Efficacy and safety of novel twincretin tirzepatide a dual GIP and GLP-1 receptor agonist in the management of type-2 diabetes: A Cochrane meta-analysis

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Abstract

Background: Till date, there is no Cochrane meta-analysis available which has analyzed efficacy and safety of tirzepatide in type-2 diabetes. This meta-analysis was undertaken to address this knowledge gap. **Methods:** Electronic databases were searched for randomized controlled trials (RCTs) involving people with diabetes receiving tirzepatide compared to a placebo/active comparator. Primary outcome was to evaluate changes in HbA1c. Secondary outcomes were to evaluate alterations in blood–glucose, glycemic targets, weight, lipids, and adverse events. **Results:** From 34 articles initially screened, data from six RCTs involving 3484 patients were analyzed. Over 12–52 weeks, individuals receiving tirzepatide had significantly greater lowering of HbA1c [mean difference (MD) = -0.75% (95% confidence interval (CI): -1.05 to -0.45); $P < 0.01$; $I^2 = 100\%$], fasting glucose [MD = -0.75 mmol/L (95% CI: -1.05 to– -0.45); $P < 0.01$; $I^2 = 100\%$], 2-h post-prandial-glucose [MD = -0.87 mmol/L (95% CI: -1.12 to -0.61); $P < 0.01$; $I^2 = 99\%$], weight [MD = -8.63 kg (95% CI: -12.89 to -4.36); $P < 0.01$; $I^2 = 100\%$], body mass index [MD = -1.80 kg/m^2 (95% CI: -2.39 to -1.21); $P < 0.01$; $I^2 = 99\%$], and waist circumference [MD = -4.43 cm (95% CI: -5.31 to -3.55); $P < 0.01$; $I^2 = 95\%$] as compared to dulaglutide, semaglutide, degludec, or glargine. Patients receiving tirzepatide had higher odds of achieving HbA1c <6.5% compared to active controls [odds ratio (OR) = 4.39 (95% CI: 2.44–7.92); $P < 0.01$; $I^2 = 90\%$]. Tirzepatide use had significantly higher odds of weight loss >5% [OR = 19.18 (95% CI: 2.34–157.17); $P < 0.01$; $I^2 = 99\%$], >10% [OR = 21.40 (95% CI: 2.36–193.94); $P < 0.01$; $I^2 = 98\%$], and >15% [OR = 32.84 (95% CI: 2.27–474.33); $P = 0.01$; $I^2 = 96\%$] compared to active-control group. Treatment-emergent adverse events [risk ratio (RR) = 1.43 (95% CI: 1.14–1.80); $P < 0.01$; $I^2 = 40\%$] and severe adverse events [RR = 1.00 (95% CI: 0.64–1.57); $P = 1.00$; $I^2 = 49\%$] were not different. High data heterogeneity and the presence of publication bias limits the grading of current data from "moderate to low." **Conclusion:** Tirzepatide has impressive glycemic efficacy and weight-loss data over 1-year clinical use. The need for higher grade, long-term efficacy, and safety data remains.

Keywords: Meta-analysis, safety, tirzepatide, twincretin, type-2 diabetes

Introduction

Glucose-dependent insulinotropic peptide (GIP) is four amino acid incretin peptide, produced by K-cells of duodenum and proximal jejunum, released in response to oral carbohydrates and lipid load, having short half-life of 4–7 min and inactivated by dipeptidyl peptidase (DPP)-4 enzyme.[1] GIP receptors have been documented in heart, pancreas, gastric mucosa, adipose tissue, bone, adrenal cortex, and brain.[1] Unlike GLP-1, GIP has glucagonostatic in the hyperglycemic state, but glucagonotropic property during normoglycemic and hypoglycemic state.[1] Glucagon is known to prevent hypoglycemia. Hence, this

