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A Review of Metabolic Health Outcomes of Tirzepatide vs Semaglutide in Obesity and Type 2 Diabetes

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Abstract

Introduction: Obesity and type 2 diabetes mellitus are a growing global concern, prompting the development of pharmacological intervention to complement traditional lifestyle approaches for long-term management strategies of these diseases. This literature aims to compare the efficacy of Tirzepatide, a dual agonist for glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) and Semaglutide, a GLP-1 receptor agonist, for weight loss, lipid metabolism, and glycemic control.

Methods: A literature review was conducted using PubMed to identify human studies published after 2000 on the effects of Tirzepatide and Semaglutide. Search terms for relevant articles included "Tirzepatide", "Semaglutide", "risk of obesity and metabolic disease", and "lipid metabolism Semaglutide versus Tirzepatide".

Results: Evidence from multiple clinical trials including SURMOUNT-5, SURPASS-2, and retrospective cohort studies, concluded Tirzepatide outperformed Semaglutide in several metabolic domains. Greater weight loss was observed with Tirzepatide (22.8 kg +/- 0.7 kg) compared to Semaglutide (15.0 kg +/- 1.3 kg), as well as greater reductions in waist circumference. Furthermore, Tirzepatide demonstrated superior improvements in lipid metabolism, with greater reductions in VLDL and triglycerides, and increased HDL levels. Glycemic control was greater improved with Tirzepatide, as indicated by greater reductions in HbA1c, fasting glucose levels, and a higher proportion of patients reaching normoglycemia.

Discussion: Tirzepatide's dual GLP-1 and GIP receptor activation results in synergetic effects – enhancing multiple physiological pathways, including appetite regulation and insulin sensitivity, leading to improved metabolic outcomes. Limitations exist due to lack of high dose comparison, long-term safety data, and limited real-world evidence.

Conclusion: Tirzepatide demonstrates superior outcomes in comparison to Semaglutide in terms of weight loss, lipid metabolism, and glycemic control, making it a promising pharmacological option for individuals with obesity and type 2 diabetes.

Keywords: tirzepatide; semaglutide; metabolic health; lipid metabolism; glycemic control; incretin based therapies; GLP-1; GLP-1/GIP

Introduction

Obesity is a growing global concern, with prevalence rates having doubled or tripled in many countries over the past three decades [1]. This epidemic is associated with increased rates of type 2 diabetes, insulin resistance, hyperlipidemia, and metabolic syndrome in both children and adults [1]. While lifestyle interventions including diet and exercise are foundational, long-term weight loss maintenance remains challenging, with high rates of weight regain over time [2]. Obesity results from an energy imbalance—where caloric intake consistently exceeds energy expenditure, defined as the total energy required to sustain physiological functions over a given period [2, 3]. Weight gain is also influenced by a combination of genetic, behavioral, environmental, and hormonal factors [2]. Similarly, rates of type two diabetes have increased globally, being classified as one of the most common metabolic diseases worldwide [4, 5]. In the US reported incidence of new onset diagnosed diabetes has increased 90% in the last decade [4]. Type two diabetes occurs via two main factors: defective insulin secretion by pancreatic beta cells, and insulin-sensitive tissues being unable to respond to insulin [5]. Consequently, pharmacological interventions are increasingly recognized for long-term diabetes and obesity management. Tirzepatide, a novel dual agonist for glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), is used to treat type 2 diabetes mellitus and promote weight loss [6]. GIP and GLP-1 are incretin hormones, released in the intestine in response to nutrient intake and stimulate pancreatic beta cell activity to help augment insulin release [7]. Additionally, these hormones are expressed in regions of

