SYSTEMATIC REVIEW

Clinical Research

Effects of tirzepatide on weight management in patients with and without diabetes: a systematic review and meta-analysis

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AIMS: To conduct a systematic review and meta-analysis comparing tirzepatide *versus* placebo for weight management, with analyses stratified by diabetes status to precisely assess its efficacy and safety in individuals with and without diabetes.
METHODS: We systematically searched MEDLINE, Embase, and Cochrane Library for randomized controlled trials comparing once-weekly tirzepatide (5–15 mg) *versus* placebo in adults with or without diabetes for at least 26 weeks. For each subpopulation analysis, the random-effects model was used to calculate pooled risk ratios (RRs) and mean differences (MDs), with their 95% confidence intervals, for dichotomous and continuous endpoints, respectively. Statistical significance was considered at $p < 0.05$.
RESULTS: We included five trials ($n = 2,174$) in patients with diabetes (BMI ≥ 23 kg/m^2) and five ($n = 4,467$) in patients without diabetes (BMI ≥ 27 [≥24 in Asia] kg/m^2). Compared with placebo, tirzepatide led to significantly greater relative and absolute weight reductions in patients with (RR −9.54%, $p < 0.01$; MD −9.06 kg, $p < 0.01$) and without diabetes (RR −17.15%, $p < 0.01$; MD −18.11 kg, $p < 0.01$). In both subpopulations, tirzepatide also significantly increased the probability of achieving weight reductions of ≥5%, ≥10%, and ≥15%, as well as improved BMI, waist circumference, blood pressure, hemoglobin A1c, and lipid levels. Notably, weight-related benefits with tirzepatide were significantly greater in patients without diabetes, whereas its safety was similar across subpopulations and predominantly consisted of mild to moderate, well-tolerated adverse events.
CONCLUSIONS: Compared with placebo, tirzepatide resulted in statistically significant and clinically meaningful weight reduction, especially in patients without diabetes (with overweight/obesity), with an acceptable safety profile.

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INTRODUCTION

Obesity is a chronic, relapsing, and progressive disease, constituting a public health problem associated with serious comorbidities and complications [1, 2]. Due to its multifactorial nature, a comprehensive therapeutic approach is recommended, encompassing lifestyle modifications and, optionally, pharmacological treatment to assist in weight loss and its long-term maintenance [3, 4]. Currently available anti-obesity medications result in mean weight reductions of 5–10%, improving metabolic, health, and quality of life parameters. However, these gains still fall short of patient and healthcare professional expectations [5–8]. Additionally, several drugs have been withdrawn due to unacceptable side effects [7, 8], intensifying the search for more effective and safer anti-obesity pharmacotherapies in recent decades [5, 6].

Originally developed for the management of type 2 diabetes, tirzepatide is a novel peptide molecule that combines glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonism. In addition to reducing glucose levels, it has demonstrated positive effects on other metabolic parameters, such as weight reduction, improvement in lipid levels, and blood pressure control [9, 10]. These findings prompted regulatory agencies to approve tirzepatide also for obesity management in several countries [11–13]. To optimize its clinical applicability, tirzepatide use in patients with overweight/obesity across different clinical scenarios is being extensively investigated [14–19]. Thus, conducting novel meta-analyses is imperative, as they can provide additional insights that individual studies are unable to offer.

Prior meta-analyses compared tirzepatide *versus* placebo for weight control, encompassing patients with and without diabetes in a unified analysis [20–24]. However, studies with other anti-obesity drugs have shown that weight loss is significantly lower in individuals with diabetes [25–29]. For this reason, a unified analysis may yield effect estimates that do not accurately reflect tirzepatide's impact in each specific scenario. Moreover, since those meta-analyses were published, novel large-scale

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randomized controlled trials (RCTs) with longer treatment periods have been published [14–17] and therefore were not incorporated into earlier meta-analyses. Given the significant number of new patients and the possibility of conducting analyses that have not been explored, we aimed to assess the efficacy and safety of tirzepatide (5–15 mg) *versus* placebo for weight management over at least 26 weeks. Analyses were stratified by diabetes status to enable a precise assessment of tirzepatide's effects in individuals with and without diabetes.

METHODS

Study design and protocol

We performed a systematic review and meta-analysis following the Cochrane Handbook for Systematic Reviews of Interventions and structured it according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations [30, 31]. The study protocol was prospectively registered (PROSPERO ID: CRD42024583763).

Search strategy

Independent examiners (EC and PAES) conducted a systematic search in MEDLINE, Embase, and Cochrane Library from inception to August 27, 2024. The complete search strategy is presented in Supplementary Table 1. Subsequently, study selection was conducted as described in Supplementary Methods.

Eligibility criteria

Inclusion was restricted to double-blind RCTs comparing once-weekly subcutaneous tirzepatide (5–15 mg) *versus* placebo in ≥18-year-old patients with or without diabetes, extending over at least 26 weeks, and reporting at least one outcome of interest. We included only original, peer-reviewed RCTs published in English with full-text availability. There was no restriction regarding publication date.

We excluded studies that (i) had overlapping populations; (ii) involved participants using another medication that causes weight loss; (iii) did not include a placebo group; (iv) had incomplete data or unavailable full texts; (v) included patients with and without diabetes in a unified analysis; or (vi) were post-hoc analyses, trial registry records, conference abstracts, comments, or brief reports.

We opted not to exclude studies that had a lead-in, open-label, non-randomized, and non-controlled phase, followed by a double-blind, randomized, placebo-controlled phase; however, only data from the second treatment period were used in our analyses. Similarly, trials assessing alternative tirzepatide doses and/or control conditions were not excluded, provided they also included treatment arms meeting our eligibility criteria; in such cases, only data from patients treated with tirzepatide at 5–15 mg or placebo were pooled in our analyses.

