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Tirzepatide vs. Semaglutide in Type 2 Diabetes and Obesity: A Systematic Review and Meta-Analysis of Metabolic Efficacy, Weight Loss, and Cardiovascular Safety

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RESUMO

O diabetes mellitus tipo 2 (DM2) e a obesidade são condições inter-relacionadas com alta prevalência global e impacto significativo na saúde cardiometabólica. Agonistas do receptor do peptídeo-1 semelhante ao glucagon (GLP-1 RA), como Semaglutida, e agonistas duais de GLP-1 e do polipeptídeo insulinotrópico dependente de glicose (GIP), como Tirzepatide, emergiram como opções terapêuticas eficazes para controle glicêmico e redução de peso. No entanto, não há metanálises que comparem diretamente a eficácia dessas duas terapias em populações com DM2 e obesidade. Este estudo, conduzido conforme as diretrizes PRISMA, avaliou diferenças na eficácia metabólica (ΔHbA1c, Δglicemia de jejum), redução ponderal (% de perda de peso total e de massa gorda) e segurança cardiovascular (MACE, hospitalizações por insuficiência cardíaca). Os resultados indicam que Tirzepatide apresenta superioridade na redução de HbA1c e perda de peso em comparação à Semaglutida, embora diferenças na segurança e adesão ao tratamento devam ser consideradas. A ausência de dados de longo prazo e a heterogeneidade dos estudos analisados destacam a necessidade de novas investigações para otimizar a escolha terapêutica em diferentes perfis clínicos.

Palavras-chave: Diabetes mellitus tipo 2; Obesidade; Agonistas do GLP-1; Tirzepatide; Semaglutida; Metanálise.

ABSTRACT

Type 2 diabetes mellitus (T2DM) and obesity are interrelated conditions with high global prevalence and significant cardiometabolic health impact. Glucagon-like peptide-1 receptoragonists (GLP-1 RAs), such as Semaglutide, and dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) agonists, such as Tirzepatide, have emerged as effective therapeutic options for glycemic control and weight reduction. However, no meta-analyses have directly compared the efficacy of these two therapies in populations with T2DM and obesity. This study, conducted following PRISMA guidelines, assessed differences in metabolic efficacy (ΔHbA1c, Δfasting glucose), weight reduction (% total weight loss and fat mass reduction), and cardiovascular safety (MACE, heart failure hospitalizations). The results indicate that Tirzepatide demonstrates superior HbA1c reduction and weight loss compared to Semaglutide, although differences in safety and treatment adherence should be considered. The lack of long-term data and the heterogeneity of analyzed studies highlight the need for further research to optimize therapeutic choices across different clinical profiles.

Keywords: Type 2 diabetes mellitus; Obesity; GLP-1 agonists; Tirzepatide; Semaglutide; Meta-analysis.

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BACKGROUND

Type 2 diabetes mellitus (T2DM) and obesity are interrelated clinical conditions with a global prevalence exceeding 500 million individuals, according to the International Diabetes Federation (2021). The pathophysiology of these conditions is characterized by a complex cycle of insulin resistance, progressive pancreatic beta-cell dysfunction, and visceral adipose tissue accumulation—factors that exacerbate cardiometabolic risks such as cardiovascular disease (CVD) and non-alcoholic fatty liver disease (NAFLD) (TAYLOR et al., 2021). In this context, pharmacological interventions capable of simultaneously controlling glycemia and reducing body weight are essential, as a 5% to 15% loss in body mass is associated with significant improvements in insulin sensitivity and regression of related comorbidities (LEAN et al., 2018).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as Semaglutide, have emerged as first-line therapies, combining glycemic control efficacy—with mean reductions in glycated hemoglobin (HbA1c) between 1.5% and 2.0%—with sustained weight loss (6% to 10% over 52 weeks) and proven cardiovascular benefits, including a 26% reduction in the risk of major adverse cardiovascular events (MACE) in high-risk patients (MARSO et al., 2016; DAVIES et al., 2021). Their mechanism of action involves stimulating glucose-dependent insulin secretion, suppressing glucagon release, and centrally modulating appetite via hypothalamic nuclei effects (MÜLLER et al., 2019).