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glucagonotropic property in hypoglycemic states makes GIP-based therapy for type-2 diabetes (T2DM) really attractive due to the lower risk of hypoglycemia. T2DM is characterized by loss of insulinotropic property of GIP along with loss of glucagonostatic in the hyperglycemic state (GIP resistance).[2] Some studies have even documented glucagonotropic property of GIP during hyperglycemia, which is otherwise normally seen only during normoglycemia or hypoglycemia.[2] Hojberg *et al*.[3] demonstrated that supraphysiologic exogenous GIP administration in people with T2DM increased the insulin response (incretin effect), partly restoring insulinotropic properties. Physiologic studies have demonstrated that coinfusion of glucagon-like peptide (GLP)-1 and GIP has a synergetic effect resulting in significantly increased insulin response and glucagonostatic response resulting in a significant lowering of blood glucose, as compared to the separate administration of each of the hormone in T2DM.[4]

This lead to development of tirzepatide, a novel dual GIP/GLP-1 receptor agonist (twincretin), formulated as a synthetic peptide containing 39-amino acids, based on the native GIP.[5] Tirzepatide has a comparable GIP receptor binding affinity to native GIP and five times lower GLP-1 receptor affinity than that of native GLP-1.[5] The clinical efficacy, tolerability, and safety of tirzepatide have been reported in different randomized controlled trials (RCTs).[6] However, to date, there is no Cochrane meta-analysis available which has analyzed the clinical efficacy and safety of this novel twincretin in T2DM. Hence, the aim of this Cochrane meta-analysis was to evaluate the efficacy and safety of tirzepatide in the management of T2DM.

Since different doses of tirzepatide have been tried (5 mg weekly, 10 mg weekly, 12 mg weekly, and 15 mg weekly); in our meta-analysis, outcomes were assessed for patients receiving tirzepatide 10 mg/12 mg weekly compared to controls. This is based on available data which suggest maximal clinical benefits of tirzepatide with 10–15 mg weekly dose.

Methods

Methodology

The recommendations of Cochrane Handbook for Systematic Reviews of Interventions were strictly followed which carrying out this meta-analysis.[7] The predefined protocol has been registered in PROSPERO having Registration number of CRD42021261242. All RCTs published till September 2021 were considered. This meta-analysis has been reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses, the filled checklist of which can be found at end of manuscript.[7] Since ethical approval already exists for individual studies, no separate approval was required for this meta-analysis. PICOS criteria were used to screen and select studies. The studies needed to have at least two treatment arms/groups, with one of the groups on tirzepatide and the other group receiving placebo or any other active comparator.

The primary outcome was to evaluate changes in HbA1c. Secondary outcomes were to evaluate alterations in fasting plasma glucose (FPG), 2-h postprandial blood–glucose (PPBG), percentage of patients achieving HbA1c <6.5%, body weight, waist circumference, hypoglycemia, lipid parameters, adverse events, insulin resistance (IR) and glucagon. Analysis of primary and secondary outcomes were done based on control group received an active comparator – marked as active-control group (ACG) or placebo – marked as passive-control group (PCG).

Search method for identification of studies

A detailed electronic databases of Embase, Cochrane central register of controlled trials, medline, clinicaltrials.gov, ctri.nic.in, Google scholar, and global health were searched using a Boolean search strategy: (tirzepatide) AND (diabetes).

Data extraction and study selection

Data extraction was carried out independently by two authors using data extraction forms. Details have been elaborated elsewhere.[8] Patient characteristics of the included studies are elaborated in Supplementary Table 1.

Assessment of risk of bias in included studies

Three authors independently assessed the risk of bias using the risk of bias assessment tool in Review Manager (Revman) Version 5.3 (The Cochrane Collaboration, Oxford, UK 2014) software. The details of the different biases looked into have already been elaborated elsewhere,[8] and for this meta-analysis, they have been elaborated in Figure 2a and 2b.

Measures of treatment effect

For continuous variables, outcomes were expressed as mean difference (MD). SI were used for analysis. Dichotomous outcomes results were expressed as risk ratio (RR) with 95% confidence interval (CI). Adverse events were presented as post treatment absolute risk differences (hazard ratios). RevMan 5.3 was used for comparing MD of outcomes.