Outcomes

The prespecified primary outcome was the percentage change in body weight from baseline to endpoint. Secondary outcomes were: (i) the probability of achieving weight reduction thresholds of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%; (ii) the absolute change from baseline to endpoint in body weight, BMI, and waist circumference; and (iii) the risk of experiencing any adverse event (AE), individual AEs (diarrhea, constipation, nausea, vomiting, dyspepsia, and gastrointestinal events [severe/serious]), any serious AE, death, and any AE leading to treatment discontinuation.

Additional outcomes were: (i) the percentage change from baseline to endpoint in lipid levels (total cholesterol, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglycerides, and free fatty acids); (ii) the absolute change from baseline to endpoint in systolic and diastolic blood pressure, hemoglobin A1c (HbA1c), and physical function-related scores (Short Form Health Survey 36 Version 2 Physical Functioning Domain Score and Impact of Weight on Quality of Life-Lite-Clinical Trials Version Physical Function Composite Score); and (iii) the risk of experiencing other individual AEs (eructation, abdominal pain, decreased appetite, cholelithiasis, acute cholecystitis, coronavirus diasease-19, upper respiratory tract infection, dizziness, injection site reaction, hepatic events [severe/serious], gallbladder disease [severe/serious], pancreatitis [adjudication-confirmed], renal events [severe/serious], major adverse cardiovascular events [adjudication-confirmed], arrhythmias or cardiac conduction disorders [severe/serious], malignancies, hypersensitivity [severe/serious], hypoglycemia [blood glucose <54 mg/dL], and major depressive disorder or suicidal behavior/ideation), and individual AEs leading to treatment discontinuation (nausea, vomiting, diarrhea, and abdominal pain).

Data extraction

Two independent authors (EC and MCO) performed standardized data extraction, as detailed in Supplementary Methods.

Main statistical analyses

For each subpopulation analysis, the DerSimonian and Laird random-effects model was used to calculate the pooled estimates along with their 95% confidence intervals (95%CIs). Risk ratios (RRs) for dichotomous outcomes were estimated using the Mantel-Haenszel method, while mean differences (MDs) for continuous outcomes were calculated using the Inverse-Variance method. We also computed the pooled proportion (mean or percentage) of each arm for primary and secondary outcomes. Heterogeneity was tested using the Cochran's Q test and quantified by the I^2 statistics. In the presence of substantial heterogeneity ($p < 0.1$ for Cochran's Q test and $I^2 > 50\%$), we conducted a leave-one-out sensitivity analysis for those outcomes involving at least three studies. Statistical significance was considered at $p < 0.05$.

Interaction and meta-regression analyses

We conducted a test for interaction to assess whether the treatment effect differed between patients with and without diabetes. This analysis was performed only for primary and secondary outcomes that were evaluated in both subpopulations (i.e., outcomes assessed exclusively in one subgroup were not included). In accordance with Cochrane's guidelines [31], a p-value less than 0.10 in the interaction test was considered indicative of a statistically significant interaction between subpopulations.

However, it is important to note that the included studies involving patients with diabetes had different baseline BMI cutoffs compared with those enrolling individuals without the disease. Thus, potential differences between subpopulations may be partially explained by variations in baseline BMI rather than by diabetes status alone. To explore this hypothesis, we performed a meta-regression for primary and secondary outcomes, using the mean baseline BMI from each study as the explanatory variable. A p-value less than 0.05 in the test of moderators was considered indicative of a statistically significant linear association [31]. Stratification by diabetes status was not retained in this analysis, as our aim was to assess the independent effect of baseline BMI. R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria) was used exclusively for this analysis, whereas all other statistical procedures were executed using Review Manager (version 5.4.1; Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Subgroup and sensitivity analyses

A predefined subgroup analysis was also performed according to tirzepatide dose (5, 10, and 15 mg) for all primary and secondary outcomes. P-values less than 0.10 were considered statistically significant for the test of subgroup interaction, in line with Cochrane's recommendations [31].

Lastly, we conducted a sensitivity analysis by excluding the SURMOUNT-3 [15] and -4 [14] trials from all weight-related outcomes. The former [15] included only individuals who had already lost 5% of body weight through lifestyle intervention prior to randomization, potentially attenuating subsequent weight loss during pharmacological treatment. The latter [14] randomized only participants who had tolerated and completed 36 weeks of tirzepatide, characterizing a maintenance phase with an expected lower total weight loss. This sensitivity analysis aimed to assess whether the inclusion of these trials significantly affected effect estimates and/or contributed to heterogeneity.

Risk of bias assessment

Two authors (EC and PAES) independently assessed the overall risk of bias based on judgments from individual domains, according to the Cochrane Risk of Bias 2 (RoB 2) tool [32]. Given that each subpopulation analysis in our study comprised only five studies, publication bias assessment using funnel plots could not be performed, as this method lacks adequate statistical power when fewer than ten studies are involved [33].

RESULTS

Study selection

The initial search yielded 1,125 records. After removing duplicates ($n = 515$), we screened 610 records by title and abstract. Subsequently, we fully reviewed 24 references and included 10 of them, encompassing a total of 6,641 patients [14–17, 34–39]. We excluded 13 studies (14 references) because they either had treatment durations shorter than 26 weeks [9, 40–44], did not include a placebo group [45–51], or included patients with and without diabetes in a unified analysis [19] (Supplementary Fig. 1).

Study and patient characteristics

Baseline characteristics of the included studies are summarized in Table 1 and detailed in Supplementary Tables 2 and 3.

Patients with diabetes (with BMI ≥ 23 kg/m^2). A total of 2,174 patients were enrolled across five RCTs [35–39], of whom 1,545 (71.1%) were randomly assigned to tirzepatide and 629 (28.9%) to placebo, with treatment duration ranging from 26–72 weeks. Within the tirzepatide group, 292 (18.9%) patients were treated with 5 mg, 603 (39.0%) with 10 mg, and 650 (42.1%) with 15 mg. Two trials (1,011 [46.4%] patients) [37, 38] recruited participants with baseline BMI ≥ 25 kg/m^2, whereas the remaining three studies (1,163 [53.6%] patients) [35, 36, 39] set the inclusion threshold at BMI ≥ 23 kg/m^2.