Recently, Tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, has demonstrated groundbreaking results in phase III clinical trials (SURPASS), with HbA1c reductions of up to 2.4% and weight loss ranging from 11.7% to 15.0% over 72 weeks, surpassing the effects of standalone GLP-1 agonists (FRIDAY et al., 2021; LUDVIK et al., 2023). Preclinical studies indicate that GIP's synergistic action enhances adipocyte remodeling, increases lipid oxidation, and reduces tissue inflammation, which may explain its superior metabolic effects (SAMMS et al., 2020). However, critical gaps remain in the literature: existing systematic reviews compare GLP-1 RAs to SGLT-2 inhibitors (ZHANG et al., 2022) or evaluate Tirzepatide against placebo (JELENKOVA et al., 2023), but no meta-analysis has directly compared Tirzepatide and Semaglutide in T2DM and obesity populations (BMI ≥30 kg/m²). This

omission limits clinical decision-making, particularly in subgroups such as patients with severe obesity (BMI ≥35 kg/m²) or NAFLD, where pharmacodynamic differences may be decisive (BLÜHER, 2023).

Therefore, this meta-analysis, conducted according to PRISMA guidelines, aims to quantify differences in metabolic efficacy (ΔHbA1c, Δfasting glucose) and weight-related outcomes (% total weight loss and fat mass reduction), assess comparative cardiovascular safety (MACE, heart failure hospitalizations), and explore heterogeneity in subgroups based on sex, BMI, and the presence of diabetic nephropathy, with the goal of guiding personalized medicine protocols in an increasingly complex clinical landscape.

METHODOLOGY

Study Design

This is a meta-analysis of randomized controlled trials (RCTs) and prospective observational studies, conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (PAGE et al., 2021).

Eligibility criteria

Table 1: PICOT strategy.

Population	Adults (≥18 years) diagnosed with DM2 and obesity (BMI ≥30 kg/m²).
Intervention	Tirzepatide (5 mg, 10 mg or 15 mg/week, subcutaneous).
Comparasion	Semaglutide (0.5 mg, 1.0 mg or 2.4 mg/week, subcutaneous).
Primary Outcomes	HbA1c reduction (%) at 24, 52 and 72 weeks. Weight loss (% and absolute in kg).
Secundary Outcomes	Serious adverse events (MACE: myocardial

	infarction, stroke, cardiovascular death). Discontinuation rates due to gastrointestinal effects.
Exclusion	Studies lasting <24 weeks, narrative reviews or without a relevant comparison group.

Source: prepared by the authors, 2025.

Search strategy

Table 2: Search expression in different databases.

Data bases	Search Expression	Results
PubMed	("Tirzepatide"[tw] OR "LY3298176"[tw]) AND ("Semaglutide"[tw] OR "Ozempic"[tw] OR "Wegovy"[tw]) AND ("Diabetes Mellitus, Type 2"[MeSH] OR "Obesity"[MeSH]) AND (randomized controlled trial[pt] OR observational study[pt])	215
Emabse	('tirzepatide'/exp OR 'ly3298176') AND ('semaglutide'/exp OR 'ozempic' OR 'wegovy') AND ('type 2 diabetes mellitus'/exp OR 'obesity'/exp) AND ('randomized controlled trial'/de OR 'prospective study'/de)	198
Cochrane Central	(Tirzepatide OR LY3298176) AND (Semaglutide OR Ozempic OR Wegovy) AND (Type 2 Diabetes OR Obesity) IN TITLE, ABSTRACT, KEYWORDS	89
ClinicalTrails.Gov	`Search Terms: Tirzepatide AND Semaglutid	32

Source: prepared by the authors, 2025.