Assessment of heterogeneity

Heterogeneity was initially assessed by studying the forest plot generated for outcomes. Subsequently heterogeneity was analyzed using a Chi-square test on *N*-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test.[9] The details of interpretation of I^2 values have already been elaborated elsewhere.[8]

Grading of the results

An overall grading of the evidence (certainty of the evidence) related to each of the outcomes of the meta-analysis was done using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach.[10] The details of how GRADE was used to generate the summary of findings (SOF) table, and how grading of evidence was done as "high," "moderate," or "low," have been elaborated elsewhere.[8] The SOF table has been presented as Table 1. Publication bias was assessed by plotting Funnel Plots.[10] The presence of one or more of the smaller studies outside inverted funnel plot signifies significant publication bias.[11] The detailed grading of results of the study has been elaborated in Table 1.

Table 1: Summary of findings of the key outcomes of this meta-analysis

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE) Comments
	Risk with Control	Risk with Tirzepatide			
HbA1c ACG	The mean hbA1c ACG was 8.28%	MD 0.77 lower (1.01 lower-0.53 lower)	-	3046 (4 RCTs)	⊕⊕◯◯ Low[a,b]
Fasting glucose ACG	The mean fasting glucose ACG was 9.39 mmol/L	MD 0.75 lower (1.05 lower-0.45 lower)	-	3046 (4 RCTs)	⊕⊕◯◯ Low[a,b]
Weight loss >5% ACG	195 per 1000	823 per 1000 (362-974)	OR 19.18 (2.34-157.17)	2956 (3 RCTs)	⊕⊕⊕◯ Moderate[a]
Weight loss >10% ACG	79 per 1000	646 per 1000 (168-943)	OR 21.40 (2.36-193.94)	2956 (3 RCTs)	⊕⊕◯◯ Low[a,b]
People with >1 treatment-emergent adverse events (TAEs) ACG	644 per 1000	721 per 1000 (674-765)	OR 1.43 (1.14-1.80)	3091 (4 RCTs)	⊕⊕⊕◯ Moderate[b]
Hypoglycemia ACG	435 per 1000	198 per 1000 (116-316)	OR 0.32 (0.17-0.60)	3091 (4 RCTs)	⊕⊕⊕⊕ High
People achieving HbA1c <6.5% ACG	426 per 1,000	765 per 1,000 (644-855)	OR 4.39 (2.44-7.92)	3046 (4 RCTs)	⊕⊕◯◯ Low[c]

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. I^2 is 100% suggestive of considerable heterogeneity in data

b. Funnel plot is suggestive of the presence of most of the studies outside the plot; hence, it is likely that significant publication bias is present

c. I^2 is more than 90% suggestive of considerable heterogeneity in data

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: mean difference; OR: odds ratio; ACG: active control group

Data synthesis

Data were pooled as a random-effect model for the analysis of outcomes. Outcomes were expressed as 95% CI. Forrest plots were plotted with the left side of graph favoring tirzepatide and the right side favoring control. RevMan 5.3 software was used to plot Forrest plots.

Results

The initial search revealed 34 articles [Figure 1]. Following screening of titles, abstracts, and full-texts, number of studies were narrowed to 23 studies which were evaluated in detail [Figure 1]. Data from six RCTs involving 3484 people with T2DM which fulfilled all criteria were analyzed.[12-17] Pirro *et al.*[18] and Wilson *et al.*[6] published outcomes of tirzepatide on extended serum metabolic and lipid parameters. Hartman *et al.*[19] published outcomes of tirzepatide on fatty liver disease. Thomas *et al.*[20] published on impact of tirzepatide on beta-cell function and IR. Since papers by Pirro *et al.,*[18] Wilson *et al.,*[6] Hartman *et al.,*[19] and Thomas *et al.*[20] were post-hoc analysis of original RCT by Frias *et al.*[12](2018); in our analysis, the results from these four papers have been pooled with data from Frias *et al.* (2018) to avoid duplicity.