Patients without diabetes (with overweight/obesity). A total of 4,467 patients were included across five RCTs [14–17, 34], of whom 2,893 (64.8%) were randomized to tirzepatide and 1,574 (35.2%) to placebo, with treatment duration ranging from 52–72 weeks. In the tirzepatide arm, 630 (21.8%) patients were treated with 5 mg, 706 (24.4%) with 10 mg, 701 (24.2%) with 15 mg, and 856 (29.6%) with the maximum tolerated dose (10 or 15 mg). All trials [14–17, 34] involved patients with obesity (BMI ≥ 30 [≥ 27 in Asia] kg/m^2) or overweight (BMI ≥ 27 [≥ 24 in Asia] kg/m^2) along with at least one weight-related complication, excluding diabetes.

Main analyses

Patients with diabetes (with BMI ≥ 23 kg/m^2). In individuals with diabetes, tirzepatide resulted in a mean weight reduction of 12.1% (10.3 kg), while placebo led to a reduction of 2.6% (1.5 kg; Table 2; Supplementary Fig. 2). Compared with placebo, tirzepatide provided a statistically greater reduction in body weight, both in relative (MD −9.54%; 95%CI −11.55, −7.53%; $p < 0.01$; $I^2 = 79\%$) and absolute terms (MD −9.06 kg; 95%CI −10.48, −7.63 kg; $p < 0.01$; $I^2 = 76\%$; Table 2; Supplementary Fig. 3). Leave-one-out sensitivity analyses are described in Supplementary Table 4.

The percentages of patients who achieved weight reductions of ≥5%, ≥10%, and ≥15% with tirzepatide were 71.3%, 46.7%, and 28.7%, respectively; while the corresponding percentages for individuals receiving placebo were 20.8%, 5.3%, and 1.3% (Table 2; Supplementary Fig. 2). Compared with the placebo group, the tirzepatide group had a statistically higher probability of achieving weight reductions of ≥5% (RR 6.03; 95%CI 2.39, 15.21; $p < 0.01$; $I^2 = 91\%$), ≥10% (RR 19.85; 95%CI 4.70, 83.89; $p < 0.01$; $I^2 = 69\%$), and ≥15% (RR 19.02; 95%CI 10.09, 35.84; $p < 0.01$; $I^2 = 0\%$; Table 2; Supplementary Fig. 4). Leave-one-out sensitivity analyses are presented in Supplementary Table 4. Pooled analyses for weight reductions of ≥20% and ≥25% were not feasible due to only one study [37] reporting these outcomes in patients with diabetes.

Tirzepatide was associated with a mean reduction of 4.1 kg/m^2 in BMI and 11.1 cm in waist circumference, while placebo reduced 0.6 kg/m^2 and 3.0 cm, respectively (Table 2; Supplementary Fig. 2). Compared with placebo, tirzepatide use resulted in a statistically greater absolute reduction in BMI (MD −3.38 kg/m^2; 95%CI −4.10, −2.66 kg/m^2; $p < 0.01$; $I^2 = 44\%$) and waist circumference (MD −7.59 cm; 95%CI −9.94, −5.25 cm; $p < 0.01$; $I^2 = 74\%$; Table 2; Supplementary Fig. 3). Leave-one-out sensitivity analyses are presented in Supplementary Table 4.

The percentages of patients in the tirzepatide and placebo groups who experienced each safety-related outcome are shown in Table 2 and Supplementary Fig. 2. Compared with placebo, tirzepatide provided a statistically higher risk of diarrhea (RR 1.85; 95%CI 1.21, 2.83; $p < 0.01$; $I^2 = 48\%$), constipation (RR 2.62; 95%CI 1.58, 4.36; $p < 0.01$; $I^2 = 0\%$), nausea (RR 2.79; 95%CI 1.56, 4.97; $p < 0.01$; $I^2 = 61\%$), vomiting (RR 3.58; 95%CI 2.18, 5.89; $p < 0.01$; $I^2 = 0\%$), and dyspepsia (RR 2.28; 95%CI 1.39, 3.74; $p < 0.01$; $I^2 = 0\%$). There were no significant differences between both groups in terms of any AE (RR 1.10; 95%CI 0.98, 1.23; $p = 0.12$; $I^2 = 66\%$), any serious AE (RR 0.97; 95%CI 0.67, 1.39; $p = 0.85$; $I^2 = 0\%$), death (RR 0.32; 95%CI 0.04, 2.71; $p = 0.30$; $I^2 = 27\%$), and any AE leading to treatment discontinuation (RR 1.54; 95%CI 0.75, 3.14; $p = 0.24$; $I^2 = 43\%$; Table 2; Supplementary Fig. 5). Leave-one-out sensitivity analyses are described in Supplementary Table 4. Pooled analyses for severe/serious gastrointestinal events was not feasible due to only one study [37] reporting this outcome in patients with diabetes.

For additional outcomes, compared with placebo, tirzepatide use granted: (i) a statistically greater improvement in blood pressure, HbA1c, and lipid levels; and (ii) a statistically higher risk of eructation and decreased appetite (Supplementary Table 5).

Patients without diabetes (with overweight/obesity). In individuals without diabetes, tirzepatide resulted in a mean weight reduction of 16.8% (13.0 kg), while placebo led to an increase of 1.8% (6.6 kg; Table 2; Supplementary Fig. 2). Compared with the placebo group, the tirzepatide group had a statistically greater reduction in body weight, both in relative (MD −17.15%; 95%CI −19.38, −14.92%; $p < 0.01$; $I^2 = 87\%$) and absolute terms (MD −18.11 kg; 95%CI −24.62, −11.61 kg; $p < 0.01$; $I^2 = 97\%$; Table 2; Supplementary Fig. 3). Leave-one-out sensitivity analyses are described in Supplementary Table 6.

