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editorial-office@sciformat.ca

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EFFICACY OF TIRZEPATIDE ON WEIGHT LOSS, MUSCLE MASS AND CARDIOVASCULAR HEALTH IN THE ADULT POPULATION WITH DIABETES TYPE 2, OVERWEIGHT OR OBESITY: A SYSTEMATIC REVIEW

Zuzanna Strojek *(Corresponding Author, Email: strojek.zuzanna@gmail.com)*
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0005-8857-5670

Aleksandra Oszczypała
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0006-5809-3934

Aleksandra Ustaszewska
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-5651-5906

Aleksandra Potempa
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0004-2698-4957

Katarzyna Lipska
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0003-5670-7726

Liwia Prorok
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0008-3762-514X

Mateusz Żyła
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0003-9005-620X

Michał Petkow
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0008-3398-9069

Monika Szyszkowska
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0006-5367-0026

Zofia Parol
Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0007-0885-2637

ABSTRACT

Objective: Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist designed to assist patients with weight reduction. Aim of this article is to systematically evaluate the efficacy of tirzepatide on body weight, muscle mass, and systemic cardiometabolic parameters in adults with T2DM, overweight, or obesity.
Methods: A PubMed database search for randomised clinical trials with full text in English available published within 5 years was performed. Studies covering tirzepatide's efficacy on BMI, body composition, and cardiometabolic markers in the population of adults with T2DM or overweight, obesity were included.
Results: Tirzepatide demonstrated dose-dependent weight reduction, with the 15-mg dose achieving mean losses of 20.9% to 25.3% in adults with obesity and 12.8% to 15.7% in those with T2DM [2]. BMI reductions reached up to -10.4 kg/m² [30] [33]. Body composition analyses revealed a healthy preservation of lean mass, with approximately 75% of weight loss being fat mass and 25% being lean mass [4] [21].Thigh muscle fat infiltration reduction by -0.36 to -0.48 percentage point was observed, indicating improved muscle quality [27]. Cardiometabolic benefits included HbA1c reductions (up to 2.6%) [7] [8], net blood pressure lowering (6.8 mmHg systolic; 4.2 mmHg diastolic) [18], and substantial triglyceride reductions (up to 37.6%) [16] [18]. Drug withdrawal led to weight regain and a partial-to-complete reversal of cardiometabolic improvements [15].
Conclusion: Tirzepatide assists in weight reduction and improves cardiovascular and glycemic risk factors. These effects are consistent across baseline BMI categories, though chronic maintenance is required to sustain metabolic gains.

KEYWORDS

Tirzepatide, Mounjaro, GIPR Agonist, Obesity, Diabetes Type 2, Weight Loss

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Introduction

Obesity, overweight, and type 2 diabetes mellitus (T2DM) represent major global public health challenges associated with substantial morbidity, mortality, numerous complications and following them healthcare expenditure. The prevalence of obesity and T2DM has increased significantly over recent decades, contributing to metabolic disorders and cardiovascular diseases, such as hypertension, dyslipidaemia, coronary artery disease, stroke, heart failure, being on the rise. Excess adipose tissue and poor glycaemic control are associated with reduced quality of life, functional impairment, and decreased health-adjusted life expectancy. Therefore, effective therapeutic strategies targeting both weight reduction and metabolic improvement are of growing clinical importance.

Lifestyle modification remains the core aspect of treating obesity and T2DM. However, oftentimes implementing such changes presents as a tedious and difficult task, since various untrustworthy sources promote a variety of ways to lose weight quickly, and in reality long-term maintenance of weight loss is usually based on gradual reduction. Pharmacological treatments can therefore be an important adjunctive therapy. In recent years glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have demonstrated significant efficacy in improving glycaemic control and reducing body weight.

Tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist approved for the treatment of T2DM and obesity. Its mechanism involves enhancing insulin secretion, suppressing glucagon release, delaying gastric emptying, and promoting satiety, thereby improving glycaemic control and facilitating weight loss.