the brain which regulate food intake and delay gastric emptying [7]. Tirzepatide's dual receptor activation is thought to offer enhanced metabolic benefits, including improved glycemic control and weight reduction, versus GLP-1 agonism (i.e., Semaglutide), due to the complementary and synergetic effects of the two incretin pathways [6]. Conversely, Semaglutide is a glucagon-like peptide (GLP-1) agonist used for glycemic control and weight loss [8]. Semaglutide primarily activates GLP-1 receptors in the GI tract, pancreas and brain to enhance glucose-dependent insulin secretion, slow gastric emptying, increase pancreatic beta cell proliferation, and reduce glucagon release [8]. Semaglutide interacts with GLP-1 receptors in the hypothalamus to mitigate senses of hunger and enhance feelings of satiety [8]. This literature compares the effects of Trizepatide and Semaglutide on weight management, lipid metabolism, and glucose homeostasis to dictate their clinical implications on metabolic diseases based on their different mechanisms of action. While the effects of Semaglutide are well established, the full effects of Trizepatide are actively being investigated.

Methods

A literature search was conducted on the database PubMed. Search terms included:"Tirzepatide and metabolic health"; "Tirzepatide and glucose metabolism"; "Tirzepatide use for weight loss"; "Tirzepatide "; "Semaglutide";"Tirzepatide for lipid metabolism"; "risk of obesity and metabolic disease"; "global prevalence of obesity"; "weight loss and maintenance strategies"; "glycemic control in Tirzepatide vs Semaglutide"; "glucose homeostasis in Tirzepatide vs Semaglutide"; and "Lipid Metabolism Tirzepatide vs Semaglutide";. Selection criteria were as follows: (1) English language; (2) Primary Research article; (3) published between 2000-2025; and (4) Human Studies (see Figure 1).

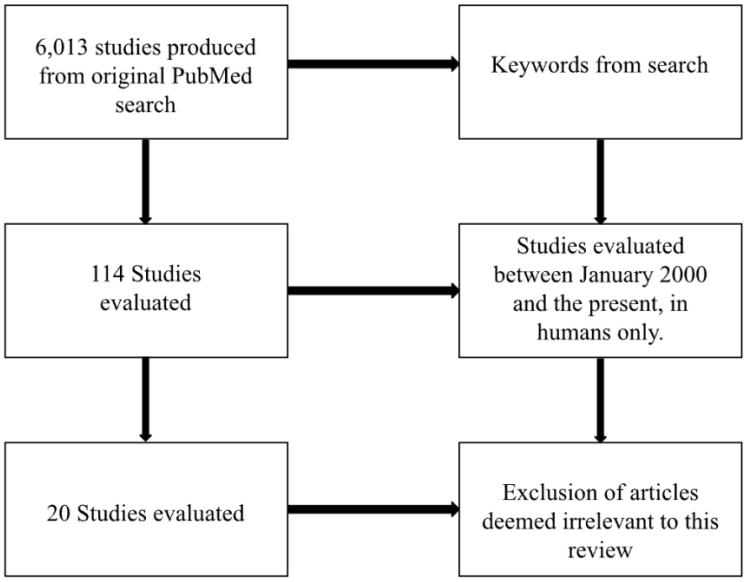

Figure 1. Search Strategy and Article Selection Process. This figure was created using Google Drawings.

Results

Weight Loss Implications

Across several clinical trials, Tirzepatide has demonstrated superior weight reduction outcomes compared to Semaglutide [9, 10, 11]. In the SURMOUNT-5 trials, patients receiving a 10- or 15mg dose of Tirzepatide lost an average of 22.8 kg, while those receiving Semaglutide at a dose of 1.7- or 2.4 mg lost 15.0 kg [9]. Additionally, changes in recorded waist circumference found an average loss of 18.4 cm with Tirzepatide and 13.0 cm with Semaglutide [9]. The results indicate Tirzepatide's superiority for both reduction in weight and waist circumference [9]. In SURPASS-2 trials, Tirzepatide at 5-, 10-, or 15 mg showed mean reductions of body weight of 7.6 kg, 9.3 kg, and 11.2 kg respectively, compared to 5.7 kg with 1 mg of Semaglutide [10]. Similar results were obtained from Rodriguez's et al. retrospective cohort study [11]. After 365 days of intravenous injections of 5.0 mg of Tirzepatide, 81.8% of patients experienced ≥5% weight loss, 62.1% experienced ≥10% weight loss, and 42.3% achieved ≥15% weight loss [11]. Compared to 0.5mg of Semaglutide, 66.5% of patients experienced ≥5% weight loss, 37.1% experienced ≥10% weight loss, and 18.1% achieved ≥15% weight loss [11].

