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# The promise of tirzepatide: A narrative review of metabolic benefits

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ABSTRACT

Obesity and type 2 diabetes mellites (T2DM) are intertwined epidemics that continue to pose significant challenges to global public health. We aim to review the available evidence on the metabolic effects of tirzepatide, focusing on weight loss and maintenance of lost weight, body composition alterations, appetite regulation, glycemic control, and lipid profile modulation. Tirzepatide administration for 72 weeks elicited significant weight reduction ranging from 5 % to 20.9 % across different trials in a dose-dependent manner. Furthermore, limited evidence showed that lost body weight may be primarily due to fat mass reduction. Tirzepatide also significantly decreased food intake, reduced overall appetite scores and increased fasting visual analog scale scores for satiety and fullness across different clinical trials. Moreover, tirzepatide exhibited favorable effects on glycemic control, with notable reductions in HbA1c levels ranging from 20.4 mmol/mol with the 5 mg dose to 28.2 mmol/mol with the 15 mg dose, following treatment durations lasting 40–52 weeks. Additionally, tirzepatide exerts a beneficial impact on lipid profile parameters, including reductions in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, while increasing high-density lipoprotein cholesterol concentrations. Despite its efficacy, tirzepatide is associated with gastrointestinal adverse effects, which requires dose escalation strategies to enhance tolerability. Mild to moderate adverse events are commonly reported at higher doses, with discontinuation rates ranging from 4 % to 10 % across different dosages. In conclusion, tirzepatide has shown multifaceted metabolic effects, along with manageable adverse profiles, which makes it a promising therapeutic agent for addressing both obesity and T2DM. However, further long-term randomized controlled trials are warranted to reveal long-term efficacy and safety outcomes, particularly in diverse patient populations.

## 1. Introduction

Obesity and type 2 diabetes mellites (T2DM) are intertwined epidemics that continue to pose significant challenges to global public health. The prevalence of obesity has tripled since 1975, affecting over 650 million adults worldwide in 2016 [1]. While the prevalence of T2DM rose from 108 million in 1980–422 million in 2014 [2]. Notably, the co-occurrence of obesity and T2DM amplifies the morbidity and mortality rates associated with each condition. Individuals with obesity are at a significantly higher risk of developing T2DM, which is characterized by insulin resistance and impaired glucose regulation [3]. This, in turn, predisposes to various complications, including cardiovascular disease, neuropathy, nephropathy, and retinopathy, leading to increased morbidity and mortality [4]. Although no global statistic is available, 89.8 % of people with T2DM were overweight or had obesity in the USA in 2014, defined as a body mass index (BMI) of 25 kg/m$^2$ or higher, in the UAE it was 85 % [5] and in Pakistan it was 84 % in the same year [6]. Nonetheless, a significant number of individuals, particularly in developing countries and among non-white populations, develop T2DM at a normal body weight [7].

In recognition of the T2DM need for effective management strategies, the development of novel medications targeting T2DM became notably high. Glucagon-like peptide-1 (GLP-1) receptor agonists, a class of medications, was approved for the first time by the U.S. Food and Drug Administration (FDA) in 2005, marking a milestone in the management of T2DM. Importantly, the GLP-1 Receptor Agonists (GLP-1RA) do not only improve glycemic control but also offer additional benefits by promoting weight loss. This additional benefit has led to a surge in the number of people using it solely for its weight lowering properties [8]. Tirzepatide is the most recently FDA approved GLP-1RA and its popularity has spiked after its approval, showing superior clinical efficacy compared to other approved GLP-1RA [9]. Tirzepatide acts as an agonist for the two main human incretins, GLP-1 and glucose-dependent insulinotropic peptide (GIP). Due to its high usage as weight loss

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medication along with other GLP-1RAs, obtaining it has become difficult for diabetic patients truly in need of it in recent years [8]. Tirzepatide, marketed under the brand name Mounjaro, has also been approved by the European Medicines Agency (EMA), and is marketed as Mounjaro in both the USA and the European countries [10]. The dosage used for weight loss generally differs from the dosage used for managing insulin resistance in type 2 diabetes [11]. Higher doses are typically prescribed for obesity and weight-related issues, while lower doses are prescribed for improving glycemic control and insulin sensitivity [10–12].

The aim of this review is to compile the available yet limited studies discussing the metabolic effects of Tirzepatide with a focus on weight loss and weight maintenance, appetite and food intake, alterations in body composition, glycemic control, and lipid profile modulation.

## 2. Methods

A comprehensive search using the PubMed (Medline), EMBASE, SCOPUS, and Web of Science databases was conducted to retrieve scientific papers published up to February 2024. Key terms of relevance were used, including “Tirzepatide", “Weight loss”, "Body composition", "Weight loss maintenance", "Hunger", “Satiety", "Glycemic control", "Lipid profile", and “Adverse effects” in combination with Boolean operators. Peer-reviewed articles such as human clinical-trial and meta-analyses we included, while non-human and non-English studies were excluded. An initial screening of titles and abstracts was conducted, afterwards, selected studies were reviewed in full-text version.

### 2.1. Physiology of GLP-1/GIP hormones and their receptors

GLP-1 and GIP are peptide hormones secreted by enteroendocrine cells in response to nutrient consumption [13]. They play a crucial role in postprandial metabolism by improving the glucose-stimulated release of insulin from the pancreas [14]. This improvement happens through the incretin effect, which is the most favorable condition for incretin hormones [15]. GIP is considered the essential incretin hormone accounting for the incretin effect, although both hormones exhibit synergistic effects when administered together [16,17].