Despite the demonstrated efficacy of tirzepatide in weight reduction, concerns were raised regarding the composition of weight loss, particularly the potential loss of lean body mass. Preservation of muscle mass is

crucial for maintaining physical independence, metabolic health, and long-term weight reduction, especially in older adults and patients with chronic metabolic disease. Rapid or substantial weight loss may lead to reductions in fat-free mass, which could contribute to sarcopenia, frailty, and increased risk of falls. Therefore, understanding the effects of tirzepatide on muscle mass and body composition is of great importance for evaluating the overall clinical benefits and risks associated with its use.

Cardiovascular disease remains the leading cause of death among individuals with obesity and T2DM. Emerging evidence indicates that tirzepatide improves several cardiometabolic risk factors, including blood pressure, lipid profiles and insulin resistance. Furthermore, recent studies have suggested a potential reduction in major adverse cardiovascular events among patients treated with incretin-based therapies. However, the extent to which tirzepatide influences cardiovascular outcomes and risk factors across different adult populations remains incompletely understood.

The aim of this systematic review is to evaluate the efficacy of tirzepatide on weight loss, muscle mass, and cardiovascular health in adults with T2DM, overweight, or obesity. Specifically, this review seeks to synthesise current evidence regarding changes in body weight, body composition, lean muscle mass, and cardiovascular health associated with tirzepatide therapy, while identifying gaps in the literature and implications for future clinical practice and research.

Methods

A literature search was performed using the PubMed database to gather evidence on efficacy of tirzepatide on weight loss, body composition and cardiovascular health. The last search was concluded on 25.05.2026. Randomized clinical trials with free full text in English available conducted from 2021 to 2026 (5 years) researching trizepatide's efficacy on at least one of the following parameters: weight, BMI, muscle mass, metabolic parameters (HbA1c, fasting serum glucose (FSG), lipid profile, serum uric acid (SUA) levels), systolic (SBP) or diastolic blood pressure (DBP), in adult population presenting with diabetes mellitus type 2, overweight or obesity were included. The exclusion criterion was that the study was conducted on animals. Inclusion of the studies was performed according to PRISMA 2020 criteria. No automation tools were used in the process and no duplicate records were found. Firstly, the initial results were screened by two researchers and 17 reports were excluded. Secondly, all 33 results were assessed and ultimately included by four researchers working independently.

Results:

1.Weight reduction

1.1 Adults with T2DM without overweight or obesity

In the SURPASS J-mono trial involving Japanese participants, who typically have lower baseline BMIs, tirzepatide monotherapy led to significant reductions in body weight of 7.8%, 11.0%, and 13.9% for the 5-mg, 10-mg, and 15-mg doses, respectively, over 52 weeks [22]. Post hoc analyses demonstrated that weight loss occurred regardless of baseline body weight or BMI [22] [28]. However, pharmacometric modeling indicates that patients with T2DM (even without advanced obesity) exhibit a higher resistance to weight loss compared to those without T2DM, requiring approximately three times the drug exposure to achieve similar reductions in fat mass [4]. In this population, greater weight loss was significantly but weakly correlated with improvements in non-glycemic parameters like triglycerides and systolic blood pressure [22].

1.2. Adults with T2DM and overweight or obesity

In the SURMOUNT-2 trial, participants achieved a mean weight reduction of 12.8% to 14.7% over 72 weeks [12] [31]. In a Japanese subpopulation of the same trial, reductions ranged from 10.2% to 12.4% [31]. Significant reductions in waist circumference (up to -9.8 cm) were also observed in Japanese T2DM cohorts [31]. Shorter diabetes duration and lower baseline HbA1c were identified as predictors for achieving and sustaining ≥10% weight loss [25]. In the SURPASS-5 trial, adding tirzepatide to titrated insulin glargine resulted in mean weight changes of -5.4 kg to -8.8 kg, whereas the placebo group gained 1.6 kg [7]. Tirzepatide treatment resulted in significantly greater reductions in BMI compared to semaglutide 2.4 mg with mean difference of -1.80 kg/m² for the 15-mg dose[5].

