7399/fh.13028

Souza, A. da S., et al. (2023). A eficácia dos medicamentos semaglutida e liraglutida no tratamento da obesidade: Uma revisão integrativa da literatura. Contribuciones a las Ciencias Sociales, 16(11), 24819–24828. https://doi.org/10.55905/revconv.16n.11-093

Stretton, B., et al. (2023). Weight loss with subcutaneous semaglutide versus other glucagon-like peptide 1 receptor agonists in type 2 diabetes: A systematic review. Internal Medicine Journal, 53(8), 1311–1320. https://doi.org/10.1111/imj.15960

Tan, H. C., et al. (2022). Efficacy and safety of semaglutide for weight loss in obesity without diabetes: A systematic review and meta-analysis. Journal of the ASEAN Federation of Endocrine Societies, 37(2), 65–72. https://doi.org/10.15605/jafes.037.02.08

Tsapas, A., et al. (2021). Comparative efficacy of glucose-lowering medications on body weight and blood pressure in patients with type 2 diabetes: A systematic review and network meta-analysis. Diabetes, Obesity & Metabolism, 23(9), 2116–2124. https://doi.org/10.1111/dom.14451

Verma, S., et al. (2020). Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: Results of the LEADER and SUSTAIN 6 trials. Diabetes, Obesity & Metabolism, 22(12), 2487–2492. https://doi.org/10.1111/dom.14160

Wegovy (semaglutida): Ampliação de uso. (2024). https://www.gov.br/anvisa/pt-br/assuntos/medicamentos/novos-medicamentos-e-indicacoes/wegovy-semaglutida-ampliacao-de-uso

Xia, L., et al. (2021). Comparative efficacy and safety of 8 GLP-1RAs in patients with type 2 diabetes: A network meta-analysis. Diabetes Research and Clinical Practice, 177, 108904. https://doi.org/10.1016/j.diabres.2021.108904