GLP-1 acts as a key regulator of glucose homeostasis by stimulating insulin secretion from pancreatic β-cells [18]. Insulin, in turn, facilitates cellular uptake and utilization of digested glucose, thereby modulating blood glucose levels [14]. Furthermore, GLP-1 exerts inhibitory effects on glucagon secretion, lowering its ability to elevate blood glucose. By impeding glucagon’s action, GLP-1 contributes to the maintenance of glycemic equilibrium [18]. Additionally, GLP-1 slows gastric emptying rates, which delays digestion and the influx of glucose into the bloodstream, further aiding in glycemic control [19]. Moreover, GLP-1 enhances feelings of satiety through peripheral vagal nerve activation and influencing brain regions involved in regulating food intake [20]. These effects contribute to weight loss in an independent manner from glycemic control. On the other hand, externally administered GIP, does not bring out a significant insulin secretory response, even at pharmacological concentrations [16]. Which is the reason it was not widely considered for the treatment of T2DM.

### 2.2. Tirzepatide

Tirzepatide, also referred to as a ’twincretin’, is a novel dual GLP-1/GIP receptor agonist and the first medication designed as a single molecule to bind to both GIP and GLP-1 receptors [21]. Administered once weekly, tirzepatide offers dosing flexibility ranging from 2.5 mg to 15 mg per 0.5 mL injection [22]. Its unique molecular structure contributes to its favorable pharmacokinetic profile, with a linear peptide backbone consisting of 39 amino acids with an acyl fat-chain conjugation designed to enhance albumin binding and extend its half-life [23]. Tirzepatide shows a high bioavailability of 81 %, with peak plasma concentrations attained at 48 hours post-administration (range: 12–96 hours) [24,25]. Notably, its half-life of 117 hours, approximately 5 days, supports its once-weekly dosing regimen [26]. While the approved indication for tirzepatide is only as an adjunct treatment to improve glycemic control in adults with T2DM, clinical trials have demonstrated significant reductions in body weight across all dosage groups, among other interesting metabolic improvements [27–29]. The mechanism of action for tirzepatide is illustrated in Fig. 1.

## 3. Metabolic effects of tirzepatide

The weight reduction subsequent to tirzepatide administration was seen to be significant [27–29]. Here, we will delve beyond the numerical representations to discuss the available evidence regarding its impact on body composition, the capacity to maintain lost weight, and its effects on hunger and satiety, as these are pivotal factors in long-term weight management. Subsequently, we will explore other metabolic benefits contributing to holistic health, including its efficacy in glycemic control and its anti-atherogenic effect on lipid profile, followed by an examination of the adverse effects observed with tirzepatide administration.

### 3.1. Weight loss

Multiple studies have investigated the effect of tirzepatide on various metabolic outcomes, summarized in Table 1. Two clinical trial programs have investigated the efficacy and safety of tirzepatide, with SURMOUNT trials [21,30] focusing mainly on its effects on bodyweight. The SURMOUNT-1 trial assessed the weight-reducing potential of tirzepatide in obese participants (BMI >30 or >27 with weight-related complications) not having T2DM. Notably, a subgroup of 1032 participants (40.6 %) had prediabetes, defined as having an HbA1c level of 5.7–6.4 % (39–47 mmol/mol). Meanwhile, the SURMOUNT-2 trial targeted weight loss in participants with T2DM and overweight status (BMI > 27). The effects of tirzepatide were examined across doses of 5 mg, 10 mg, and 15 mg subcutaneously once weekly in SURMOUNT-1, while SURMOUNT-2 only examined the 10 mg and 15 mg doses [21,30].

In the SURMOUNT-1 trial, a reduction in bodyweight of up to 20.9 % after 72 weeks of treatment with the 15 mg dose of tirzepatide was reported, while placebo exhibited a 3.1 % weight loss. Similarly, in the SURMOUNT-2 trial placebo treatment experienced a weight loss of 3.2 %, whereas participants in the 15 mg treatment dose experienced a weight reduction of 14.7 % after 72 weeks. The SURMOUNT-3 clinical trial tested the effect of using tirzepatide after a successful intensive lifestyle intervention in adults with overweight or obesity and at least one weight-related complication. The participants experienced an 18.5 % weight loss after 72 weeks of tirzepatide injections, while placebo had a 2.5 % weight loss (treatment difference of 20.8 %; 95 % confidence interval (CI) −23.2 %, −18.5 %; $P < 0.001$). Additionally, the trial also found that 87.5 % of participants lost more than 5 % additional weight loss with tirzepatide while 16.5 % of the participants receiving placebo met that threshold [31].

Additionally, findings from the SURPASS trials [27,29], which investigated the effect of tirzepatide in participants with T2DM, revealed weight reductions ranging from 5 % to 14 % across doses of tirzepatide. Additionally, in the SURPASS-2 trial, all doses of tirzepatide were compared to a once-weekly subcutaneous injection of 1 mg semaglutide. The trial findings indicated that, on average, the 15 mg tirzepatide dose resulted in a 6.6 % greater absolute reduction in body weight compared to semaglutide [27]. The SURPASS-3 trial revealed that tirzepatide doses decreased bodyweight by 7.5 kg to 12.9 kg from baseline, while Insulin degludec increased bodyweight by 2.3 kg [32]. SURPASS-5 and SURPASS-6 also showed that the addition of tirzepatide to insulin glargine resulted in a significant weight loss ranging from −7.1 kg to −10.5 kg compared to placebo [28] and −12.2 kg compared to addition of insulin lispro [29].