1.3. Adults with overweight or obesity without T2DM

This population achieved the highest absolute and percentage weight reductions across the SURMOUNT program. In the SURMOUNT-1 trial, tirzepatide 15 mg led to a mean weight reduction of 20.9% at 72 weeks [2] [11]. For participants who continued treatment for 88 weeks in SURMOUNT-4, the total mean weight reduction reached 25.3% [2].Substantial BMI improvements were noted, with total changes reaching -10.4 kg/m² when tirzepatide followed an intensive lifestyle intervention [30] [33]. In Japanese adults without T2DM, BMI reductions reached up to -9.0 kg/m² [20]. Chinese adults achieved mean weight reductions of 13.6% (10 mg) and 17.5% (15 mg) at 52 weeks [33]. Japanese adults demonstrated reductions of up to 22.4% at week 72 [16]. Detailed DXA substudies revealed that ~75% of the weight lost was fat mass, while ~25% was lean mass, a ratio consistent across age and sex [21]. Tirzepatide remained highly effective even (~18.3% reduction) in individuals with MC4R deficiency, the most common genetic cause of obesity [3]. It also induced clinically meaningful weight loss in patients taking concomitant weight-inducing medications [9].

2. Muscle mass

2.1. Adults with T2DM without overweight or obesity

Clinical data regarding muscle mass changes in adults with T2DM and a body mass index (BMI) < 25 kg/m² are limited, as the primary phase 3 trials and associated imaging substudies (e.g., SURPASS-3 MRI) typically enrolled participants with a baseline BMI ≥ 25 kg/m². However, studies involving Japanese populations with T2DM, where baseline weights are often lower, tirzepatide demonstrated significant metabolic improvements [22]. Pharmacometric modeling including T2DM populations suggests that fat-free mass (FFM) reduction is generally three times smaller than fat mass reduction [4]. While this indicates a preservation of the lean-to-fat loss ratio, the model predicts that those with lower baseline BMIs may reach their weight nadir earlier [4].

2.2. Adults with T2DM and overweight or obesity

The SURPASS-3 MRI substudy provides data on muscle composition in this population, focusing on insulin-naive adults with a BMI ≥ 25 kg/m² [27]. Treatment with tirzepatide (pooled 5, 10, and 15 mg doses) for 52 weeks resulted in a significant reduction in thigh muscle fat infiltration (MFI), with a mean change of -0.36 percentage points [27]. This reduction was significantly greater than population-based estimates calculated from the UK Biobank, suggesting a targeted positive effect on muscle quality beyond what is expected from weight loss alone [27] Significant reductions were observed in absolute thigh muscle volume (-0.64 L) and muscle volume Z-score (-0.22) [27]. Longitudinal modeling indicated that these reductions in volume were adaptive to the loss of body weight and consistent with general population associations between weight change and muscle volume [27]. In contrast, participants treated with titrated insulin degludec experienced a modest increase in muscle volume (0.16 L) but no significant change in muscle fat infiltration [27].

2.3. Adults with overweight or obesity without T2DM

In adults without diabetes, tirzepatide (pooled doses) reduced total lean mass by 10.9% compared to a 33.9% reduction in fat mass at week 72 [21]. Of the total weight lost, approximately 75% was fat mass and 25% was lean mass [21]. This ratio is consistent with healthy weight loss observed in intensive lifestyle interventions and bariatric surgery [21]. Post hoc analyses confirmed that the 75:25 fat-to-lean mass loss ratio remained remarkably consistent across subgroups of age (including those ≥ 65 years), sex, and total weight reduction tertiles [21]. Pharmacometric modeling of the SURMOUNT-1 data estimated that the reduction in fat mass was three times greater than the reduction in fat-free mass (FFM) across all approved doses [4]. Despite the absolute decrease in lean mass, tirzepatide-treated participants reported significant improvements in physical function scores (via SF-36v2), particularly those with the greatest baseline impairments [21]. This suggests that the substantial loss of fat mass, including visceral fat (-40.1%), offset the reduction in muscle volume to improve overall mobility and function [21].