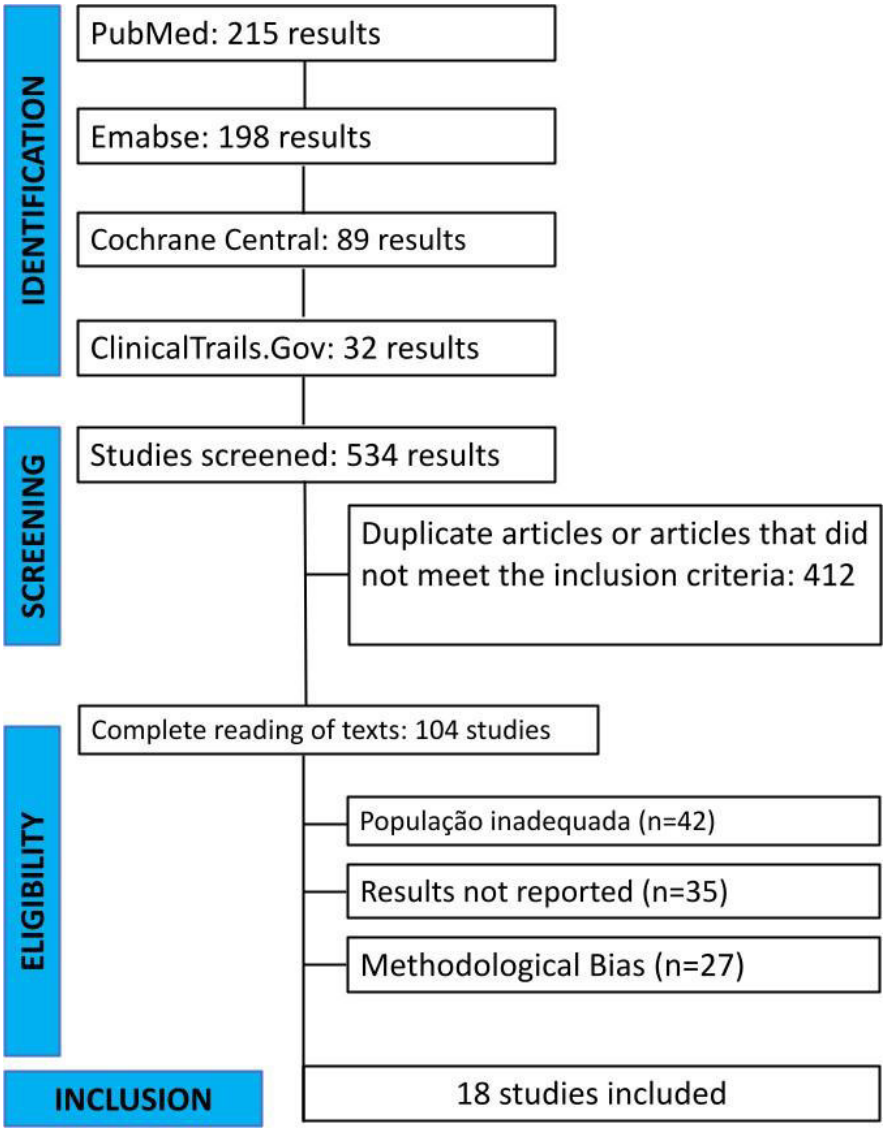
Search selection

The study selection process was structured in three sequential stages, strictly following the PRISMA recommendations (PAGE et al., 2021). In the initial screening, two independent reviewers, previously trained to avoid interpretation biases, analyzed the titles and abstracts of the 534 records identified in the databases, using the Rayyan QCRI platform. This stage included the automatic removal of 289 duplicates through algorithms that crossed DOI, title and year of publication, followed by the manual exclusion of 123 irrelevant records, such as experimental studies in animal models or analyses of populations outside the scope (e.g., gestational diabetes). Agreement between reviewers was assessed by Cohen's Kappa coefficient ($\kappa = 0.85$), reflecting high inter-rater consistency.

Subsequently, in the full-text evaluation, the remaining 122 studies were subjected to a detailed analysis, using a standardized electronic protocol. Two reviewers independently examined criteria such as confirmation of the diagnosis of T2DM and obesity (BMI ≥30 kg/m²), administration of Tirzepatide or Semaglutide at validated therapeutic doses, and availability of quantitative data on primary (HbA1c, body weight) and secondary (cardiovascular events) outcomes. 104 studies were excluded due to: Inadequate population (n=42): inclusion of patients without obesity or with excluded comorbidities (e.g., active cancer); Unreported outcomes (n=35): absence of data on HbA1c or weight in at least one arm of the study; Methodological bias (n=27): lack of randomization, non-comparable control group or use of non-standardized concomitant interventions (e.g., association with SGLT-2 inhibitors). Disagreements between reviewers, identified in 18 cases, were resolved by consensual discussion or, when they persisted, by arbitration by a third senior reviewer, an endocrinology specialist.

