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Beyond Weight Loss: Comparative Efficacy, Safety, and Cardiometabolic Effects of Tirzepatide versus Semaglutide — A Systematic Review and Meta-Analysis

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ABSTRACT/BACKGROUND

Obesity and type 2 diabetes mellitus (T2DM) are chronic metabolic disorders associated with increased cardiovascular morbidity and mortality. Incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1RAs), have transformed metabolic disease management. Semaglutide has demonstrated robust efficacy in weight reduction and cardiovascular risk reduction, whereas tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, has emerged as a potentially superior metabolic therapy.

Methods: A systematic review and meta-analysis was conducted following PRISMA guidelines. PubMed, Embase, Cochrane Library, and Scopus were searched up to February 2026. Randomized controlled trials and comparative observational studies evaluating tirzepatide versus semaglutide were included. Outcomes included weight reduction, HbA1c reduction, cardiometabolic parameters, and adverse events.

Results: Tirzepatide demonstrated significantly greater weight reduction compared to semaglutide (mean difference − 4.5% to − 5.2%) and superior HbA1c reduction.[1-3] Both agents improved lipid parameters and blood pressure. However, semaglutide demonstrated more robust evidence for cardiovascular event reduction in large outcome trials.[12-14] Gastrointestinal adverse effects were the most common in both groups with comparable discontinuation rates.[4-6]

Conclusion: Tirzepatide provides superior metabolic efficacy, while semaglutide retains stronger cardiovascular outcome evidence. Therapeutic selection should be individualized based on patient comorbidities and clinical priorities.

INTRODUCTION

Obesity has become one of the most significant global health challenges, affecting more than 650 million adults

worldwide and contributing substantially to morbidity, mortality, and healthcare burden.[7–9] It is strongly associated with insulin resistance, T2DM, dyslipidemia, hypertension, and cardiovascular disease (CVD), forming a complex cardiometabolic syndrome that requires multifaceted therapeutic strategies.

Traditional pharmacological approaches to obesity have demonstrated limited long-term effectiveness. The emergence of incretin-based therapies has fundamentally changed the treatment landscape. GLP-1 receptor agonists enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying, and promote satiety, thereby improving both glycemic control and body weight.[10,11]

Semaglutide, a long-acting GLP-1 receptor agonist, has shown significant efficacy in weight reduction and cardiovascular outcomes in large-scale trials including STEP, SUSTAIN, and SELECT programs.[3,12–14] Its role in reducing major adverse cardiovascular events (MACE) has established it as a cornerstone therapy in patients with T2DM and obesity.

Tirzepatide is a novel dual GIP and GLP-1 receptor agonist that enhances insulin secretion and metabolic regulation through complementary incretin pathways.[1,2] Clinical trials including SURPASS and SURMOUNT have demonstrated unprecedented weight loss and glycemic improvements, surpassing those observed with GLP-1 monotherapy.[1,17]

Despite these advances, direct comparative evidence between tirzepatide and semaglutide remains limited. This systematic review aims to synthesize current evidence regarding their comparative efficacy, safety, and cardiometabolic outcomes.

METHODS

This systematic review followed PRISMA 2020 guidelines.[19] A comprehensive search of PubMed, Embase, Scopus, and Cochrane Library was performed using keywords including “tirzepatide,” “semaglutide,” “GLP-1 receptor agonist,” “GIP,” “obesity,” and “type 2 diabetes mellitus.”

Eligibility Criteria

Included studies met the following criteria:

- Randomized controlled trials or observational studies
- Direct or indirect comparison of tirzepatide and semaglutide
- Adult patients with obesity or T2DM
- Reported outcomes including weight loss, HbA1c, cardiometabolic markers, or adverse events

Data Extraction and Quality Assessment

Two independent reviewers extracted data. Risk of bias was assessed using Cochrane RoB-2 tool for RCTs and Newcastle-Ottawa Scale for observational studies.[20]

Statistical Analysis

A random-effects model was used to account for heterogeneity. Outcomes were expressed as mean differences (MD) or odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Study Characteristics

A total of 11 studies involving approximately 27,800 participants were included. Study duration ranged from 24 to 72 weeks.[1–3,15–18]

Primary Outcomes Weight Loss

Tirzepatide demonstrated significantly greater weight loss compared to semaglutide across all studies. Mean weight reduction ranged from −11.5% to −20.9% with tirzepatide versus −7.0% to −15.0% with semaglutide.[1–3]

Patients receiving tirzepatide were more likely to achieve ≥10% and ≥15% weight loss thresholds (OR 2.3 and OR 2.8 respectively).[1] This superior effect is attributed to dual GIP/GLP-1 receptor activation, which enhances satiety and energy homeostasis.[10,24]

Glycemic Control

Tirzepatide achieved greater HbA1c reduction compared to semaglutide. Mean reductions ranged from −2.0% to −2.4% versus −1.3% to −1.8% with semaglutide.[1,15] This reflects enhanced insulin secretion and improved beta-cell responsiveness via GIP signaling.[24]

Secondary Outcomes

Lipid Profile and Blood Pressure

Both therapies improved lipid parameters, including reductions in LDL cholesterol and triglycerides. [25] Tirzepatide demonstrated slightly greater triglyceride reduction. Systolic blood pressure reductions ranged between 4–8 mmHg in both groups.[26]

Cardiovascular Outcomes

Semaglutide has demonstrated significant reduction in major adverse cardiovascular events (MACE) in the SUSTAIN-6 and SELECT trials.[12–14] These findings support its established cardioprotective role.

In contrast, tirzepatide has shown favorable metabolic and surrogate cardiovascular improvements but lacks definitive long-term outcome data.[1,2]

Safety and Tolerability

Both agents demonstrated similar safety profiles. Gastrointestinal adverse effects (nausea, vomiting, diarrhea) were the most common events and were dose-dependent.[4–6] Discontinuation rates were comparable between groups.

Serious adverse events such as pancreatitis and gallbladder disease were rare and similar across both therapies.[30]

DISCUSSION

This systematic review demonstrates that tirzepatide provides superior weight loss and glycemic control compared to semaglutide. The magnitude of weight reduction observed with tirzepatide approaches outcomes seen in bariatric surgery populations, highlighting its clinical significance.[27]

The mechanistic advantage of tirzepatide lies in dual incretin receptor activation. GIP enhances insulin sensitivity and lipid metabolism, while GLP-1 reduces appetite and gastric emptying. Their synergistic effect leads to amplified metabolic benefits.[10,24]

However, semaglutide retains a critical advantage in cardiovascular outcome evidence. The SELECT trial demonstrated significant reduction in MACE in obese individuals without diabetes.[14] Therefore, semaglutide remains the preferred agent in patients with established cardiovascular disease.

Clinical decision-making should be individualized. Tirzepatide may be preferred for patients requiring maximal weight loss and glycemic control, while semaglutide may be prioritized in those with high cardiovascular risk.

LIMITATIONS

This review is limited by heterogeneity among included studies, relatively short follow-up durations, and absence of long-term head-to-head cardiovascular outcome trials.

CONCLUSION

Tirzepatide demonstrates superior efficacy in weight reduction and glycemic control compared to semaglutide. However, semaglutide remains superior in cardiovascular outcome evidence. Future long-term randomized trials are needed to define their comparative cardiometabolic benefits.

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