In the study by Frias *et al.* (2018), patients were randomly assigned to receive tirzepatide 1 mg weekly, tirzepatide 5 mg weekly, tirzepatide 10 mg weekly, tirzepatide 15 mg weekly, dulaglutide 1.5 mg weekly, and placebo. In this meta-analysis, the outcomes of patients tirzepatide 10 mg weekly compared to those receiving dulaglutide 1.5 mg weekly have been analyzed under ACG as Frias 2018a. The outcomes of patients receiving tirzepatide 10 mg weekly compared to those receiving placebo have been analyzed under PCG as Frias 2018b. In the study by Frias *et al.* (2020),[13] the outcomes of patients gradually built up to tirzepatide 12 mg weekly and 15 mg weekly were compared to placebo. Since this study did not have tirzepatide 10 mg weekly arm, the outcomes of patients receiving tirzepatide 12 mg weekly were compared to those receiving placebo were analyzed under PCG. In the study by Frias *et al.* (2021),[14] patients were randomized to receive tirzepatide 5 mg weekly, 10 mg weekly, 15 mg weekly, or semaglutide 1 mg weekly.[14] The outcomes of patients tirzepatide 10 mg weekly compared to those receiving semaglutide 1 mg weekly have been analyzed under ACG. In the study by Rosenstock e*t al.* (2021),[15] patients were randomized to receive tirzepatide 5 mg weekly, 10 mg weekly, 15 mg weekly, or placebo. The outcomes of patients receiving tirzepatide 10 mg weekly were compared to those receiving placebo were analyzed under PCG (Rosenstock *et al.* 2021). In the study by Ludvik *et al.* (2021),[16] patients were randomized to receive tirzepatide 5 mg weekly, 10 mg weekly,