The percentages of individuals who achieved weight reductions of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% with tirzepatide were 88.2%, 76.2%, 61.7%, 45.5%, and 28.0%, respectively; while the corresponding percentages for patients receiving placebo were 34.0%, 15.6%, 7.1%, 2.8%, and 1.5% (Table 2; Supplementary Fig. 2). Compared with placebo, tirzepatide provided a statistically higher probability of achieving weight reduction of ≥5% (RR 2.59; 95%CI 2.33, 2.87; $p < 0.01$; $I^2 = 0\%$), ≥10% (RR 5.45; 95%CI 3.25, 9.14; $p < 0.01$; $I^2 = 85\%$), ≥15% (RR 11.22; 95%CI 5.52, 22.78;

Table 1. Baseline characteristics of the included studies.

Source	Study ID	Country	Design	Sample size, n	Age, yr[a] (SD)	Female, n (%)	Body weight, kg[a] (SD)	BMI, kg/m^{2a} (SD)	Waist circumference, cm[a] (SD)	Tirzepatide dose, mg	Treatment duration, wk
Patients with diabetes (with BMI ≥ 23 kg/m^2)											
Dahl et al. [35]	NCT04039503 (SURPASS-5)	Multinational	RCT multicenter	475	60.7 (10.0)	211 (44.4)	95.2 (21.6)	33.4 (6.1)	NR	5, 10, or 15	40
Frias et al. [36]	NCT03131687	Multinational	RCT multicenter	210	56.8 (8.6)	95 (45.2)	91.5 (21.0)	32.5 (5.9)	NR	5, 10, or 15	26
Garvey et al. [37]	NCT04657003 (SURMOUNT-2)	Multinational	RCT multicenter	938	54.2 (10.6)	476 (50.7)	100.7 (21.1)	36.1 (6.6)	114.9 (14.4)	10 or 15	72
Heise et al. [38]	NCT03951753	Germany	RCT dual center	73	60.8 (7.3)	21 (28.8)	95.9 (14.3)	31.6 (4.6)	NR	15	28
Rosenstock et al. [39]	NCT03954834 (SURPASS-1)	Multinational	RCT multicenter	478	54.1 (11.9)	231 (48.3)	85.9 (19.8)	31.9 (6.6)	NR	5, 10, or 15	40
Patients without diabetes (with overweight/obesity)											
Aronne et al. [14]	NCT04660643 (SURMOUNT-4)	Multinational	RCT multicenter	670	48.5 (12.5)	473 (70.6)	85.2 (21.1)	30.5 (6.4)	97.5 (15.1)	10 or 15	52
Jastreboff et al. [34]	NCT04184622 (SURMOUNT-1)	Multinational	RCT multicenter	2539	44.9 (12.5)	1714 (67.5)	104.8 (22.1)	38.0 (6.8)	114.1 (15.2)	5, 10, or 15	72
Malhotra et al. [17]	NCT05412004 (SURMOUNT-OSA)	Multinational	RCT multicenter	469	49.8 (11.4)	142 (30.3)	115.1 (22.8)	38.9 (6.5)	121.0 (14.6)	10 or 15	52
Wadden et al. [15]	NCT04657016 (SURMOUNT-3)	Multinational	RCT multicenter	579	45.6 (12.2)	364 (62.9)	101.9 (21.4)	35.9 (6.3)	109.4 (15.0)	10 or 15	72
Zhao et al. [16]	NCT05024032 (SURMOUNT-CN)	China	RCT multicenter	210	36.1 (9.0)	103 (49.0)	91.8 (16.0)	32.3 (3.8)	104.8 (10.5)	10 or 15	52

BID twice daily, *cm* centimeter, *ID* identification number, *kg* kilograms, *kg/m*^{2} kilograms per square meter, *mg* milligrams, *n* number, *NR* not reported, *RCT* randomized controlled trial, *SD* standard deviation, *wk* weeks, *yr* year(s).

[a]Mean.

Table 2. Results from pooled analyses for primary and secondary outcomes.

Outcome	*k*	Tirzepatide arm (proportion[a]/total)	Placebo arm (proportion[a]/total)	Effect estimate (95%CI)	*P*-value	I^2, %
Change in body weight, %						
Patients with diabetes	2	−12.1/986	−2.6/430	MD −9.54 (−11.55, −7.53)	<0.0001	79
Patients without diabetes	5	−16.8/2893	1.8/1574	MD −17.15 (−19.38, −14.92)	<0.0001	87
Change in body weight, kg						
Patients with diabetes	5	−10.3/1545	−1.5/629	MD −9.06 (−10.48, −7.63)	<0.0001	76
Patients without diabetes	3	−13.0/763	6.6/696	MD −18.11 (−24.62, −11.61)	<0.0001	97
Weight reduction of ≥5%						
Patients with diabetes	4	71.3%/1070	20.8%/125	RR 6.03 (2.39, 15.21)	0.0001	91
Patients without diabetes	2	88.2%/2037	34.0%/712	RR 2.59 (2.33, 2.87)	<0.0001	0
Weight reduction of ≥10%						
Patients with diabetes	4	46.7%/1500	5.3%/601	RR 19.85 (4.70, 83.89)	<0.0001	69
Patients without diabetes	3	76.2%/2324	15.6%/1004	RR 5.45 (3.25, 9.14)	<0.0001	85
Weight reduction of ≥15%						
Patients with diabetes	4	28.7%/1500	1.3%/601	RR 19.02 (10.09, 35.84)	<0.0001	0
Patients without diabetes	3	61.7%/2324	7.1%/1004	RR 11.22 (5.52, 22.78)	<0.0001	76
Weight reduction of ≥20%						
Patients without diabetes	2	45.5%/2183	2.8%/935	RR 16.03 (10.94, 23.48)	<0.0001	0
Weight reduction of ≥25%						
Patients without diabetes	2	28.0%/2183	1.5%/935	RR 18.72 (11.07, 31.64)	<0.0001	0
Change in BMI, kg/m^2						
Patients with diabetes	3	−4.1/1137	−0.6/486	MD −3.38 (−4.10, −2.66)	<0.0001	44
Patients without diabetes	3	−4.8/763	2.5/696	MD −6.70 (−8.83, −4.56)	<0.0001	98
Change in WC, cm						
Patients with diabetes	2	−11.1/782	−3.0/366	MD −7.59 (−9.94, −5.25)	<0.0001	74
Patients without diabetes	4	−14.7/2659	−0.1/1339	MD −12.44 (−13.79, −11.09)	<0.0001	61
Any AE						
Patients with diabetes	5	73.3%/1545	70.7%/629	RR 1.10 (0.98, 1.23)	0.1200	66
Patients without diabetes	5	79.5%/2893	70.3%/1574	RR 1.12 (1.08, 1.16)	<0.0001	0
Diarrhea						
Patients with diabetes	5	18.1%/1545	9.1%/629	RR 1.85 (1.21, 2.83)	0.0050	48
Patients without diabetes	5	22.0%/2893	7.7%/1574	RR 2.84 (2.35, 3.43)	<0.0001	0
Constipation						
Patients with diabetes	5	7.3%/1545	2.5%/629	RR 2.62 (1.58, 4.36)	0.0002	0
Patients without diabetes	3	16.2%/2417	5.6%/1170	RR 3.02 (2.34, 3.90)	<0.0001	0
Nausea						
Patients with diabetes	5	19.1%/1545	6.4%/629	RR 2.79 (1.56, 4.97)	0.0005	61
Patients without diabetes	5	27.7%/2893	8.5%/1574	RR 3.07 (2.58, 3.66)	<0.0001	0
Vomiting						
Patients with diabetes	5	9.7%/1545	2.7%/629	RR 3.58 (2.18, 5.89)	<0.0001	0
Patients without diabetes	5	11.1%/2893	1.8%/1574	RR 6.04 (4.11, 8.87)	<0.0001	0