A recent network meta-analysis including 47 randomized controlled trials with 17,163 subjects, showed tirzepatide to be the most effective

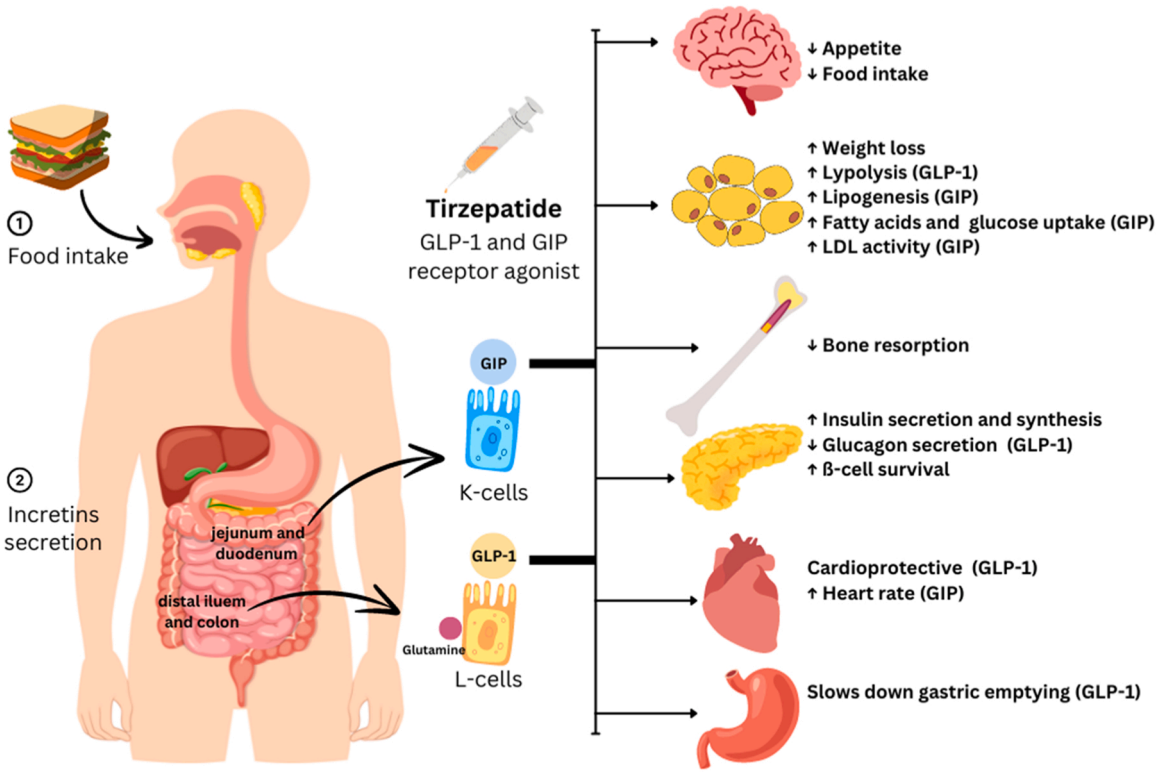


**Fig. 1.** Mechanism of Action for Tirzepatide.

FDA-approved GLP1RA in weight reduction, resulting in a mean weight loss of 8.47 kg (95 % CI −9.68 to −7.26); with high confidence in presented evidence [33]. Tirzepatide also resulted in the most significant reduction in BMI by −2.85 kg/m2 (95 % CI −3.70 to −2.01) and waist circumference by −6.77 cm (95 % CI −8.97 to −4.57) [33]. Additionally, An interesting subgroup analysis by Ma et al. [34] included 235 T2DM patients with normal body weight by body mass index indicator (<25 kg/m$^2$) at baseline and showed that tirzepatide doses 5, 10 and 15 mg resulted in significant reductions in body weight of −3.5 kg (5.5 %), −6.8 kg (10.8 %) and −6.1 kg (9.8 %), respectively [34]. This raises the concern that tirzepatide may induce unintended weight loss in T2DM patients seeking glycemic control rather than weight reduction. Therefore, medical supervision and personalized dosing strategies are needed to balance metabolic benefits with the risk of side effects.

### 3.2. *Inflammation*

Chronic inflammation is a common underlying factor in various metabolic disorders, including obesity, T2DM, and non-alcoholic fatty liver disease (NAFLD). These conditions are characterized by persistent low-grade inflammation, which contributes to their pathogenesis and progression. Certain blood parameters such as Mean Platelet Volume (MPV) [35], Prognostic Nutritional Index (PNI) [36], and the Uric Acid-to-HDL Cholesterol Ratio (UHR) [37] can serve as potential indicators of inflammation [35], metabolic syndrome [37], and disease progression in patients with T2DM [36,38], obesity [35], prediabetes [38], non-alcoholic fatty liver disease (NAFLD) [39], and diabetic kidney disease [40].