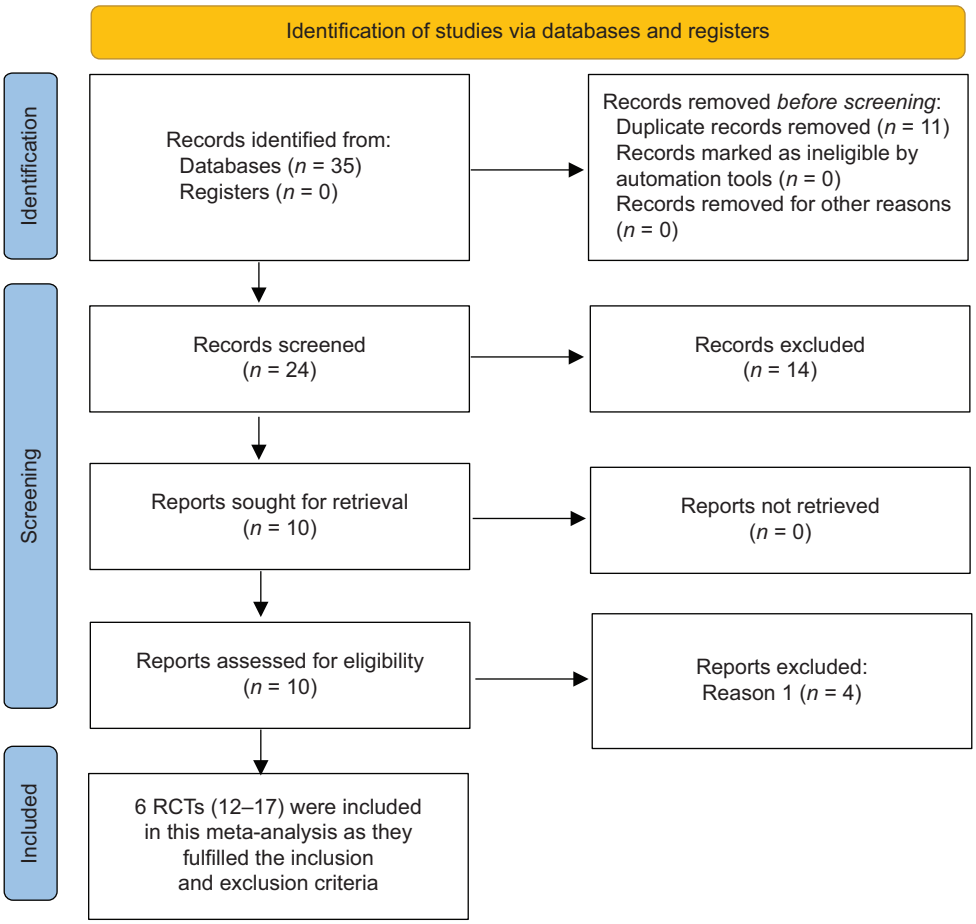

Figure 1: Flowchart elaborating on study retrieval and inclusion in the meta-analysis Reason-1: Four studies were found to be post-hoc analysis of RCTs[6,18-20] and hence have not been analyzed separately RCT: randomized controlled trial

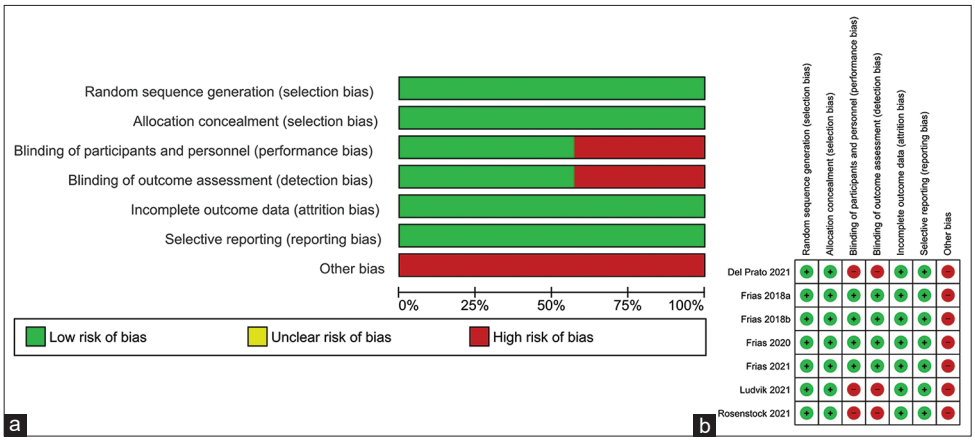

Figure 2: (a) Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies and (b) risk of bias summary: review authors' judgments about each risk of bias item for each included study

15 mg weekly, or insulin degludec. The outcomes of patients receiving tirzepatide 10 mg weekly were compared to those receiving insulin degludec were analyzed under ACG (Ludvik *et al.* 2021). In the study by del Prato *et al.* (2021),[17] patients were randomized to receive tirzepatide 5 mg weekly, 10 mg weekly, 15 mg weekly, or insulin glargine. The outcomes of patients receiving tirzepatide 10 mg weekly were compared to those receiving insulin glargine were analyzed under ACG (del Prato *et al.* 2021). The durations of follow-up in the studies by Frias *et al.* (2018),[12] Frias *et al.* (2020),[13] Frias *et al.* (2021),[14] Rosenstock *et al.* (2021),[15] Ludvik *et al.* (2021),[16] and del Prato *et al.* (2021)[17] were 26, 12, 40, 40, 52, and 52 weeks respectively. Supplementary Table 1 elaborates the details of studies included. The details of four

papers which have been post-hoc analysis of RCT by Frias *et al.* (2018) have been elaborated in Supplementary Table 2.

Risk of bias in the included studies

Summaries of risk of bias of the three studies included in the meta-analysis have been elaborated in Figure 2a, 2b, and Supplementary Table 3. Random sequence generation, allocation concealment bias, incomplete outcome data, and reporting bias were found to be at low risk in all six studies. Performance bias and detection bias were found to be low risk in three out of six studies (50%). Source of funding, especially funding from pharmaceutical organizations, and conflict of interests were looked into "other bias." All six studies had high "other bias" risk [Figure 2a, 2b].