Improvements in Lipid Metabolism

Lipid metabolism is characterized as the synthesis, breakdown, and storage of fats (lipids) within cells [12]. Both Semaglutide and Tirzepatide have demonstrated improvements in lipid profiles, though Tirzepatide

exhibited more pronounced benefits across several profiles [10]. SURPASS-2 trials indicated that patients receiving Tirzepatide displayed triglyceride level reductions of 19.0% at 5 mg, 24.1% at 10 mg, and 24.8% at 15 mg, compared to an 11.5% reduction with 1 mg of Semaglutide [10]. Similar results were obtained for very-low-density lipoproteins (VLDL) with reductions of 17.5%, 23.1%, and 27.3% observed for Tirzepatide at 5 mg, 10 mg, and 15 mg respectively, in contrast to a loss of 11.1% for Semaglutide [10]. High-density lipoprotein cholesterol, increased across all doses of Tirzepatide, including 6.8% at 5mg, 7.9% at 10 mg, and 7.1% at 15 mg, versus 4.4% with 1 mg Semaglutide [10]. However, total cholesterol and low-density lipoprotein (LDL) cholesterol, did not differ significantly between treatment groups [10]. Total cholesterol levels were lowered slightly in both groups with Tirzepatide, showing reductions of 5.5% to 6.3% across doses of 5-, 10-, and 15 mg, compared to 4.3% with 1mg Semaglutide [10]. Similar results were observed with LDL, with reductions ranging from 5.2% to 7.7% for all Tirzepatide doses (5- to 15 mg), versus 6.4% for 1 mg Semaglutide [10]. The greater improvements in VLDL, HDL, and triglycerides with Tirzepatide indicated improved long-term cardiovascular benefits especially for those with metabolic syndrome compared to Semaglutide, providing greater positive secondary outcomes. Although, changes in LDL and total cholesterol were minor, the overall lipid profile improvement supports Tirzepatide as a more effective agent for lipid metabolism.

Glycemic Control and HbA1c Reduction

Tirzepatide demonstrated greater efficacy than Semaglutide in both lowering HbA1c and aiding in glycemic regulation [9, 10, 13]. Gebre et al. demonstrated Semaglutide users improved an average of 0.40% in HbA1c, while Trizepatide users experienced a 0.67% improvement [13]. SURPASS-2 Investigators determined glycated hemoglobin levels (A1c) decreased 2.01, 2.24, and 2.30 points for 5mg, 10mg, and 15mg of Tirzepatide, respectively, compared to 1.86 points with 1mg Semaglutide [10]. Further, a greater percentage of patients using Tirzepatide reached significant HbA1c targets, with 82-86% of patients reached glycated hemoglobin levels below 7%, compared to 79% of patients receiving Semaglutide; 69-80% of patients reached glycated hemoglobin levels of ≤6.5% versus 64% of patients receiving Semaglutide; and 27-46% of patients reached HbA1c levels less than 5.7% (normoglycemia) compared to only 19% of patients in the Semaglutide group [10]. Moreover, the study indicated changes in fasting blood glucose [10]. Patients began the trial with an average fasting serum glucose of 173mg/DL, and over the trial's four weeks, a rapid decline in fasting glucose was observed [10]. Ending glucose levels were, on average, 109.6 mg/DL, 111.3 mg/DL, and 117.0 mg/DL for 15 mg, 10 mg, and 5 mg of Tirzepatide, respectively, compared to 124.4 mg/DL of Semaglutide [10]. Reductions in daily 2-hour postprandial glucose levels ranged from -71.6 to -81.9 mg/dL with 5- to 15 mg of Tirzepatide and 67.2 mg/dL with 1 mg of Semaglutide [10]. Although data was not provided, SURMOUNT-5 trials indicated glycated hemoglobin and fasting serum glucose improved with both treatment trials, with results consistent with previous trials [9]. The increased glycemic control seen by Tirzepatide groups can aid in reduction of long-term diabetic complications and may allow more patients to reach normoglycemia.