Recent studies have demonstrated that tirzepatide possesses anti-inflammatory properties that may beneficially impact these metabolic disorders [41]. For instance, research indicates that tirzepatide can reduce inflammation in cardiac tissues, suggesting potential protective effects against diabetes-related cardiac dysfunction [42]. Additionally, tirzepatide has been shown to alleviate oxidative stress and inflammation by modulating lipid metabolism pathways, which could be advantageous in managing NAFLD and related conditions [43]. Moreover, tirzepatide has been associated with reductions in key inflammatory markers. A post hoc analysis of a phase 2 trial found that treatment with tirzepatide led to significant decreases in biomarkers such as YKL-40, intercellular adhesion molecule 1 (ICAM-1), C-reactive protein (CRP), leptin, and growth differentiation factor 15 over 26 weeks [44]. These findings underscore the potential anti-inflammatory effects of tirzepatide; however, further large-scale, controlled studies are needed to determine whether these reductions are a result of weight loss induced by the treatment or occur independently of it.

### 3.3. *Body composition*

Analysis of the effect of tirzepatide on body composition, as demonstrated in clinical trials, reveals notable alterations in adiposity and muscle characteristics. In the SURPASS-1 trial, pooling data from all tirzepatide doses (5 mg, 10 mg, and 15 mg) yielded a substantial reduction in total body fat mass, with a reported decrease of 26 % (95 % CI: 20–31 %) compared to placebo [45]. Additionally, magnetic resonance imaging (MRI) assessments conducted as part of the SURPASS-3 study provided insights into the impact of tirzepatide on muscle composition [46]. While the analysis revealed a larger-than-expected decrease in muscle fat infiltration, indicative of improved muscle quality, it also highlighted an overall reduction in fat-free muscle mass [46]. Specifically, participants receiving the 15 mg subcutaneous once-weekly dose exhibited a decrease of 0.76 liters in fat-free muscle mass [46]. Moreover, a subgroup analysis by Heise et al. [47] found that participants receiving once weekly 15 mg tirzepatide for 28 weeks showed body weight loss predominantly driven by fat mass reduction [47].

The effect of tirzepatide on muscle mass loss remains an area of limited investigation, despite its clinical significance. A study by Jastreboff et al. [21] utilized dual-energy X-ray absorptiometry (DXA) to analyze the body composition of a subgroup of participants and found that they lost 10.9 % of their lean mass during the treatment period.

**Table 1**
Characteristics of Completed Trials Studying The Effect of Tirzepatide.

| Reference, Trial Acronym | Country | Design | Number of Participants, Background Hypoglycemic Treatment | Baseline Age, HbA1c, Weight, BMI, And Gender | Treatment, Dosage, And Study Duration | Primary Outcome | Significant Results |
|---|---|---|---|---|---|---|---|
| [21] **SURMOUNT−1** | Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan, USA. | Double-blind placebo-controlled RCT | 2539, none | Age: 44.7 years<br>Weight: 104.8 kg<br>HbA1c: NA<br>BMI: 38 kg/$m^2$<br>Gender: 67.5 % female | Tirzepatide 5 mg, 10 mg, 15 mg QW sc, or placebo<br>72 weeks | The percent change in bodyweight from baseline and the bodyweight reduction of 5 % or more | The mean percentage change in weight at week 72 was −15.0 %, −19.5 %, −20.9 %, with 5, 10, and 15-mg doses of tirzepatide respectively, and −3.1 % with placebo ($P < 0.001$).<br>Weight reduction of 5 % or more was 85 %, 89 %, and 91 % |
| [30] **SURMOUNT−2** | Argentina, Brazil, India, Japan, Russia, Taiwan China, USA | Double-blind, placebo-controlled RCT | 938, using any oral glycemic-lowering agent | Age: 54.2 years<br>HbA1c: 8.03 %<br>Weight: 100.7 kg<br>BMI: 36.1 kg/$m^2$<br>Gender: 51 % female | Tirzepatide 10 mg, 15 mg QW sc, or placebo<br>72 weeks | The percent change in bodyweight from baseline and the bodyweight reduction of 5 % or more. | **Bodyweight:** estimated treatment differences with tirzepatide 10 mg vs. placebo: −9·6 % percentage points (95 % CI −11·1 to −8·1) and with tirzepatide 15 mg: −11·6 % percentage points (−13·0 to −10·1) (all $p < 0·0001$) |
| [31] **SURMOUNT−3** | Argentina, Brazil, Taiwan, and USA | Double-blind, placebo-controlled RCT | 579, none | Age: 45.6 years<br>HbA1c: NA<br>Weight: 109.5 kg<br>BMI: 38.6 kg/$m^2$<br>Gender: 62.9 % female | Tirzepatide 10 mg, 15 mg QW sc, or placebo<br>72 weeks | Additional mean percent weight change from randomization to week 72 and the percentage of participants achieving additional weight reduction ≥ 5 % | **Weight change:** estimated treatment difference −20.8 percentage points (95 % CI: −23.2 %, −18.5 %; $P < 0.001$) |
| [48] **SURMOUNT−4** | Argentina, Brazil, Taiwan, and USA | Double-blind, placebo-controlled RCT | 670, none | Age: 48 years<br>HbA1c: NA<br>Weight: 107.3 kg<br>BMI: 38.4 kg/$m^2$<br>Gender: 71 % female | Tirzepatide 10 or 15 mg QW sc, or placebo<br>52 weeks | The mean percent change in weight from week 36 (randomization) to week 88 | Mean percent **weight** change difference between tirzepatide vs. placebo: −19.4 %)95 % CI, −21.2 % to −17.7 %( 89.5 % of participants maintained at least 80 % of weight loss with tirzepatide at 88 weeks, compared to 16.6 % with placebo ($P < 0.001$). |
| [45] **SURPASS−1** | India, Japan, Mexico, USA | Double-blind, placebo-controlled RCT | 478, none | Age: 54.1 years<br>HbA1c: NA<br>Weight: 85.75 kg<br>BMI: 31.9 kg/$m^2$<br>Gender: 48 % female | Tirzepatide 5 mg, 10 mg, 15 mg QW sc, or placebo<br>40 weeks | The mean change in HbA1c | **HbA1c: e**stimated treatment differences vs. placebo: –1•91 %, –1•93 %, –2•11 % for the 5 mg. 10, and 15 mg doses, respectively.<br>Tirzepatide induced a dose-dependent **bodyweight** loss ranging from 7 to 9.5 kg. |
| [27] **SURPASS−2** | USA, Argentina, Australia, Brazil, Canada, Israel, Mexico, UK | Open-label RCT | 1878, none | Age: 56.6 years<br>HbA1c: NA<br>Weight: 93.7 kg<br>BMI: 34.2 kg/$m^2$<br>Gender: 53 % female | Tirzepatide 5 mg, 10 mg, 15 mg, or Semaglutide 1 mg, all QW sc<br>40 weeks | The change in HbA1c | **HbA1c** estimated difference between the 5-mg, 10-mg, and 15-mg tirzepatide groups and the semaglutide group were −0.15 % points ($P = 0.02$), −0.39 % points ($P < 0.001$), and −0.45 % points ($P < 0.001$), respectively.<br>Least-squares mean estimated treatment difference for **bodyweight**, −1.9 kg, −3.6 kg, and −5.5 kg, for the doses 5, 10 and |

