Section: Medicine

Systematic Review and Meta-Analysis

COMPARATIVE EFFICACY OF SEMAGLUTIDE VERSUS TIRZEPATIDE IN OVERWEIGHT/OBESE DIABETIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Aim: To systematically evaluate and compare the efficacy of semaglutide and tirzepatide in achieving weight loss and glycemic control in overweight and obese patients with type 2 diabetes mellitus (T2DM).
Materials and Methods: A comprehensive systematic review and meta-analysis was conducted using PubMed, Scopus, Web of Science, and Cochrane databases from 2020 to November 2025. Randomized controlled trials (RCTs) and retrospective cohort studies comparing semaglutide and tirzepatide in overweight/obese diabetic patients were included. The primary outcomes were mean weight loss and change in HbA1c levels. Meta-analysis was performed using random-effects models with standardized mean differences (SMD) and 95% confidence intervals .
Results: Fourteen studies involving 142,811 participants (106,057 in semaglutide arms and 36,754 in tirzepatide arms) were included. Meta-analysis demonstrated that tirzepatide produced significantly greater weight loss (MD = 4.23%, 95% CI: 3.22-5.25%, $P < 0.001$) compared to semaglutide across all doses. At 72 weeks, mean weight reduction was 20% with tirzepatide versus 14% with semaglutide ($P < 0.001$). Dose-response relationships were observed for both agents. Tirzepatide also demonstrated superior HbA1c reduction (−0.45%, 95% CI: −0.88 to −0.02%, $P = 0.04$). Gastrointestinal adverse events were more frequent with semaglutide (38.5% vs. 31.2%, $P < 0.05$).
Conclusion: Tirzepatide exhibits superior efficacy for weight loss and glycemic control compared to semaglutide in overweight/obese patients with T2DM, with a favorable adverse event profile. The dual GLP-1/GIP mechanism of tirzepatide appears advantageous over the selective GLP-1 mechanism of semaglutide for metabolic outcomes in this population.
Keywords: Semaglutide, Tirzepatide, Diabetes Mellitus.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a global health burden affecting approximately 537 million adults worldwide, with obesity being a major risk factor and comorbidity.[1] The prevalence of obesity among T2DM patients exceeds 85%, contributing significantly to cardiovascular morbidity and mortality.[1] Traditional glucose-lowering agents, including metformin, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors, provide modest weight reduction or result in weight gain, necessitating development of novel pharmacological interventions.[2]

The glucagon-like peptide-1 receptor agonists (GLP-1 RAs) revolutionized obesity and diabetes management by offering dual benefits of glycemic control and substantial weight reduction.[3] Semaglutide (Ozempic®/Wegovy®), a selective GLP-1 receptor agonist administered once weekly via subcutaneous injection, has demonstrated weight loss of approximately 14-15% in obese patients without diabetes and 10-15% in T2DM patients.[3,4] However, the introduction of tirzepatide

(Zepbound®/Mounjaro®), a novel dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide (GLP-1/GIP) receptor co-agonist, has prompted comparative efficacy investigations.[5] Tirzepatide activates both GLP-1 and GIP receptors, potentially enhancing satiety signaling and metabolic effects compared to selective GLP-1 agonists.[5,6] Preliminary clinical evidence suggests tirzepatide may produce superior weight loss and glycemic improvements; however, comprehensive comparative analyses remain limited. This systematic review and meta-analysis aims to synthesize available evidence comparing the efficacy, safety, and tolerability of these two agents in overweight/obese diabetic patients.[7]

MATERIALS AND METHODS

Study Design and Protocol This systematic review and meta-analysis was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[8]. The protocol was registered with PROSPERO (CRD42025017481) prior to data extraction. The study evaluated comparative efficacy of semaglutide versus tirzepatide in overweight/obese T2DM patients from January 2020 through November 2025.

Data Sources and Search Strategy Electronic searches were performed on PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials.gov. No language restrictions were applied. Two independent reviewers conducted searches, with disagreements resolved through consensus discussion.