Table 1. Summary of Tirzepatide and Semaglutide's Physiological Effects

Outcome	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1-2.4 mg
Weight loss (kg)	-7.6 [10]	-9.3 [10]	-11.2 [10]	-5.7 [10]
Waist Circumference (cm)			-18.4 [9]	-13.0 [9]
Triglyceride Reduction	-19.0% [10]	-24.1% [10]	-24.8% [10]	-11.5% [10]
VLDL Reduction	-17.5% [10]	-23.1% [10]	-27.3% [10]	-11.1% [10]
HDL increase	6.8% [10]	7.9% [10]	7.1% [10]	4.4% [10]
HbA1c Reduction (points)	-2.01[10]	-2.24 [10]	-2.30 [10]	-1.86 [10]
Fasting Glucose (mg/dL)	117.0 [10]	111.3 [10]	109.6 [10]	124.4 [10]

Discussion

The literature review highlights the efficacy differences of incretin mimetics regarding weight management and improving glucose homeostasis, with Tirzepatide demonstrating superior clinical outcomes across all parameters. These findings support the growing need for effective long-term pharmacological interventions for maintaining weight loss and treating type 2 diabetes, given resistance to lifestyle-based interventions.

Across multiple clinical trials Tirzepatide demonstrated greater weight reduction results verus Semaglutide [9, 10, 11]. SURMOUNT-5 and SURPASS-2 trials produced up to a 22.8 kg weight loss for some doses of Tirzepatide compared to 15 kg with Semaglutide [9].

Furthermore, waist circumference reductions were higher with Tirzepatide, indicating not just superior weight loss but more significant loss of visceral fat, a major driver for metabolic disease [9, 14]. The dual agonism of Tirzepatide of both GLP-1 and GIP receptors can explain the difference because it allows it to engage in additional physiological pathways. GLP-1 activation – a shared property of both drugs – leads to suppression of appetite within the hypothalamus and induces peripheral satiety by reducing gastric emptying [15]. Further, the synergetic effects of GIP activation regulates energy balance through cell surface receptor signalling in adipose tissue and the brain, aiding in increased energy expenditure and further decreased appetite [15]. GIP activation is thought to enhance the hypothalamic satiety signalling initiated by GLP-1, improving overall weight loss [15]. The drastic difference in waist circumference and weight loss changes highlights Tirzepatide's potential to become a firstline pharmacological intervention for weight loss, especially for those struggling with obesity-related conditions.

Beyond its superior effects on weight loss, Tirzepatide also demonstrates enhanced benefits on lipid metabolism. Tirzepatide has demonstrated significantly greater improvements in lipid profiles, with reductions in triglyceride levels reaching up to 24.8% and VDLD levels up to 27.3%—both key risk factors for atherosclerotic cardiovascular disease [10, 16]. Additionally, patients receiving Tirzepatide experienced greater increases in HDL cholesterol compared to those on Semaglutide, indicating more favorable shifts in lipid metabolism [10]. Of note, changes in total cholesterol and LDL remained relatively limited and did not differ drastically between the two groups [10]. These findings suggest both medications aid in lipid metabolism, however, Tirzepatide may contribute to further cardiovascular protective benefits compared to Semaglutide. The addition of activated GIP receptors in Tirzepatide increases adipose tissue blood flow and promotes lipid uptake, suggesting that GIP receptor agonism in adipocytes plays a critical role in postprandial lipid clearance and overall lipid homeostasis [17].