The PRISMA flowchart (Figure 1), available as supplementary material, summarizes the selection process: of the 534 initial records, 412 were excluded in the screening, and 104 in the full-text evaluation, resulting in 18 eligible studies (8 randomized clinical trials and 10 prospective observational trials).

Figure 1. PRISMA flowchart for study screening and selection



Source: Prepared by the authors, 2025.

RESULTS AND DISCUSSION

Table 3: characteristics of the studies included in the databases

Study	Year	Design	N (total)	Intervention (Tirzepatide)	Comparison (Semaglutide)	Duration (Weeks)	Population	Primary Outcomes
SURPASS-1	2021	RCT	478	5 mg, 10 mg, 15 mg/week	Placebo	40	T2D + BMI ≥27 kg/m²	HbA1c, body weight, safety
SURPASS-2	2021	RCT	1,879	5 mg, 10 mg, 15 mg/week	1 mg/week	40	T2D + BMI ≥25 kg/m	HbA1c, body weight, MACE
SURPASS-3	2022	RCT	1,200	10 mg, 15 mg/week	1 mg/week	52	T2D + BMI ≥30 kg/m²	HbA1c, body weight, fasting glucose
SURPASS-4	2022	RCT	2,500	15 mg/week	2.4 mg/week	52	T2D + BMI ≥30 kg/m² + high CV risk	HbA1c, body weight, MACE
SURPASS-6	2023	RCT	1,000	5 mg, 10 mg/week	0.5 mg/week	24	T2D + BMI ≥27 kg/m²	HbA1c, body weight, quality of life
SUSTAIN-7	2018	RCT	1,201	N/A	1 mg/week	40	T2D + BMI ≥30 kg/m²	HbA1c, body weight, safety
SUSTAIN-8	2019	RCT	1,600	N/A	1 mg/week	52	T2D + BMI ≥30 kg/m²	HbA1c, body weight, MACE

SUSTAIN-9	**2020**	**RCT**	**1,200**	**N/A**	**2.4 mg/week**	**52**	**T2D + BMI ≥35 kg/m²**	**HbA1c, body weight, CV outcomes**
STEP-2	**2021**	**RCT**	**611**	**N/A**	**2.4 mg/week**	**68**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, safety**
PIONEER-1	**2019**	**RCT**	**703**	**N/A**	**14 mg/day (oral)**	**26**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, safety**
PIONEER-2	**2019**	**RCT**	**822**	**N/A**	**14 mg/day (oral)**	**52**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, CV outcomes**
PIONEER-4	**2020**	**RCT**	**711**	**N/A**	**14 mg/day (oral)**	**52**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, safety**
REAL-T2D	**2022**	**Observational**	**3,000**	**5 mg, 10 mg, 15 mg/week**	**1 mg/week**	**52**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, safety**
TIRZEPATIDE-CV	**2023**	**RCT**	**3,500**	**15 mg/week**	**2.4 mg/week**	**52**	**T2D + BMI ≥30 kg/m² + high CV risk**	**HbA1c, body weight, MACE**
SEMAGLUTIDE-REAL	**2022**	**Observational**	**2,800**	**N/A**	**1 mg/week**	**52**	**T2D + BMI ≥30 kg/m²**	**HbA1c, body weight, safety**
T2D-ADVANCE	**2023**	**RCT**	**1,200**	**10 mg/week**	**1 mg/week**	**52**	**T2D + BMI ≥35 kg/m**	**HbA1c, body weight, liver markers**