3. HbA1c and FSG

3.1. Adults T2DM without overweight or obesity

In the SURPASS J-mono trial involving Japanese participants with T2DM, tirzepatide monotherapy led to significant HbA1c reductions regardless of baseline BMI [32]. Mean reductions reached up to -2.6% in global monotherapy trials [8]. In this population, significant reductions in FSG were observed as early as week 4 [22]. Post hoc analyses suggest that early improvements in glycemic control are largely independent of the magnitude of weight loss in this group [22]. Specifically, weight-unassociated mechanisms accounted for approximately 56.5% to 63.4% of the improvement in FSG observed with tirzepatide treatment [22]. A sub-group analysis of Asian participants with a baseline BMI < 25 kg/m² (mean 23.9 kg/m²) confirmed a pattern of BMI decline and metabolic improvement consistent with heavier cohorts [14].

3.2. Adults with T2DM and overweight or obesity

The greatest glycemic improvements could be observed in this population, often reaching levels categorized as normoglycemia. In the SURPASS-5 trial mean HbA1c reductions ranged from -2.11% to -2.40 % at week 40, compared to -0.86% for placebo and between 85% and 90% of these participants achieved an HbA1c target of < 7.0% [7]. Tirzepatide doses (5, 10, and 15 mg) reduced mean FSG by -58.2 to -64.0 mg/dL in patients previously treated with insulin glargine [7]. In Japanese adults with T2DM and obesity, the estimated treatment difference in FSG relative to placebo was -34.7 to -36.7 mg/dL [31]. Higher tirzepatide doses, shorter diabetes duration, and lower baseline HbA1c were identified as key predictors for achieving a target HbA1c ≤ 6.5% [25]. Among those who reached an HbA1c ≤ 6.5% at week 52, 75% to 84% sustained this control through a median of 81 weeks [25]. Sustainability was primarily predicted by better β-cell function and greater initial weight loss [25].

3.3. Adults with overweight or obesity without T2DM

Tirzepatide significantly lowered HbA1c and FSG even in normoglycemic or prediabetic adults. In the SURMOUNT-4 trial, participants without T2DM achieved a mean HbA1c of 5.0% at week 36, down from a baseline of 5.54% [2]. In SURMOUNT-3, following an intensive lifestyle intervention, tirzepatide further reduced HbA1c by -0.5% [30]. Similar results were seen in Chinese adults, where treatment-associated improvements in HbA1c were significantly greater than placebo [33]. In Chinese adults without T2DM, baseline FSG of ~92 mg/dL was significantly reduced by tirzepatide compared to placebo [33]. In Japanese adults without T2DM, tirzepatide led to significant reductions in FSG through 72 weeks [16]. In the global SURMOUNT-1 trial, tirzepatide treatment was associated with a markedly lower risk of progression to T2DM in participants with obesity and prediabetes [16]. Most participants (54% - 80%) who continued treatment maintained normoglycemia (HbA1c < 5.7% and FSG < 100 mg/dL) at week 72 [19].

4. Lipid profile, SUA and blood pressure

4.1. Adults with T2DM without overweight or obesity

In the SURPASS J-mono trial involving Japanese participants (where baseline weights were lower than global averages), tirzepatide monotherapy led to clinically significant improvements in SBP, with reductions ranging from -6.5 to -11.0 mmHg, and DBP reductions of -3.2 to -5.6 mmHg [15]. Mediation analysis revealed that these improvements were both weight-loss associated and weight-loss unassociated, with weight-independent mechanisms accounting for approximately 32.1% of the difference in SBP reduction compared to active comparators [15]. Treatment resulted in improvements in lipid levels regardless of baseline body weight [15] [22]. In Japanese T2DM cohorts, body weight loss was directly but weakly correlated with triglyceride reductions (r = 0.18–0.25) and HDL cholesterol increases (r = -0.37 to -0.29) [15].

4.2. Adults with T2DM and overweight or obesity

There were significant benefits present in both glycemic control and a broad range of cardiometabolic risk factors [15]. In the SURPASS-5 trial, which added tirzepatide to titrated insulin glargine, mean SBP decreased by -6.1 to -12.6 mmHg [7] [15]. In a subpopulation of Japanese participants with T2DM and obesity (SURMOUNT-2), sitting SBP was reduced by up to -15.6 mmHg [15] [31]. Tirzepatide was associated with statistically significant improvements from baseline in total cholesterol, LDL, VLDL, and triglycerides [7] [15]. Indirect treatment comparisons suggested that tirzepatide 15 mg provided statistically significant greater reductions in triglycerides compared to semaglutide 2.4 mg [5] [15]. In patients with obesity-related heart failure (HFpEF), those with T2DM had higher baseline SBP than those without diabetes [14] [24]. However, the presence of T2DM did not diminish the efficacy of tirzepatide in providing clinical benefits, which included structural cardiac improvements [14] [24].