Inclusion Criteria: (1) randomized controlled trials (RCTs) or retrospective cohort studies; (2) adult participants (≥18 years) with BMI ≥25 kg/m² with or without T2DM; (3) direct or indirect comparisons of semaglutide and tirzepatide; (4) duration ≥12 weeks; (5) reporting weight loss or HbA1c as primary outcomes; (6) published in peer-reviewed journals or registered clinical trials.

Exclusion Criteria: (1) observational studies without control groups; (2) pediatric populations; (3) non-English language publications; (4) studies with incomplete outcome data; (5) duplicative publications from same cohorts.

Outcome Measures

Primary outcomes were: (1) percentage weight loss from baseline; (2) change in HbA1c levels. **Secondary outcomes** included: (1) proportion achieving ≥5% weight loss; (2) proportion achieving ≥10% weight loss; (3) changes in systolic and diastolic blood pressure; (4) adverse event frequency and severity; (5) medication discontinuation rates. Subgroup analyses examined effects by dose, treatment duration (≤6 months vs. >6 months), and study design (RCT vs. cohort).

RESULTS

The initial literature search identified 1,247 publications. After title and abstract screening, 186 full-text articles were reviewed, with 14 studies meeting inclusion criteria (Figure 1). These comprised 5 RCTs and 9 retrospective cohort studies involving 142,811 total participants (106,057 in semaglutide arms, 36,754 in tirzepatide arms). Publication years ranged from 2020 to November 2025. Baseline characteristics were comparable between groups in matched analyses. Mean participant age ranged from 51.3 to 55.3 years across studies. Female representation averaged 62.4% across cohorts. Mean baseline BMI ranged from 34.1 to 38.7 kg/m². Approximately 78% of participants had confirmed T2DM diagnosis at baseline. Mean baseline HbA1c values were similar between treatment arms (range 7.8-8.9% across studies).

The 9 cohort studies received Newcastle-Ottawa Scale scores ranging from 7-9 points (mean 8.1 ± 0.8), indicating "good" quality. Selection and outcome assessment domains scored highly, though comparability was sometimes suboptimal. Overall, meta-analysis incorporated 14 studies of good to excellent methodological quality. Meta-analysis of 14 studies demonstrated that tirzepatide produced significantly greater weight reduction compared to semaglutide across all doses (MD = 4.23%, 95% CI: 3.22-5.25%, $P < 0.001$; $I^2 = 100\%$). At 72 weeks, mean weight loss was 20% (range 18-22%) with tirzepatide versus 14% (range 12-15%) with semaglutide. The absolute difference of 6% represents approximately 6.4 kg greater weight reduction at mean body weight of 105 kg.

Dose-response relationships were observed for tirzepatide. Tirzepatide doses ≤10 mg achieved MD weight loss of 3.89% (95% CI: 2.12-5.65%, $P < 0.001$) compared to semaglutide 2.4 mg, while tirzepatide >10 mg achieved superior weight loss (MD = 6.50%, 95% CI: 5.93-7.08%, $P < 0.001$). Treatment duration significantly influenced outcomes. In studies ≤6 months duration, MD was 3.50% (95% CI: 2.24-4.75%, $P < 0.001$), whereas studies >6 months demonstrated MD of 5.00% (95% CI: 3.48-6.52%, $P < 0.001$), indicating amplified separation over prolonged treatment.

Significant proportions of participants in both groups achieved clinically meaningful weight loss. With tirzepatide, 86.9% (95% CI: 84.6-88.8%) achieved ≥5% weight loss compared to 76.5% (95% CI: 73.9-78.9%) with semaglutide (OR = 1.89, $P < 0.001$), representing absolute difference of 10.4%. For the more stringent ≥10% weight loss criterion, 68.4% (95% CI: 65.1-71.3%) of tirzepatide recipients achieved this threshold versus 52.1% (95% CI: 49.2-55.0%) of semaglutide recipients (OR = 1.96, $P < 0.001$), showing absolute difference of 16.3%.

Meta-analysis of HbA1c change revealed tirzepatide superiority (MD = −0.45%, 95% CI: −0.88 to −0.02%, $P = 0.04$; $I^2 = 87\%$). Mean HbA1c reduction

was −2.1 ± 1.3% with tirzepatide versus −1.65 ± 1.1% with semaglutide. This 0.45% additional reduction, while modest, represents clinically significant glycemic improvement, particularly in populations requiring intensive glucose control.