Table 2. continued

Outcome	*k*	Tirzepatide arm (proportion[a]/total)	Placebo arm (proportion[a]/total)	Effect estimate (95%CI)	*P*-value	I^2, %
Dyspepsia						
Patients with diabetes	5	6.9%/1545	2.9%/629	RR 2.28 (1.39, 3.74)	0.0010	0
Patients without diabetes	3	9.6%/2417	3.3%/1170	RR 2.66 (1.90, 3.71)	<0.0001	0
Severe/serious GI events						
Patients without diabetes	5	3.0%/2893	0.9%/1574	RR 3.16 (1.81, 5.51)	<0.0001	0
Any serious AE						
Patients with diabetes	5	5.9%/1545	6.4%/629	RR 0.97 (0.67, 1.39)	0.8500	0
Patients without diabetes	5	5.9%/2893	5.9%/1574	RR 0.93 (0.73, 1.20)	0.6000	0
Death						
Patients with diabetes	5	0.1%/1545	0.3%/629	RR 0.32 (0.04, 2.71)	0.3000	27
Patients without diabetes	5	0.3%/2893	0.4%/1574	RR 0.69 (0.24, 1.95)	0.4800	0
Any AE (treatment discontinuation)						
Patients with diabetes	5	6.1%/1545	3.7%/629	RR 1.54 (0.75, 3.14)	0.2400	43
Patients without diabetes	5	5.6%/2893	2.4%/1574	RR 2.23 (1.22, 4.06)	0.0090	49

95%CI 95% confidence interval, *AE* adverse event, *BMI* body mass index, *cm* centimeter, *GI* gastrointestinal, *kg* kilograms, *kg/m²* kilograms per square meter, *MD* mean difference, *n* number, *RR* risk ratio, *WC* waist circumference.

[a]$Mean = \frac{(X1 \cdot N1)+(X2 \cdot N2)+\ldots+(Xn \cdot Nn)}{N1+N2+\ldots+Nn}$ or $percentage = \frac{Et \cdot 100}{Nt}$ (Xn mean value of each study, Nn number of patients of each study, Et total number of events in the arm, Nt total number of patients in the arm).

p < 0.01; $I^2 = 76\%$), ≥20% (RR 16.03; 95%CI 10.94, 23.48; p < 0.01; $I^2 = 0\%$), and ≥25% (RR 18.72; 95%CI 11.07, 31.64; p < 0.01; $I^2 = 0\%$; Table 2; Supplementary Fig. 4). Leave-one-out sensitivity analyses are presented in Supplementary Table 6.

Tirzepatide was associated with a mean reduction of 4.8 kg/m^2 in BMI and 14.7 cm in waist circumference, while placebo increased 2.5 kg/m^2 and reduced 0.1 cm, respectively (Table 2; Supplementary Fig. 2). Compared with the placebo group, the tirzepatide group had a statistically greater absolute reduction in BMI (MD −6.70 kg/m^2; 95%CI −8.83, −4.56 kg/m^2; p < 0.01; $I^2 = 98\%$) and waist circumference (MD −12.44 cm; 95%CI −13.79, −11.09 cm; p < 0.01; $I^2 = 61\%$; Table 2; Supplementary Fig. 3). Leave-one-out sensitivity analyses are described in Supplementary Table 6.