Effect of tirzepatide on primary outcomes

HbA1c

Data from four studies involving 3046 people were analyzed to find the impact of tirzepatide on HbA1c compared to ACG. Tirzepatide had significantly greater lowering HbA1c compared to dulaglutide/semaglutide/degludec/glargine [MD = -0.75% (95% CI: -1.05 to -0.45); $P < 0.01$; $I^2 = 100\%$ (considerable heterogeneity); Figure 3a]. Data from three studies involving 371 people was analyzed to find the impact of tirzepatide on HbA1c compared to PCG. Tirzepatide had significantly greater lowering HbA1c compared to placebo [MD = -1.93% (95% CI: -1.95 to -1.90); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity); Figure 3b]

Effect of tirzepatide on secondary outcomes

Fasting glucose

Data from four studies involving 3046 people were analyzed to find impact of tirzepatide on FPG compared to ACG. Tirzepatide had significantly greater lowering of FPG compared to dulaglutide/semaglutide/degludec/glargine [MD = -0.75 mmol/L (95%CI: -1.05 to -0.45); $P < 0.01$; $I^2 = 100\%$; Figure 3c]. Data from three studies involving 371 people was analyzed to find the impact of tirzepatide on FPG compared to PCG. Tirzepatide had significantly greater lowering of FPG compared to placebo [MD = -3.42 mmol/L (95% CI: -4.08 to -2.76); $P < 0.01$; $I^2 = 98\%$; Figure 3d].

Postprandial glucose

Data from three studies involving 1,743 people were analyzed to find the impact of tirzepatide on PPBG compared to ACG. Tirzepatide had significantly greater lowering of PPBG as compared to active controls [MD = -0.87 mmol/L (95% CI: -1.12 to -0.61); $P < 0.0$; $I^2 = 99\%$; Figure 3e]. Data from one study involving 90 people were analyzed to find the impact of tirzepatide on PPG compared to PCG. Individuals receiving tirzepatide had significantly greater lowering of PPG as compared to placebo [MD-3.36 mmol/L (95% CI: -3.50 to -3.22); $P < 0.01$; Figure 3f].

Body weight

Data from four studies involving 3046 people were analyzed to find the impact of tirzepatide on body weight compared to ACG. Tirzepatide had significantly greater body weight lowering compared to dulaglutide/semaglutide/degludec/glargine [MD = -8.63 kg (95% CI: -12.89 to -4.36); $P < 0.01$; $I^2 = 100\%$; Figure 4a]. Data from three studies involving 375 people were analyzed to find the impact of tirzepatide on bodyvweight compared to PCG. Tirzepatide had a significantly greater body weight lowering compared to placebo [MD = -6.84 kg (95% CI: -8.02 to– -5.65); $P < 0.01$; $I^2 = 97\%$ (considerable heterogeneity); Figure 4b].

Body mass index (BMI)

Data from two studies (Frias 2018a and Frias 2021) involving 1028 people were analyzed to find the impact of tirzepatide on BMI compared to ACG. Tirzepatide had significantly greater BMI lowering compared to dulaglutide/semaglutide [MD = -1.80 kg/m^2 (95% CI: -2.39 to -1.21); $P < 0.01$; $I^2 = 99\%$ (considerable heterogeneity)]. Data from one study (Frias 2018b) involving 86 people were analyzed to find the impact of tirzepatide on BMI as compared to PCG. Tirzepatide had significantly greater BMI lowering compared to placebo [MD = -3.00 kg/m^2 (95% CI: -3.12 to -2.88); $P < 0.01$].