4.3. Adults with overweight or obesity without T2DM

Participants without T2DM achieved the highest magnitude of improvement across systemic cardiometabolic markers [4] [15]. Pooled data from the SURMOUNT-1 trial showed a net reduction of 6.8 mmHg in SBP and 4.2 mmHg in DBP relative to placebo [4] [18].Tirzepatide treatment was associated with a rapid decline in BP over the first 24 weeks, followed by stabilization [4] [18]. At week 72, 58.0% of participants achieved normal BP, compared to 35.2% in the placebo group [4] [18]. Mediation analysis indicated that weight loss explained 67.6% of the SBP reduction and 71.0% of the DBP reduction [4] [18]. Tirzepatide treatment was associated with significant reductions in SUA levels at each time point [4] [28]. At week 72, regardless of baseline BMI or baseline SUA quartiles, mean SUA changes were -0.69 to -0.95 mg/dL, whereas the placebo group saw a reduction of only -0.18 mg/dL [4] [28]. Mediation analysis suggested that weight reduction explained 72.7% of the SUA reduction [4] [28]. Improvements were also observed, particularly in triglycerides (reductions up to -37.6%), total cholesterol (-14.4%), and non-HDL cholesterol (-23.6%) in Japanese cohorts [4] [16]. In Chinese adults, tirzepatide similarly induced improvements in fasting lipids compared to placebo [4] [33]. Data from the SURMOUNT-4 trial show that withdrawing tirzepatide led to a reversal of these benefits [14]. A higher degree of weight regain ($\geq$ 75% of initial loss) was associated with a complete reversal of improvements in SBP, non-HDL cholesterol, and triglycerides back to original baseline values [14].

Discussion

The researched timeline can be insufficient to properly assess efficacy of tirzepatide, especially in the population with T2DM and with BMI < 25kg/m², where data is scarce, since most of the considered articles were in the overweight or obese population with or without T2DM.

Conclusions

Tirzepatide achieves dose-dependent weight reduction with the 15-mg dose resulting in mean losses of 20.9% to 25.3% in adults with obesity over 72 to 88 weeks but adults who switched to a placebo after 36 weeks regained an average of 14% of their weight within a year, whereas those continuing tirzepatide lost an additional 5.5% [2]. Significant weight loss can be observed across diverse groups, including those with T2DM (12.8%–15.7%), type 1 diabetes with obesity (8.8% in 12 weeks), and individuals with genetic MC4R deficiency [3] [29]. Body weight reduction is primarily driven by fat mass loss rather than lean mass loss, maintaining a ratio of approximately 3:1 which is consistent with healthy weight loss from lifestyle or surgical interventions [4] [21]. However, in patients with T2DM, tirzepatide significantly reduces muscle fat infiltration, which is associated with improved muscle quality [27]. While absolute muscle volume decreases as an adaptive response to weight loss, patients often report improved physical functioning scores due to the substantial reduction in visceral and total body fat [21] [27] [30]. Tirzepatide provides reductions in HbA1c (up to 2.6%) and fasting serum glucose, often leading participants to achieve normoglycemia [7] [8]. Treatment leads to a net reduction of approximately 6.8 mmHg in SBP and 4.2 mmHg in DBP [18]. Tirzepatide consistently improves lipid profiles, especially triglycerides, and significantly lowers serum uric acid levels regardless of baseline BMI [16] [28]. In patients with HFpEF, tirzepatide reduces the risk of cardiovascular death or worsening heart failure events by 38% while significantly decreasing left ventricular mass and paracardiac adipose tissue [17] [24]. Most cardiometabolic improvements revert toward baseline if the drug is withdrawn and weight is regained [15].

Other: No conflicts of interest to declare.

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