The percentages of individuals in the tirzepatide and placebo groups who experienced each safety-related outcome are shown in Table 2 and Supplementary Fig. 2. Compared with placebo, tirzepatide provided a statistically higher risk of any AE (RR 1.12; 95%CI 1.08, 1.16; p < 0.01; $I^2 = 0\%$), diarrhea (RR 2.84; 95%CI 2.35, 3.43; p < 0.01; $I^2 = 0\%$), constipation (RR 3.02; 95%CI 2.34, 3.90; p < 0.01; $I^2 = 0\%$), nausea (RR 3.07; 95%CI 2.58, 3.66; p < 0.01; $I^2 = 0\%$), vomiting (RR 6.04; 95%CI 4.11, 8.87; p < 0.01; $I^2 = 0\%$), dyspepsia (RR 2.66; 95%CI 1.90, 3.71; p < 0.01; $I^2 = 0\%$), severe/serious gastrointestinal events (RR 3.16; 95%CI 1.81, 5.51; p < 0.01; $I^2 = 0\%$), and any AE leading to treatment discontinuation (RR 2.23; 95%CI 1.22, 4.06; p < 0.01; $I^2 = 49\%$). There were no significant differences between both groups in terms of any serious AE (RR 0.93; 95%CI 0.73, 1.20; p = 0.60; $I^2 = 0\%$) and death (RR 0.69; 95%CI 0.24, 1.95; p = 0.48; $I^2 = 0\%$; Table 2; Supplementary Fig. 6).

For additional outcomes, compared with placebo, tirzepatide use resulted in: (i) a statistically greater improvement in blood pressure, HbA1c, lipid levels, and physical function-related scores; and (ii) a statistically higher risk of eructation, abdominal pain, decreased appetite, dizziness, injection site reaction, and nausea leading to treatment discontinuation (Supplementary Table 5).

Interaction and meta-regression analyses

In contrast to patients with diabetes, those without the disease showed significantly more pronounced reductions in BMI (−6.70 *versus* −3.38 kg/m^2), waist circumference (−12.44 *versus* −7.59 cm), and body weight, both in relative (−17.15 *versus* −9.54%) and absolute terms (−18.11 *versus* −9.06 kg), as confirmed by the test for interaction (p < 0.10; Fig. 1; Table 3). Furthermore, the probabilities of experiencing diarrhea and achieving a weight reduction of ≥5% and ≥10% were significantly higher in patients without diabetes (Table 3).

In short, the meta-regression analysis showed no significant relationships according to BMI (test of moderators with p-value ≥ 0.05), except for the probability of achieving weight reduction of ≥15% (p < 0.01). For this outcome, increasing baseline BMI was associated with a reduced magnitude of tirzepatide's effect relative to placebo (Supplementary Table 7).

Subgroup and sensitivity analyses

Subgroup analyses revealed no significant differences in safety outcomes across tirzepatide doses, regardless of diabetes status. On the other hand, its efficacy on weight loss over placebo increased proportionally with the administered dose. Heterogeneity was reduced or eliminated in most analyses (Supplementary Tables 8 and 9).

Sensitivity analyses omitting the SURMOUNT-3 [15] and/or -4 [14] trials indicated no significant change in pooled effect estimate or heterogeneity for weight-related outcomes among individuals without diabetes. Exceptionally, excluding the SURMOUNT-3 [15] trial eliminated heterogeneity for the ≥10% weight-loss outcome, yet tirzepatide remained statistically favored (Supplementary Table 10).