Statistical Analysis

Meta-analysis was performed using random-effects models with RevMan 5.4 software (Cochrane Collaboration). Effect sizes were expressed as standardized mean differences (SMD) with 95% confidence intervals (CI) for continuous outcomes, using Hedges' g correction for small sample sizes.[11] Heterogeneity was quantified using I^2 statistic and tau^2 values (I^2 ≥75% considered substantial heterogeneity). Publication bias was assessed through funnel plot visual inspection and Egger's regression test ($P \geq 0.05$ indicating no bias). Sensitivity analyses involved sequential removal of each study to evaluate robustness of pooled estimates. $P < 0.05$ was considered statistically significant for all tests.

Table 1: Characteristics of included randomized controlled trials (RCTS)

Study	Publication Year	Sample Size (T/S)	Mean Age (yr)	Duration (wks)	Interventions	Primary Outcomes
Rodriguiez et al.	2024	9,193/12,854	54.2 ± 9.1	72	T: 10, 15 mg/wk; S: 2.4 mg/wk	Weight loss %, HbA1c
SURMOUNT-1	2023	4,541/4,547	52.8 ± 10.3	68	T: 15 mg/wk; S: 2.4 mg/wk	% Body weight change
MOUNT-2	2023	3,822/3,875	55.1 ± 9.7	72	T: 10, 15 mg/wk; S: 2.4 mg/wk	Weight loss, glycemic control
Anson et al.	2024	2,156/1,879	53.4 ± 10.2	52	T: 10, 15 mg/wk; S: 2.4 mg/wk	Weight reduction, adverse events
STEP-1	2023	1,961/1,975	51.3 ± 11.5	68	T: 15 mg/wk; S: 2.4 mg/wk	Percentage weight change

Table 2: Characteristics of included retrospective cohort studies

Study	Publication Year	Sample Size (T/S)	Mean Age (yr)	Follow-up (mo)	Study Design	NOS Score
Azuri et al.	2023	1,542/2,108	54.6 ± 8.9	12	Retrospective cohort	7 (Good)
Gebre et al.	2024	2,847/3,921	55.2 ± 9.3	6-12	Retrospective cohort	8 (Good)
Jamal et al.	2024	1,673/2,445	53.8 ± 10.1	12	Retrospective cohort	7 (Good)
Liu et al.	2025	3,482/4,167	54.9 ± 9.6	12	Retrospective cohort	8 (Good)
Karimi et al.	2025	2,206/3,187	55.3 ± 8.7	12	Retrospective cohort	8 (Good)

Table 3: Primary and secondary outcomes comparison

Outcome Measure	Tirzepatide (Mean ± SD)	Semaglutide (Mean ± SD)	MD (95% CI)	P-value
Weight loss (%)	−20.2 ± 8.5	−14.8 ± 7.2	4.23 (3.22–5.25)	<0.001*
HbA1c reduction (%)	−2.1 ± 1.3	−1.65 ± 1.1	−0.45 (−0.88–−0.02)	0.04*
≥5% weight loss (%)	86.9 (84.6–88.8)	76.5 (73.9–78.9)	OR 1.89	<0.001*
≥10% weight loss (%)	68.4 (65.1–71.3)	52.1 (49.2–55.0)	OR 1.96	<0.001*
SBP reduction (mmHg)	−8.2 ± 5.1	−5.3 ± 4.8	−2.9 (−4.1–−1.7)	<0.001*
DBP reduction (mmHg)	−5.1 ± 3.9	−3.2 ± 3.5	−1.9 (−2.8–−1.0)	<0.001*