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**Table 1** (*continued*)

| Reference, Trial Acronym | Country | Design | Number of Participants, Background Hypoglycemic Treatment | Baseline Age, HbA1c, Weight, BMI, And Gender | Treatment, Dosage, And Study Duration | Primary Outcome | Significant Results |
|---|---|---|---|---|---|---|---|
| | | | | | | | 15 mg tirzepatide, respectively ($P < 0.001$ for all comparisons) |
| [32] **SURPASS−3** | Argentina, Austria, Italy, Greece, Hungary, Poland, Puerto Rico, Romania, South Korea, Spain, China Taiwan, Ukraine, USA | Open-label RCT | 1437, using sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinedione, glinides, or SGLT2 | Age: 57.4 years Weight: 94.3 kg HbA1c: NA BMI: 33.5 kg/m$^2$ Gender: 44 % female | Tirzepatide 5 mg, 10 mg, 15 mg QW sc 52 weeks | Mean change in HbA1c | **HbA1c:** 1.93 %, 2.20 %, and 2.37 % for tirzepatide 5 mg, 10 mg, and 15 mg respectively. Tirzepatide doses decreased **bodyweight** (–7.5 kg to –12.9 kg) while insulin degludec increased bodyweight by 2.3 kg. |
| [53] **SURPASS−4** | Argentina, Australia, Brazil, Canada, Greece, Israel, Mexico, Poland, Romania, Russia, Slovakia, Spain, Taiwan, and the USA | Open-label RCT | 1995, any combination of metformin, sulfonylurea, or SGLT2 | Age: 63.6 years HbA1c: 8.52 % Weight: 90.3 kg BMI: 32.6 kg/m$^2$ Gender: 38 % female | Tirzepatide 5 mg, 10 mg, or 15 mg or glargine 100 U/mL QW sc 52 weeks | Mean change in HbA1c | **HbA1c:** The estimated treatment difference for tirzepatide 10 mg vs. glargine was −0.99 % (multiplicity adjusted 97.5 % CI −1.13 to −0.86) and for 15 mg −1.14 % (−1.28 to −1.00). **Bodyweight:** Tirzepatide vs. glargine estimated treatment differences: –9.0 kg (95 % CI –9.8 to –8.3) at 5 mg, –11.4 kg (–12.1 to –10.6) with 10 mg, and –13.5 kg (–14.3 to –12.8) with 15 mg (all $p < 0{\cdot}0001$). |
| [28] **SURPASS−5** | USA, Japan, Czech Republic, Germany, Poland, Puerto Rico, Slovakia, and Spain | Double-blind, placebo-controlled RCT | 336, using insulin glargine with/without metformin | Age: 60.6 years HbA1c: 8.31 % Weight: 95.175 kg BMI: 33.4 kg/m$^2$ Gender: 44 % female | Tirzepatide 5 mg, 10 mg, 15 mg QW sc, or placebo 30 weeks | The mean change in HbA1c | **HbA1c** difference vs. placebo: 5 mg: −1.24 %; 10 mg: −1.53 %; 15 mg: −1.47 %; $P < 0.001$ for all. **Bodyweight** difference vs. placebo: 5 mg: −7.1 kg; 10 mg: −9.1 kg; 15 mg: −10.5 kg ($P < 0.001$ for all) |
| [29] **SUPRASS−6** | Argentina, Belgium, Brazil, Czech Republic, Germany, Greece, Hungary, Italy, Mexico, Romania, Russia, Slovakia, Spain, Turkey, and the US | Open-label RCT | 1428, using insulin glargine | Age: 58.8 years HbA1c: 8.8 % Weight: 90.5 kg BMI: 33 kg/m$^2$ Gender: 57.7 % female | 5 mg, 10 mg, 15 mg QW sc, or titrated insulin lispro 52 weeks | Mean change in HbA1c | **HbA1c:** estimated treatment difference for tirzepatide vs. insulin lispro: −0.98 % (95 % CI, −1.17 % to −0.79 %); $P < .001$ **Bodyweight:** estimated treatment difference for tirzepatide vs. insulin lispro: −12.2 kg [95 % CI, −13.4 to −10.9 |
| [54] **SURPASS J-mono** | Japan | RCT | 636, none | Age: 56.6 years HbA1c: 8.2 % BMI: 28.1 kg/m$^2$ Gender: 24.25 % female | Tirzepatide 5 mg, 10 mg, 15 mg, or Dulaglutide 0.75 mg, all QW sc 30 weeks | The mean change in HbA1c | **HbA1c**: Estimated mean treatment differences vs. dulaglutide were −1.1 (95 % CI −1.3 to −0.9) for tirzepatide 5 mg, −1.3 (CI −1.5 to −1.1) for tirzepatide 10 mg, and −1.5 (CI −1.71 to −1.4) for tirzepatide 15 mg (all $p < 0{\cdot}0001$). **Bodyweight**: least square mean difference of −5.8 kg for 5 mg, −8.5 kg for 10 mg, and −10.7 kg for 15 mg of tirzepatide compared |