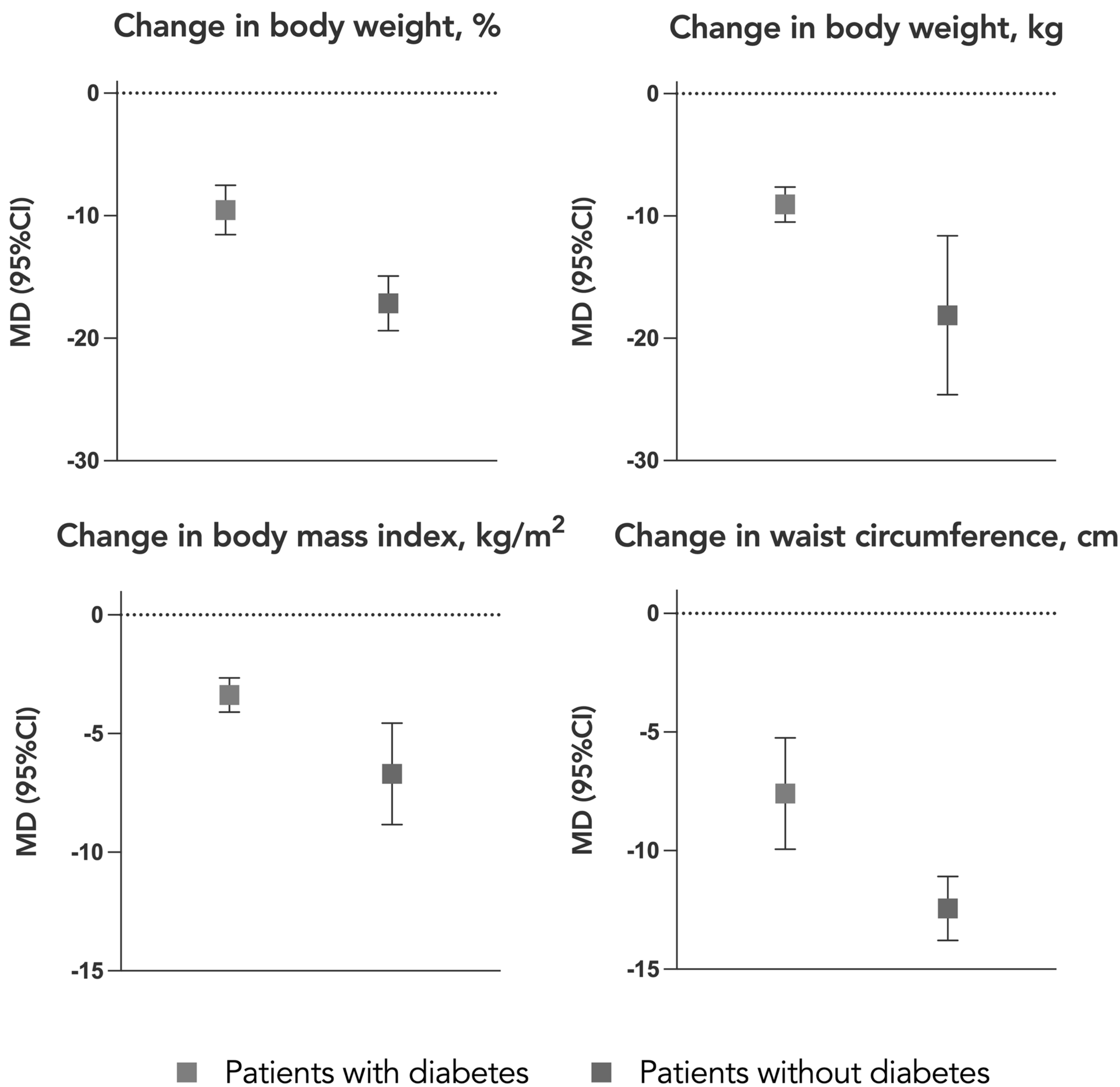

Fig. 1 Graphical summary of pooled mean differences (95%CI) comparing tirzepatide versus placebo for changes in body weight (relative and absolute), body mass index, and waist circumference, stratified by diabetes status. Greater reductions were observed in patients without diabetes, as confirmed by statistically significant interaction tests. 95%CI 95% confidence interval, cm centimeter, kg kilograms, *kg/m²* kilograms per square meter, MD mean difference.

Risk of bias assessment

As shown in Supplementary Fig. 7, some concerns emerged for one RCT [38] due to deviations from the intended intervention, and for two others [15, 17] owing to dropout rates exceeding 20%. All remaining trials [14, 16, 34–37, 39] were at low overall risk of bias, according to the RoB 2 tool [32].

DISCUSSION

This systematic review and meta-analysis enrolling 6,641 participants compared tirzepatide (5–15 mg) *versus* placebo for weight management over 26–72 weeks. Analyses were stratified by diabetes status, enabling precise assessment of tirzepatide's effects in individuals with and without diabetes. Across both subpopulations, tirzepatide significantly outperformed placebo, yielding: (i) greater relative and absolute weight reductions; (ii) higher probability of achieving weight-loss thresholds of ≥5%, ≥10%, and ≥15%; and (iii) greater improvements in BMI, waist circumference, blood pressure, HbA1c, and lipid levels. These benefits were accompanied by an acceptable safety profile, characterized by predominantly mild to moderate, well-tolerated AEs. Notably, tirzepatide led to significantly greater weight-related improvements in patients without diabetes, while safety outcomes were statistically similar across subpopulations.

Given that included patients with diabetes had a baseline BMI ≥ 23 kg/m^2 and those without diabetes ≥27 (≥ 24 in Asia) kg/m^2, we considered that differences in treatment response between these subpopulations might be attributable not only to diabetes status but also to baseline BMI. However, our meta-regression analysis did not support a significant association

Table 3. Results from interaction assessment.

Outcome	k	Tirzepatide arm, n	Placebo arm, n	Effect estimate (95%CI)	I^2, %	P-value[a]
Change in body weight, %						<0.0001
Patients with diabetes	2	986	430	MD −9.54 (−11.55, −7.53)	79	
Patients without diabetes	5	2893	1574	MD −17.15 (−19.38, −14.92)	87	
Change in body weight, kg						0.0080
Patients with diabetes	5	1545	629	MD −9.06 (−10.48, −7.63)	76	
Patients without diabetes	3	763	696	MD −18.11 (−24.62, −11.61)	97	
Weight reduction of ≥5%						0.0700
Patients with diabetes	4	1070	125	RR 6.03 (2.39, 15.21)	91	
Patients without diabetes	2	2037	712	RR 2.59 (2.33, 2.87)	0	
Weight reduction of ≥10%						0.0982
Patients with diabetes	4	1500	601	RR 19.85 (4.70, 83.89)	69	
Patients without diabetes	3	2324	1004	RR 5.45 (3.25, 9.14)	85	
Weight reduction of ≥15%						0.2800
Patients with diabetes	4	1500	601	RR 19.02 (10.09, 35.84)	0	
Patients without diabetes	3	2324	1004	RR 11.22 (5.52, 22.78)	76	
Change in BMI, kg/m^2						0.0040
Patients with diabetes	3	1137	486	MD −3.38 (−4.10, −2.66)	44	
Patients without diabetes	3	763	696	MD −6.70 (−8.83, −4.56)	98	
Change in WC, cm						0.0004
Patients with diabetes	2	782	366	MD −7.59 (−9.94, −5.25)	74	
Patients without diabetes	4	2659	1339	MD −12.44 (−13.79, −11.09)	61	
Any AE						0.7800
Patients with diabetes	5	1545	629	RR 1.10 (0.98, 1.23)	66	
Patients without diabetes	5	2893	1574	RR 1.12 (1.08, 1.16)	0	
Diarrhea						0.0700
Patients with diabetes	5	1545	629	RR 1.85 (1.21, 2.83)	48	
Patients without diabetes	5	2893	1574	RR 2.84 (2.35, 3.43)	0	
Constipation						0.6300
Patients with diabetes	5	1545	629	RR 2.62 (1.58, 4.36)	0	
Patients without diabetes	3	2417	1170	RR 3.02 (2.34, 3.90)	0	
Nausea						0.7500
Patients with diabetes	5	1545	629	RR 2.79 (1.56, 4.97)	61	
Patients without diabetes	5	2893	1574	RR 3.07 (2.58, 3.66)	0	
Vomiting						0.1000
Patients with diabetes	5	1545	629	RR 3.58 (2.18, 5.89)	0	
Patients without diabetes	5	2893	1574	RR 6.04 (4.11, 8.87)	0	
Dyspepsia						0.6200
Patients with diabetes	5	1545	629	RR 2.28 (1.39, 3.74)	0	
Patients without diabetes	3	2417	1170	RR 2.66 (1.90, 3.71)	0	
Any serious AE						0.8900
Patients with diabetes	5	1545	629	RR 0.97 (0.67, 1.39)	0	
Patients without diabetes	5	2893	1574	RR 0.93 (0.73, 1.20)	0	
Death						0.5300
Patients with diabetes	5	1545	629	RR 0.32 (0.04, 2.71)	27	
Patients without diabetes	5	2893	1574	RR 0.69 (0.24, 1.95)	0	
Any AE (treatment discontinuation)						0.4400
Patients with diabetes	5	1545	629	RR 1.54 (0.75, 3.14)	43	
Patients without diabetes	5	2893	1574	RR 2.23 (1.22, 4.06)	49	