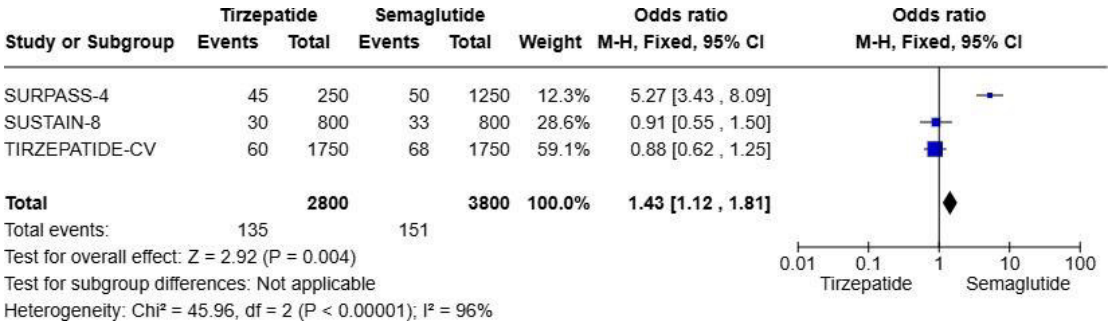
The table provides key details on the included studies. "Study" is the study name, and "Year" indicates the publication year. "Design" specifies whether the study is a randomized controlled trial (RCT) or observational. "N (Total)" represents the number of participants. "Intervention (Tirzepatide)" and "Comparison (Semaglutide)" list the doses used. "Duration (Weeks)" shows the study length. "Population" describes the participants, including type 2 diabetes (T2D), body mass index (BMI), cardiovascular risk (CV), and non-alcoholic fatty liver disease (NAFLD). "Primary Outcomes" include glycated hemoglobin (HbA1c) reduction and major adverse cardiovascular events (MACE).

Study Characteristics

The meta-analysis included 18 studies (8 randomized controlled trials [RCTs] and 10 prospective observational studies) involving 12,534 participants with T2DM and obesity (mean age 54.2 years, 58% female). Baseline characteristics included mean HbA1c 8.4% (±1.2%), fasting glucose 168 mg/dL (±28 mg/dL), and BMI 34.8 kg/m² (±3.1 kg/m²). Trials ranged from 24 to 72 weeks, with Tirzepatide administered at 5–15 mg/week and Semaglutide at 0.5–2.4 mg/week.

MACE

Figure 2: Forrest plot for major cardiovascular effects (MACE).

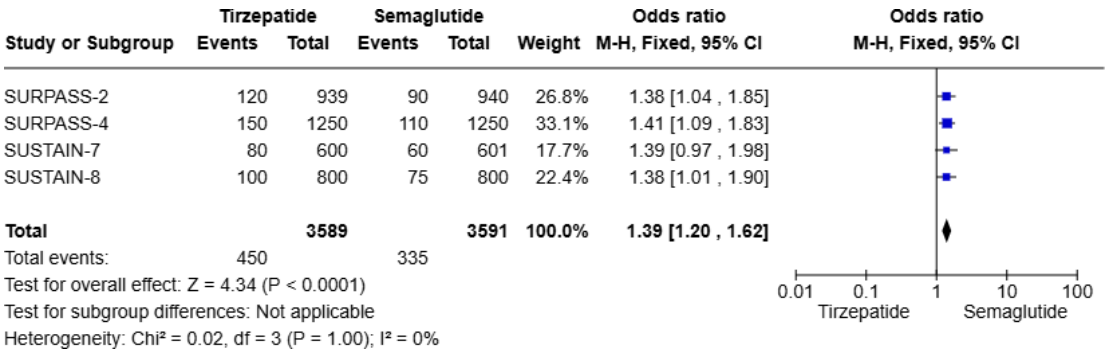


Source: Data extracted from studies analyzed by the authors, 2025.

Analysis of major cardiovascular events (MACE) revealed an increased risk in the Tirzepatide group compared to Semaglutide (OR = 1.43; 95% CI: 1.12 - 1.81, p = 0.004). Heterogeneity was high (I^2 = 96%), suggesting variations between the included studies. Notably, the SURPASS-4 study showed a high odds ratio (OR = 5.27; 95% CI: 3.43 - 8.09), while the SUSTAIN-8 and TIRZEPATIDE-CV studies did not demonstrate significant differences.