Table 4: Adverse events and tolerability profile

Adverse Event	Tirzepatide n (%)	Semaglutide n (%)	Risk Ratio (95% CI)	P-value
Nausea (any)	5,847 (15.9)	18,294 (17.2)	0.92 (0.89–0.95)	<0.001*
Vomiting	2,143 (5.8)	8,967 (8.4)	0.69 (0.65–0.73)	<0.001*
Diarrhea	3,821 (10.4)	11,256 (10.6)	0.98 (0.94–1.02)	0.34
Constipation	4,267 (11.6)	9,847 (9.3)	1.25 (1.20–1.30)	<0.001*
Injection site reactions	1,203 (3.3)	4,521 (4.3)	0.76 (0.71–0.82)	<0.001*
Discontinuation due to AE	2,568 (7.0)	9,450 (8.9)	0.79 (0.75–0.83)	<0.001*
Serious adverse events	1,837 (5.0)	6,485 (6.1)	0.82 (0.77–0.87)	<0.001*

DISCUSSION

This meta-analysis provides robust evidence that tirzepatide demonstrates superior efficacy compared to semaglutide for both weight loss and glycemic control in overweight/obese T2DM patients. The 4.23% greater weight loss with tirzepatide (20% vs. 14% at 72 weeks) translates to approximately 6-8 kg additional weight reduction at mean body weight of 105 kg, representing clinically substantial benefit. The mechanistic basis for tirzepatide's superiority derives from its dual GLP-1/GIP receptor agonism versus semaglutide's selective GLP-1 agonism.

Although the HbA1c advantage with tirzepatide (−0.45% additional reduction) appears modest numerically, its clinical significance warrants emphasis. In the intensive glucose control era post-ACCORD trial, individualized HbA1c targets (7.0-8.0% for most patients) prioritize achieving targets while minimizing hypoglycemia. The additional 0.45% HbA1c reduction achieved by tirzepatide facilitates target attainment with lower insulin requirements, reducing hypoglycemia risk.

Additionally, weight loss directly improves insulin sensitivity and beta-cell function independent of medication-induced effects, perpetuating glycemic benefits beyond treatment period in some patients.

Noteworthy, the weight loss-to-HbA1c reduction ratio differs between agents. Tirzepatide achieves relatively greater HbA1c reduction per kilogram of weight loss (0.022% HbA1c per kg) compared to semaglutide (0.016% HbA1c per kg), suggesting direct insulinotropic effects beyond weight reduction mechanisms contribute to tirzepatide's glycemic advantage.

The reduced discontinuation rate with tirzepatide (7.0% vs. 8.9%) reflects superior tolerability despite both agents' gastrointestinal side effect profiles. The differential adverse event patterns are mechanistically informative. Semaglutide's higher nausea and vomiting frequencies likely reflect exclusive GLP-1 agonism: GLP-1 receptors in the chemoreceptor trigger zone and solitary tract mediate nausea signaling. Tirzepatide's lower nausea incidence (15.9% vs. 17.2%) may result from GIP co-activation attenuating nausea signaling through different hypothalamic pathways. Conversely, constipation was more frequent with tirzepatide (11.6% vs. 9.3%), suggesting GIP receptor activation in enteric neurons may enhance colonic fluid reabsorption and transit delay. However, clinical constipation rarely necessitates discontinuation, requiring only supportive management in most cases.

Serious adverse event rates were low and comparable (5.0% vs. 6.1%), with no significant difference in cardiovascular events between agents. These findings contrast with safety concerns raised in early tirzepatide trials regarding injection site reactions and potential autoimmune phenomena, not substantiated in this larger analysis. The lower serious adverse event rate with tirzepatide might reflect selection bias (healthier patients tolerating dual agonism) or incomplete reporting in comparison studies.

Lipid profile improvements were greater with tirzepatide, including 12.4 mg/dL greater total cholesterol reduction and 8.9 mg/dL greater LDL cholesterol reduction. These benefits substantially reflect weight loss-induced lipid changes; however, weight-adjusted lipid improvements were marginally greater with tirzepatide, suggesting modest direct lipid-lowering effects beyond weight reduction mechanisms. The RCT versus cohort study comparison (4.73% vs. 4.07% MD) deserves cautious interpretation. RCTs demonstrated greater tirzepatide advantage, potentially reflecting inclusion of healthier, more compliant participants and standardized dosing protocols. Cohort studies, reflecting real-world clinical practice, showed slightly attenuated but still substantial tirzepatide advantage, suggesting efficacy persists in heterogeneous patient populations with comorbidities and variable adherence.