Tirzepatide also offers enhanced glycemic control, which is a crucial component in managing type 2 diabetes. Regarding glucose homeostasis, Tirzepatide demonstrates clear advantages over Semaglutide, as reflected in greater reductions in HbA1c, fasting glucose, and 2-hour postprandial glucose levels. The SURPASS-2 studies indicated lowered HbA1c levels of up to 2.3 points for Tirzepatide versus 1.86 points for Semaglutide [10]. Furthermore, a greater proportion of patients who received Semaglutide reached HbA1c targets of normoglycemia (<5.7%) and near normoglycemia (<6.5%) [10]. This reinforced previous findings that Tirzepatide demonstrated stronger improvements in glycemic control. Differences in efficacy are likely due to additional GIP receptor activation leading to synergetic action on beta-cell function, causing improved insulin sensitivity and glycemic control compared to GLP-1 receptor agonists alone [17, 18]. Together, GIP and GLP-1 promote beta-cell proliferation and inhibit apoptosis, contributing to preservation of insulin-producing capacity [19]. Additionally, Semaglutide only stimulates insulin secretion in hyperglycemic states, suppressing glucagon secretion [10]. Conversely, Tirzepatide is insulinotropic, stimulating insulin release under hyperglycemic conditions to lower glucagon levels, while additionally better preserving and enhancing beta-cell function in the pancreas, reducing beta-cell dysfunction helping maintain glucose homeostasis [10, 20]. Tirzepatide's superior efficacy supports both short-term glycemic improvements and could aid in potential long-term stabilization of glucose regulation and in reducing the risk of complications related to diabetes.

While both incretin-based therapies are effective and well tolerated, gastrointestinal side effects including nausea, vomiting, and diarrhea are frequently reported [10]. Tirzepatide may be associated with slightly higher rates of gastrointestinal effects, especially at higher doses and during periods of dose escalation [9, 10]. Higher rates of side effects are likely due to Tirzepatide's dual receptor action. Although more serious adverse effects such as pancreatitis are very rare, they are more common in the Tirzepatide (4.8%) groups versus the Semaglutide groups (3.5%) [9, 10]. Most side effects appear short lived or stop with discontinuation and can be managed via gradual dose escalation [6, 8]. Long-term safety data for both Semaglutide and Tirzepatide is emerging, and further research is needed to fully understand the risks and benefits in different populations and over long periods of time.

The results of this analysis indicate Tirzepatide is a more effective treatment for patients with obesity and type 2 diabetes than Semaglutide. Although Semaglutide's efficacy is well established, further clinical research is necessary to fully understand the long-term benefits, safety profile, and broader therapeutic potential of Tirzepatide. Several gaps remain in the studies that have been conducted. First, there is a lack of direct comparison between Tirzepatide and Semaglutide at higher approved doses. Comparison would clarify whether the advantages observed between the two incretin-based therapies persist across comparable dosing regimens. Second, real world data beyond randomized control trials would help understand patient compliance, cost-effectiveness, and long-term sustainability of weight loss and glycemic control in more diverse populations. While current safety profiles are promising, long-term monitoring of adverse effects remains essential to ensure a comprehensive safety profile. Further research focusing on biomarker identification and clinical predictors of drug response could help guide individualized therapeutic decisions and optimize outcomes. As the burden of diabetes and obesity continues to rise globally, prioritizing research in therapies

such as Semaglutide and Tirzepatide can significantly improve public health outcomes.

Conclusions

Tirzepatide demonstrates superiority over Semaglutide for weight management, lipid metabolism, and glycemic control. These advantages likely result from Tirzepatide's dual GIP and GLP-1 receptor activation, allowing engagement in further physiological mechanisms. While Semaglutide is highly effective and well established, emerging research and evidence suggests Tirzepatide may emerge as a viable option for selected patients. Ongoing trials are critical to define Tirzepatide's long-term benefits and risks. Treatment plans that combine both pharmacological interventions and lifestyle changes should be prioritized for optimal outcomes and for improvements in population health.

List of Abbreviations

GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide-1
VLDL: very-low-density lipoproteins
HDL: High-density lipoprotein cholesterol
LDL: low-density lipoprotein cholesterol
HbA1c: hemoglobin A1c test
A1c: glycated hemoglobin levels
T2DM: type 2 diabetes mellitus

Conflicts of Interest

The author declares that she has no conflicts of interest.

Ethics Approval and/or Participant Consent

No ethics/participant consent was required to conduct this study.

Authors' Contributions

CAIF: designed the study, collected and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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