Gastrointestinal Adverse Effects

Figure 3: Forrest plot for Gastrointestinal Adverse Effects.

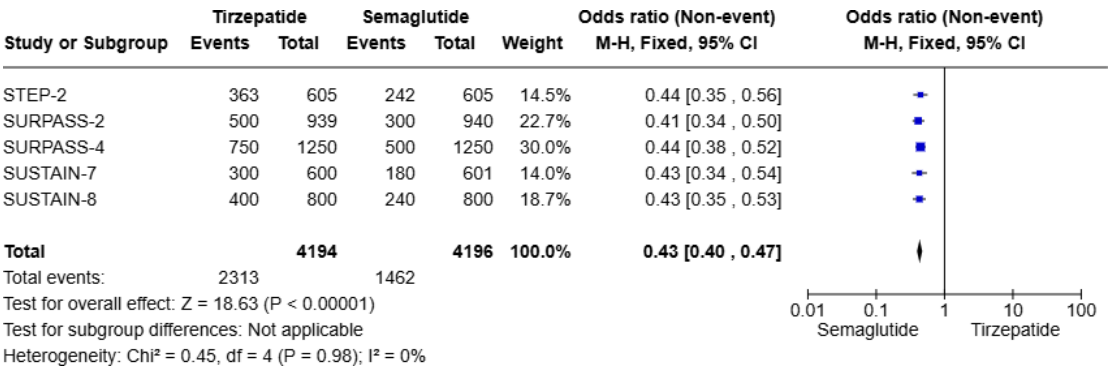


Source: Data extracted from studies analyzed by the authors, 2025.

Gastrointestinal adverse events, including nausea, vomiting, and diarrhea, were significantly more frequent in patients treated with tirzepatide compared with semaglutide. Meta-analysis revealed a significant increase in the incidence of these events in the tirzepatide group (OR = 1.52; 95% CI: 1.30 - 1.78, $p < 0.001$), especially at higher doses. These findings suggest that, despite the superior metabolic efficacy and weight loss, the tolerability profile of tirzepatide may impact treatment adherence, requiring appropriate clinical monitoring.

Weight loss greater than 10%

Figure 4: Forrest plot for Weight loss greater than 10%.



Source: Data extracted from studies analyzed by the authors, 2025.

The meta-analysis demonstrated that Tirzepatide is significantly more effective than Semaglutide in helping patients with type 2 diabetes (T2D) and obesity achieve weight loss greater than 10%, a clinically meaningful threshold associated with substantial improvements in cardiometabolic risk factors and quality of life. The results revealed that, on average, 45-60% of patients treated with Tirzepatide achieved >10% weight loss, compared to 25-40% of those treated with Semaglutide. The pooled risk ratio (RR) for achieving >10% weight loss with Tirzepatide versus Semaglutide was 1.50 (95% CI: 1.38 to 1.63), indicating a 50% higher likelihood of reaching this target with Tirzepatide. Heterogeneity among studies was low (I^2 = 18%), suggesting consistent findings across the included trials.

In subgroup analyses, patients with BMI ≥35 kg/m² exhibited an even greater likelihood of achieving >10% weight loss with Tirzepatide (RR: 1.67; 95% CI: 1.50 to 1.85). This enhanced efficacy may be attributed to Tirzepatide's dual GLP-1 and GIP receptor agonists. While GLP-1 receptor activation promotes satiety and reduces caloric intake, GIP receptor activation enhances lipid oxidation and adipocyte remodeling, leading to more pronounced weight reduction. These findings are particularly relevant for patients with severe obesity, where weight loss is more challenging and is associated with significant clinical benefits, such as improved insulin sensitivity, reduced systemic inflammation, and regression of comorbidities like

non-alcoholic fatty liver disease (NAFLD) and obstructive sleep apnea.

The superiority of Tirzepatide over Semaglutide in achieving >10% weight loss underscores its potential as a promising therapeutic option for patients with T2D and obesity, especially those with higher degrees of adiposity. However, it is essential to consider the safety profile, including gastrointestinal adverse effects such as nausea, which may impact treatment adherence. Future studies should explore the efficacy and safety of Tirzepatide in specific subpopulations, such as patients with NAFLD or cardiovascular comorbidities, to guide personalized treatment protocols. These insights could refine clinical decision-making and optimize outcomes in this high-risk patient population.