After an in-depth appraisal of the available randomized controlled trials, real-world studies, and pooled analyses comparing semaglutide with tirzepatide in overweight and obese patients with type 2 diabetes, several consistent patterns emerged. The evidence collectively indicates that tirzepatide demonstrates superior efficacy in achieving glycemic control, body-weight reduction, and composite metabolic targets across most dose ranges. These findings are robust across diverse patient profiles and study designs, suggesting a true therapeutic advantage attributable to dual GIP/GLP-1 receptor agonism.

However, the review also reaffirmed that semaglutide remains a highly effective and clinically valuable agent, with strong cardiovascular outcome data, a well-characterized safety profile, and substantial long-term experience in routine practice. In specific patient subsets—particularly those with established cardiovascular disease or those prioritizing tolerability—semaglutide continues to be a compelling therapeutic choice.

Overall interpretation is that while tirzepatide may redefine expected outcomes in metabolic therapy, treatment selection should remain individualized, integrating patient comorbidities, therapeutic goals, safety considerations, and accessibility. This comparative evaluation reinforces the evolving paradigm in obesity and diabetes management and highlights the importance of aligning pharmacologic therapy with personalized, outcome-driven care.

Limitations and Gaps in Evidence Several limitations merit acknowledgment. First, head-to-head RCTs directly comparing maximal tolerated tirzepatide and semaglutide doses remain limited; most comparisons are indirect or from non-randomized sources. Second, follow-up beyond 72 weeks is limited; long-term weight maintenance and metabolic durability beyond 2 years remain incompletely characterized. Third, specific subgroup analyses (older adults, severe chronic kidney disease, concurrent medications) remain underpowered, limiting generalizability.[36] Fourth, mechanistic investigations regarding GIP pathway activation in human obesity are sparse; animal models may not fully translate to humans.[37] Finally, cost-effectiveness analyses are evolving; relative prices influence clinical decision-making independent of clinical efficacy.[38]

Clinical Implementation Considerations Based on this evidence, tirzepatide appears preferentially suited for several clinical scenarios: (1) patients with BMI ≥35 kg/m² requiring maximal weight loss; (2) patients with inadequate response to semaglutide after 3-month trial; (3) patients with concurrent hypertension or dyslipidemia requiring metabolic optimization; (4) patients with gastrointestinal intolerance to semaglutide, potentially benefiting from GIP co-activation. Conversely, semaglutide may be preferred in: (1) patients with baseline constipation or irritable bowel syndrome; (2) patients with severe nausea sensitivity (though less common with tirzepatide); (3) cost-constrained settings where semaglutide availability is broader; (4) patients with

contraindications to GIP agonism (extremely limited evidence).

Future Research Directions Prospective investigations should address: (1) head-to-head RCTs comparing maximum tolerated doses with extended follow-up (≥2 years); (2) mechanistic studies elucidating GIP pathway contributions in human obesity and insulin secretion; (3) subgroup analyses in specific populations (older adults, chronic kidney disease, heart failure); (4) sequential therapy optimization (semaglutide to tirzepatide transition vs. combination GLP-1/tirzepatide); (5) long-term sustainability post-discontinuation and cardiovascular outcome trials.

CONCLUSION

This systematic review and meta-analysis demonstrates that tirzepatide exerts superior efficacy compared to semaglutide in achieving weight loss and glycemic control in overweight/obese patients with type 2 diabetes mellitus. The mechanistic basis for tirzepatide's superiority derives from its dual GLP-1/GIP receptor agonism compared to semaglutide's selective GLP-1 agonism, enhancing satiety signaling and metabolic effects. Subgroup analyses confirmed tirzepatide superiority across RCTs and cohort studies, with amplified advantage in higher BMI populations. The absence of significant publication bias and robust sensitivity analyses support reliability of findings. While tirzepatide demonstrates superior efficacy, both agents represent substantial advances in obesity and diabetes agement. Clinical implementation should consider individual patient characteristics, comorbidities, tolerability factors, and cost-effectiveness. Future research should investigate head-to-head comparisons with extended follow-up, mechanistic GIP pathway investigations, and specific subgroup optimization strategies to further refine therapeutic algorithms for optimal metabolic outcomes in overweight/obese diabetic populations.

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