95%CI 95% confidence interval, *AE* adverse event, *BMI* body mass index, *cm* centimeter, *GI* gastrointestinal, *kg* kilograms, *kg/m^2* kilograms per square meter, *MD* mean difference, *n* number, *RR* risk ratio, *WC* waist circumference.
[a]Interaction test.

between higher baseline BMI and greater weight-loss response. These findings underscore that individuals with diabetes tend to experience reduced improvements in weight-related outcomes with weight-loss treatments [25–29]. The reason for this discrepancy is not yet fully understood, despite the existence of several theories [52–56]. However, it does not seem to represent a significant limitation for tirzepatide use in patients with diabetes, as even modest weight reductions are sufficient to achieve improvements in metabolism, risk factors, and quality of life for this population [56–61]. Furthermore, tirzepatide leads to a clinically significant reduction in HbA1c in people with diabetes, which indicates that its benefits in this population extend far beyond weight loss.

Another noteworthy finding is that tirzepatide increases the probability of achieving different percentages of weight loss compared with placebo. Currently, there is a significant long-term difficulty in attaining these weight reductions through non-pharmacological strategies, particularly at thresholds of ≥15% and ≥20% [3, 62, 63]. These results enable physicians to inform patients that the likelihood of reaching certain weight loss goals is higher with tirzepatide than with lifestyle modifications alone. Notably, this advantage is even more relevant for those seeking more ambitious goals.

Our safety analyses revealed that, overall, tirzepatide is associated with a higher incidence of AEs compared with placebo in both subpopulations. Nevertheless, these events were generally referred as mild to moderate and the most common AEs – diarrhea and nausea – were predominantly reported as well tolerated by patients. This is backed up by the low occurrence of treatment discontinuation due to diarrhea (< 1.0%) and nausea (< 2.0%). On the other hand, while there was a non-significant difference in any serious AEs in both subpopulations, tirzepatide showed a statistically increased risk of severe/serious gastrointestinal events in patients without diabetes, though these were infrequent (3.0%). Therefore, tirzepatide use often results in AEs that are generally well tolerated and of mild to moderate intensity. Severe and poorly tolerated events may also occur, but less frequently.

Subgroup analyses by tirzepatide dose also provided clinically relevant findings. In patients with and without diabetes, a consistent safety pattern was observed across the entire dose spectrum, while weight reduction increased proportionally with the dose. This suggests that higher doses could be used to achieve greater efficacy without compromising the safety profile.

To the best of our knowledge, this is the first systematic review and meta-analysis stratified by diabetes status comparing tirzepatide *versus* placebo for weight management. Separate analyses were adopted to address the distinct biological characteristics and therapeutic needs of individuals with and without diabetes [52–56]. This methodological approach offers deeper insights into tirzepatide's effects, identifies subgroup-specific benefits and risks, and guides individualized clinical decision-making.

The current study presents additional advantages over previous meta-analyses. It incorporates the four most recent RCTs [14–17], adding 1928 patients to the evidence base, thereby increasing the robustness and statistical power of our analyses. Additionally, we included only trials lasting ≥26 weeks to enhance analytical homogeneity, given tirzepatide's markedly distinct weight-loss pattern – with more pronounced reductions before week 24 and an attenuated phase thereafter toward a plateau [64]. We also restricted the intervention to the 5–15 mg dose range, in line with regulatory provisions [11]. Lastly, safety analyses were broadened to include clinically relevant outcomes such as major adverse cardiovascular events and cardiac rhythm disorders.

This study has several limitations. First, we were unable to assess how different diet and exercise regimens prescribed in the included RCTs may have influenced participant outcomes. Second, it was unfeasible to conduct treatment comparisons in long-term outcomes, as the included studies had a limited treatment duration. Third, our pooled analysis was based on published study-level data rather than real-world patient data; therefore, this may have contributed to a potential overestimation of tirzepatide's clinical benefits. Fourth, some outcomes had significant between-study heterogeneity; however, additional analyses could identify the source of heterogeneity in most cases. Fifth, the absence of stratified data in the primary studies precluded analysis of tirzepatide response by other baseline variables, including sex – despite prior reports suggesting greater tirzepatide-induced weight loss in women [65, 66]. Lastly, it is important to note as a limitation the specific designs of two included studies [14, 15], as they included a preparation period before randomization; however, sensitivity analyses excluding these studies showed consistent results.

To conclude, tirzepatide resulted in statistically significant and clinically meaningful weight reduction compared with placebo, especially in patients without diabetes (with overweight/obesity), while maintaining an acceptable safety profile in both subpopulations. In addition, higher tirzepatide doses could be used to achieve greater efficacy without compromising the safety profile. Further RCTs are needed to overcome the limitations identified.

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AUTHOR CONTRIBUTIONS

EC: design, conduct/data collection, analysis, writing manuscript. PAES: design, conduct/data collection, analysis. MCO: conduct/data collection, analysis. CCPSJ: design, analysis, writing manuscript. BH: design, analysis, writing manuscript.

COMPETING INTERESTS

BH is on the Advisory Board of Novo Nordisk, Eli-Lilly, Astra Zeneca, Merck S/A, and received speaker honoraria from Novo Nordisk, Eli-Lilly, Astra Zeneca, Boehringer Ingelheim, Merck S/A and Abbott Nutrition. BH is Primary Investigator in BrTrials, and has conducted clinical trials by Eli-Lilly, Novo Nordisk and Boehringer Ingelheim. EC, PAES, MCO, and CCPSJ have no conflicts of interest to declare.

ADDITIONAL INFORMATION

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