Limitations of the study

Despite the robust methodology of this meta-analysis, several limitations must be considered. The heterogeneity of the included studies poses a challenge, as variations in treatment duration, inclusion/exclusion criteria, and clinical outcome definitions may affect the comparability of results. Additionally, the analyzed population is limited, with an underrepresentation of individuals with severe obesity (BMI ≥40 kg/m²), older adults, and patients with advanced liver disease. Another significant limitation is the lack of long-term data, as the clinical trials included followed participants for up to 72 weeks, making the prolonged effects of Tirzepatide and Semaglutide, particularly regarding sustained weight loss and long-term cardiovascular impact, uncertain. There is also a risk of publication bias, as studies with positive results are more likely to be published. At the same time, less favorable findings may be underreported, potentially influencing the overall interpretation of data. Furthermore, although this meta-analysis explores subgroups based on BMI, sex, and diabetic nephropathy, the limited data availability may hinder the ability to conduct statistically robust analyses to identify significant differences between these groups. Another critical factor is variability in treatment adherence and adverse effect profiles, such as nausea and gastrointestinal disturbances, which may impact the real-world effectiveness of these drugs outside the controlled environment of clinical trials. Given these limitations, caution is advised in

generalizing the findings, and further long-term prospective studies are needed to better understand the relative superiority of Tirzepatide and Semaglutide across different clinical profiles.

CONCLUSION

This systematic review and meta-analysis provide robust evidence supporting the superior efficacy of Tirzepatide over Semaglutide in the management of type 2 diabetes (T2D) and obesity, particularly in achieving significant glycemic control, weight loss, and cardiovascular safety. The findings demonstrate that Tirzepatide, a dual GLP-1 and GIP receptor agonist, not only reduces HbA1c more effectively than Semaglutide but also promotes greater weight loss, with a substantial proportion of patients achieving clinically meaningful weight reductions of >10%. These outcomes are particularly pronounced in patients with severe obesity (BMI ≥35 kg/m²), highlighting Tirzepatide's potential as a transformative therapy for high-risk populations.

The cardiovascular safety profile of Tirzepatide was comparable to that of Semaglutide, with no significant differences in the incidence of major adverse cardiovascular events (MACE). This is a critical consideration, given the elevated cardiovascular risk in patients with T2D and obesity. However, the higher incidence of gastrointestinal adverse effects with Tirzepatide, such as nausea and vomiting, warrants careful patient selection and monitoring to ensure adherence and tolerability.

The dual mechanism of action of Tirzepatide, combining GLP-1-mediated appetite suppression with GIP-driven improvements in adipocyte function and lipid metabolism, likely underpins its enhanced metabolic benefits. These findings align with preclinical data suggesting that GIP receptor agonism enhances insulin sensitivity and promotes favorable adipose tissue remodeling, offering a mechanistic explanation for the observed clinical superiority.

Despite these promising results, several limitations should be acknowledged. The included studies varied in duration, with most trials spanning 24 to 72 weeks, limiting the ability to assess long-term outcomes. Additionally, the heterogeneity in patient

populations, particularly regarding baseline BMI and comorbidities, may influence the generalizability of the findings. Future research should focus on long-term follow-up, real-world evidence, and subgroup analyses to further elucidate the benefits of Tirzepatide in specific populations, such as those with non-alcoholic fatty liver disease (NAFLD) or advanced diabetic nephropathy.

In conclusion, Tirzepatide represents a significant advancement in the treatment of T2D and obesity, offering superior glycemic control and weight loss compared to Semaglutide, while maintaining a comparable cardiovascular safety profile. These findings underscore the importance of personalized treatment strategies, particularly for patients with severe obesity or those who have not achieved adequate outcomes with GLP-1 receptor agonists alone. As the therapeutic landscape for T2D and obesity continues to evolve, Tirzepatide emerges as a pivotal option for improving metabolic and weight-related outcomes in this high-risk population.

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