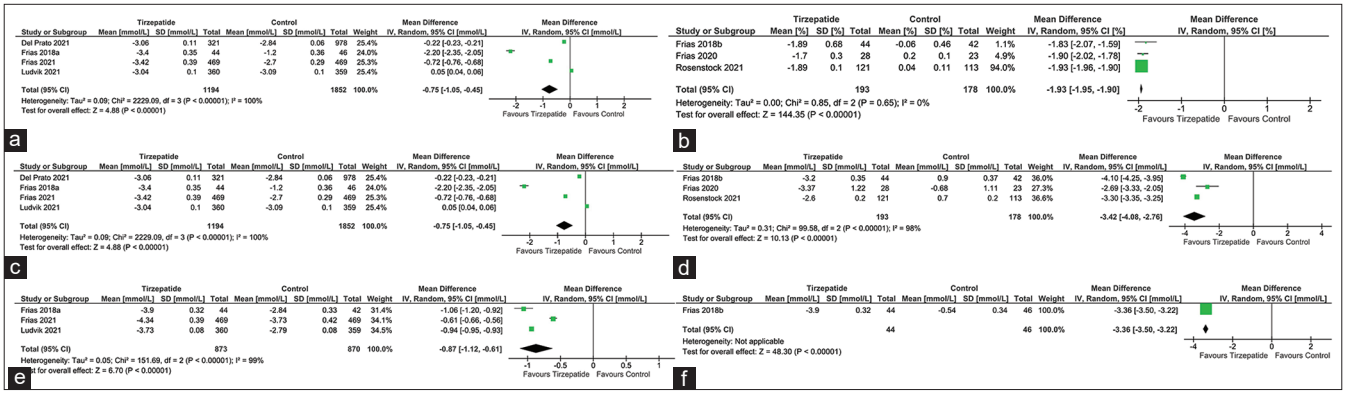

Figure 3: Forest plot highlighting the impact of tirzepatide on (a) HbA1c as compared to ACG; (b) HbA1c as compared to PCG; (c) fasting glucose as compared to ACG; (d) fasting glucose as compared to PCG; (e) postprandial group as compared to ACG; and (f) postprandial glucose as compared to PCG

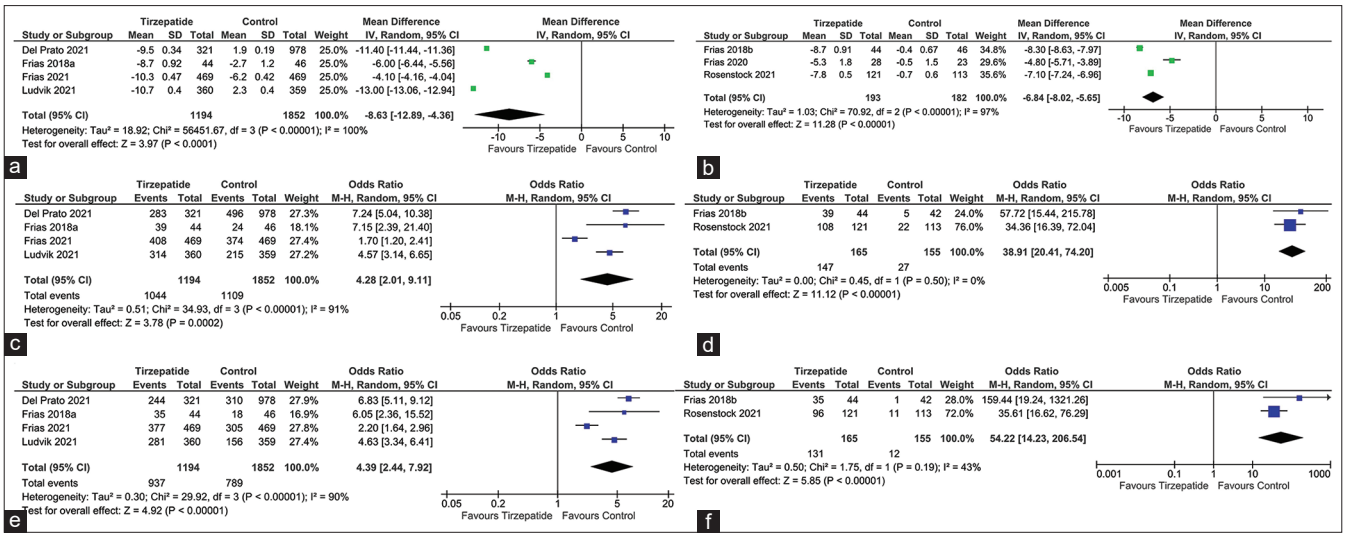

Figure 4: Forest plot highlighting the impact of tirzepatide on (a) body weight as compared to ACG; (b) body weight as compared to PCG; (c) percentage of people HbA1c <7% as compared to ACG; (d) percentage of people HbA1c <7% as compared to PCG; (e) percent of people achieving HbA1c <6.5% as compared to ACG; and (f) percent of people achieving HbA1c <6.5% as compared to PCG