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**Table 1** (*continued*)

| Reference, Trial Acronym | Country | Design | Number of Participants, Background Hypoglycemic Treatment | Baseline Age, HbA1c, Weight, BMI, And Gender | Treatment, Dosage, And Study Duration | Primary Outcome | Significant Results |
|---|---|---|---|---|---|---|---|
| | | | | | | | with −0.5 kg for dulaglutide. |
| [55] **SURPASS J-combo** | Japan | RCT | 443, using sulfonylureas, biguanides, α-glucosidase inhibitors, thiazolidinedione, glinides, or SGLT2 | Age: 57 years HbA1c: 8.5 % BMI: 28.1 kg/m$^2$ Gender: 24.4 % female | Tirzepatide 5 mg, 10 mg, 15 mg QW sc 30 weeks | Safety and tolerability during treatment, assessed as incidence of treatment-emergent adverse events in the modified intention-to-treat population | Mean changes from baseline in **bodyweight** were −3.8 kg in the 5 mg group, −7.5 kg in the 10 mg group, and −10.2 kg in the 15 mg group. Least squares mean **HbA1c** at baseline reduced from 8.5 % to 6.0 % in the 5 mg tirzepatide group, from 8.6 % to 5.6 % in the 10 mg group, and from 8.6 % to 5.6 % in the 15 mg group. |
| [56] **N/A** | Germany | RCT | 127, using metformin, with or without one additional stable dose of any other oral glycemic-lowering agent | Age: 61.7 years HbA1c: 7.8 % BMI: 31.4 kg/m$^2$ Gender: 26.3 % female | Tirzepatide 15 mg, or Semaglutide 1 mg, all QW sc, or placebo 28 weeks | The effect of tirzepatide vs. placebo on the change in clamp disposition index | Clamp disposition index estimated treatment difference: **Tirzepatide vs. placebo**: 1.92 pmol m$^{-2}$ L min$^{-2}$ kg$^{-1}$ (95 % CI 1.59–2.24); p < 0·0001). **Tirzepatide vs. semaglutide**: 0.84 pmol m$^{-2}$ L min$^{-2}$ kg$^{-1}$)95 % CI 0.46–1.21). |

Abbreviations: BMI: Body Mass Index; HbA1c: Glycated Hemoglobin A1C; NA: Not Available; QW: Once Weekly; RCT: Randomized Controlled Trial; sc: Subcutaneous; SGLT2: Sodium-Glucose Transporter; vs: Versus.

Notably, in the overall trial, tirzepatide-treated patients experienced a body weight reduction of 15–20.9 % [21]. Overall, the available evidence on the impact of tirzepatide on body composition following weight loss is limited and more studies are needed to clarify where the weight lost following tirzepatide treatment is primarily driven from.

### 3.4. Weight loss maintenance / weight regain

The SURMOUNT-4 phase 3 [48] randomized withdrawal clinical trial investigated the effect of tirzepatide, with diet and physical activity, on the maintenance of weight reduction. The trial included adults with a BMI $\geq$ 30 or $\geq$ 27 with weight-related complications, excluding T2DM, were enrolled. Participants received once-weekly subcutaneous tirzepatide at the maximum tolerated dose (10 or 15 mg) for 36 weeks open-label, followed by a 52-week double-blind, placebo-controlled period. Afterwards, 670 participants out of 783 were randomized (1:1) to either continue receiving tirzepatide (n = 335) or switch to placebo (n = 335) for the subsequent 52 weeks. The primary endpoint was the mean percent change in weight from week 36 to week 88. Another secondary endpoint was the proportion of participants at week 88 maintaining at least 80 % of weight lost during the lead-in period. Results showed that participants completing the lead-in period experienced a mean weight reduction of 20.9 %. From week 36 to week 88, continuing tirzepatide resulted in a mean percent weight change of −5.5 %, which is significantly lower than the 14.0 % increase observed with placebo. Additionally, 89.5 % of participants on tirzepatide maintained at least 80 % of the weight loss, compared to only 16.6 % on placebo [48]. This indicates that continued treatment of tirzepatide maintains and augments weight reduction, whereas discontinuation results in significant regain of weight lost. This raises the question about the termination point of tirzepatide, with the potential of being a life-long treatment instead of a temporary therapy for weight loss.

Maintenance of body weight lost is still an on-going challenge in obesity therapies and interventions. Currently, substantial weight reduction is attainable for the majority of individuals struggling with obesity through rigorous lifestyle modifications, pharmacotherapy, or surgical procedures [49]. Nevertheless, weight loss frequently plateaus before reaching an optimal medical or aesthetic threshold [49]. Following lifestyle interventions, a substantial portion ranging from 30 % to 50 % of lost body weight is typically regained within a year, while over half of patients revert to their initial body weight within five years post-treatment initiation [50]. Altogether, the prevention of weight regain subsequent to weight loss stands out as a big challenge in obesity management [51].

### 3.5. Hunger and satiety

Appetite regulation plays a crucial role in weight loss maintenance due to its impact on controlling food intake and energy balance [52]. Tirzepatide exerts a multifaceted influence on appetite regulation and food intake through its activation of GIP and GLP-1 receptors [47]. A clinical trial showed that after 28 weeks of 15 mg tirzepatide dose, energy intake during a buffet lunch significantly decreased from baseline, in contrast to the placebo group [47]. This calorie intake was significantly lower with tirzepatide compared to placebo (−309.8 kcal; 95 % CI: −423.0, −196.6; P < 0.001). Moreover, the reduction in energy intake with tirzepatide was numerically higher compared to a 1 mg semaglutide dose, although not statistically significant (−64.3 kcal; 95 % CI: −160.3, 31.7; P = 0.187) [47].

The study also found that by week 28, both tirzepatide and semaglutide elicited a reduction in appetite compared to baseline, as evidenced by higher overall appetite scores (P < 0.001), whereas placebo did not show a significant change (P = 0.241). This effect on appetite was again comparable between tirzepatide and semaglutide. Over the

course of the study, both tirzepatide and semaglutide led to rising scores on the fasting visual analog scale for satiety and fullness, alongside declining scores for hunger and anticipated food consumption [47]. These changes in subjective appetite measures indicate the appetite-suppressing effects of tirzepatide. The influence of tirzepatide on appetite and food intake through its mechanism of action is clear and is well-documented, and few studies are showing agreeing evidence. However, a larger pool of evidence is still needed and more long-term randomized clinical trials are required to be able to derive robust conclusions about the effect of tirzepatide on appetite and food intake.

### 3.6. Glycemic control

The completed clinical trial program, known as SURPASS, was primarily designed to assess the glucose-lowering efficacy of tirzepatide in participants with T2DM. These trials utilized mean change in HbA1c as the primary endpoint, with weight loss outcomes evaluated as secondary measures. Across the SURPASS trials, tirzepatide was investigated both as monotherapy in the SURPASS-1 trial and as an add-on to various glucose-lowering therapies, including metformin, insulin, SGLT2 inhibitors, sulfonylurea, or combinations thereof. Notably, the SURPASS-2 trial compared tirzepatide to semaglutide 1 mg subcutaneously once weekly, while in the "SURPASS J-Mono" trial it was compared against dulaglutide 0.75 mg subcutaneously once weekly. Results from the SURPASS trials showed significant reductions in HbA1c levels, ranging from 20.4 mmol/mol with the 5 mg dose to 28.2 mmol/mol with the 15 mg dose, after treatments lasting between 40 and 52 weeks [27–29,32,45,46,53].

Moreover, trials conducted in Japanese populations demonstrated even greater reductions in HbA1c, with a remarkable decrease of 33.0 mmol/mol observed with the 15 mg dose of tirzepatide [54,55]. In a separate trial conducted within the German population, it was found that the enhancement in clamp disposition index with tirzepatide surpassed that achieved with semaglutide (estimated treatment difference: 0.84 pmol m-2 L min-2 kg-1 (95 % CI: 0.46–1.21)) [56]. These findings indicate notable enhancements in both total insulin secretion rate (estimated treatment difference: 102.09 pmol min-1 m-2) and insulin sensitivity compared to semaglutide. Also, tirzepatide significantly reduced glucose excursions on meal tolerance testing compared to placebo, with these observed effects being greater than semaglutide [56].

A recent network meta-analysis showed that tirzepatide significantly reduced HbAIc, with a mean difference of −2.10 % (95 % CI −2.47 % to −1.74 %) pooled from all studies involving tirzepatide. This reduction marked the most significant compared to all other GLP1RA. Tirzepatide was also the most effective in reducing fasting blood glucose (mean difference −3.12 mmol/L (95 % CI −3.59 to −2.66), proving to be the most effective GLP1RA drug for glycemic control [33].

### 3.7. Lipid profile

Tirzepatide demonstrates significant effects on lipid profile parameters, as evidenced by data from various clinical trials. Across different trials, total cholesterol exhibited reductions ranging from 2.2 % to 15.4 %, while low density lipoprotein cholesterol levels decreased by 5.3–19.3 %, with the exception of findings from the SURMOUNT-2 trial, which reported a modest increase of 2.3–3.2 % in LDL-C. Notably, high density lipoprotein cholesterol levels showed improvements, with increases ranging from 0.9 % to 10.8 % [21,28,30,32,45,53–55].

Furthermore, magnetic resonance imaging investigations conducted as part of the SURPASS-3 trial elucidated the impact of tirzepatide on liver fat content. Participants with a fatty liver index $\geq$ 60 demonstrated a substantial absolute reduction of 8.1 % in liver fat content from baseline following treatment with pooled 10 mg and 15 mg doses of tirzepatide, compared to a 3.4 % reduction observed in participants treated with insulin degludec [32,46]. Additionally, a network meta-analysis revealed that tirzepatide significantly lowered triglyceride levels by an average of −0.89 mmol/L (95 % CI −1.64 to −0.13) compared to placebo [33]. These findings although may be primary driven from the weight loss seen in these trials, underscore the favorable impact of tirzepatide on lipid parameters, and thereafter its impact on cardiovascular health.

## 4. Adherence and adverse effects of tirzepatide

The use of tirzepatide has been linked with gastrointestinal adverse effects, occasionally presenting with severity. A network meta-analysis showed a significantly higher odds ratio of discontinuation due to adverse events compared with placebo (2.30 (95 % CI 1.30–4.09)), which reflects the adherence level to medication [33]. The analysis also found a positive association with diarrhea (2.88 (95 % CI 2.09–3.96)), a significantly elevated odds ratio of nausea, as well as a higher risk of vomiting than placebo [33]. However, to increase patient adherence to medication, findings from a 12-week phase 2 clinical trial using moderate dose-escalation protocols have demonstrated promising insights into enhancing gastrointestinal tolerability [57,58]. Thus, within the trial programs, tirzepatide administration was initiated at a dosage of 2.5 mg once weekly, with subsequent incremental increases of 2.5 mg every 4 weeks. This approach to dose escalation suggests a potential for mitigating adverse reactions associated with tirzepatide therapy, thereby enhancing patient adherence. After implementing this strategy, in the SURMOUNT-1 trial, adverse events led to treatment discontinuation in 4.3 %, 7.1 %, 6.2 %, and 2.6 % of participants receiving tirzepatide doses of 5 mg, 10 mg, and 15 mg, as well as placebo, respectively. Similarly, in the SURPASS-5 trial, premature treatment discontinuation due to adverse events occurred at rates of 6.0 % (7/116) in the 5 mg dose, 8.4 % (10/119) in the 10 mg dose, 10.8 % (13/120) in the 15 mg dose, and 2.5 % (3/120) in the placebo group. These findings show that the drug discontinuation rate ranged between 4 % and 10 % across different tirzepatide doses. The collective evidence show that the adverse effects associated with tirzepatide are usually mild to moderate in intensity and is more intense with higher dosages.

Notably, individuals with severe gastrointestinal disorders, encompassing conditions such as severe gastroparesis, are advised against the use of tirzepatide due to potential exacerbation of symptoms as per the Mounjaro official website [59]. Additionally, A case report recently mentioned an incident where a 67-year-old female with T2DM, previously treated with basal insulin, metformin, and semaglutide (a GLP-1 agonist), experienced systemic hypersensitivity to tirzepatide after the first dose [60]. This highlights the importance of allergic testing of tirzepatide before initiating the treatment.

Multiple comorbid populations are advised to be cautious when using tirzepatide. Patients with renal impairment, are at risk of acute kidney injury, particularly as gastrointestinal side effects like nausea and diarrhea can lead to dehydration [22]. Pregnant women should only be prescribed tirzepatide when the benefits outweigh potential risks, given animal studies showing malformations and the lack of human data on its teratogenicity [22]. Additionally, patients on insulin or sulfonylureas may experience a dose-dependent risk of hypoglycemia, especially at higher doses. Therefore, careful dosing adjustments and monitoring for adverse events are essential when using tirzepatide in these populations [22,61]. Finally, patients with hepatic impairment should practice caution with tirzepatide treatment, as cases of cholelithiasis and cholecystitis have been reported, likely due to the rapid weight loss induced by tirzepatide [22,62].

## 5. Conclusion

In conclusion, the escalating global burden of T2DM and obesity mandates innovative advancements to currently available therapies to enhance dosing convenience and tackle multifaceted health challenges with single medications. This review synthesizes existing albeit limited research elucidating the metabolic impact of tirzepatide, particularly

emphasizing its effects on weight regulation, glycemic control, lipid profile modulation, appetite regulation, and body composition alterations. Tirzepatide enhances glycemic control and is the most effective medication in lowering HbA1c levels available in the market. Moreover, existing clinical trials indicate that tirzepatide leads to significant weight loss, with preliminary findings suggesting better weight maintenance with continued administration compared to termination, which has been associated with weight regain.

Additionally, few studies have highlighted the positive effect of tirzepatide on lipid profile parameters, however, it is still unclear if these effects are independent or are a results of weight loss. The weight lost due to tirzepatide administration was seen to be driven mainly from the fat mass however, more studies are needed to confirm this effect. Finally, clinical trials have reported reduction in appetite and food intake with tirzepatide, though further research is needed to determine the long-term sustainability of these effects. The adverse effects most commonly reported were gastrointestinal and usually mild to moderate in intensity. Important trials are still ongoing regarding the effect of tirzepatide on mortality and cardiovascular events. Therefore, caution should be practiced with long-term administration of tirzepatide and continuous monitoring must be in place. As investigations continue to explore tirzepatide's therapeutic potential, it emerges as a promising agent not only for optimizing glycemic management, but also for addressing the complex interplay between T2DM, obesity, and cardiovascular disease.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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### *Conflict of interest*

All authors declare no conflict of interest.

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