Waist circumference

Data from two studies (Frias 2018a and Frias 2021) involving 1028 people were analyzed to find the impact of tirzepatide on waist circumference compared to ACG. Tirzepatide had significantly greater waist-circumference lowering compared to dulaglutide/semaglutide [MD = -4.43 cm (95% CI: -5.31 to -3.55); $P < 0.01$; $I^2 = 95\%$ (considerable heterogeneity)]. Data from two studies (Frias 2018b and Frias 2020) involving 137 people were analyzed to find the impact of tirzepatide on waist circumference compared to PCG. Tirzepatide had greater waist circumference lowering compared to placebo [MD = -4.83 cm (95% CI: -9.73 to 0.07); $P = 0.05$; $I^2 = 99\%$ (considerable heterogeneity)].

Percentage of people achieving HbA1c <7%, <6.5%, and <5.7%

Data from four studies involving 3046 patients were analyzed to evaluatethe impact of tirzepatide on attaining HbA1c <7% and <6.5% compared to ACG. Patients receiving tirzepatide had significantly higher odds of achieving HbA1c <7% [odds ratio (OR) = 4.28 (95% CI: 2.01–9.11); $P < 0.01$; $I^2 = 91\%$ (considerable heterogeneity); Figure 4c] and <6.5% [OR = 4.39 (95% CI: 2.44–7.92); $P < 0.01$; $I^2 = 90\%$ (considerable heterogeneity); Figure 4e] compared to active controls. Data from two study involving 320 patients were analyzed to evaluate the impact of tirzepatide on HbA1c <7% and <6.5% compared to PCG. Patients receiving tirzepatide had significantly higher odds of achieving HbA1c <7% [OR = 38.91 (95% CI: 20.41–74.20); $P < 0.01$; $I^2 = 0\%$ (low heterogenity); Figure 4d] and <6.5% [OR = 55.42 (95% CI: 14.23– 206.54); $P < 0.01$; $I^2 = 43\%$ (moderate heterogeneity); Figure 4f] as compared to placebo.

Diabetes reversal has often been defined as achieving normoglycemia (HbA1c <5.7%). Data from two studies (Del Prato 2021 and Ludvick 2021) involving 2018 patients were analyzed to evaluate the impact of tirzepatide on attaining HbA1c <5.7% compared to ACG. Patients receiving tirzepatide had significantly higher odds of achieving HbA1c <5.7% [OR = 12.54 (95% CI: 9.08–17.32); $P < 0.01$; $I^2 = 0\%$ (low heterogeneity)], compared to active controls. Data from one study (Rosenstock 2021) involving 234 patients were analyzed to evaluate the impact of tirzepatide on attaining HbA1c <5.7% compared to PCG. Patients receiving tirzepatide had significantly higher odds of achieving HbA1c <5.7% [OR = 47.44 (95% CI: 6.38–352.93); $P < 0.01$], compared to placebo.

People achieving weight loss of >5, 10, and 15%

Data from three studies involving 2956 patients were analyzed to evaluate the impact of tirzepatide on attaining more than 5, 10, and 15% weight loss as compared to active controls. Patients receiving tirzepatide had significantly higher odds of achieving weight loss more than 5% [OR = 19.18 (95% CI: 2.34–157.17); $P < 0.01$; $I^2 = 99\%$ (considerable heterogeneity); Supplementary Figure 1a], 10% [OR = 21.40 (95% CI: 2.36–193.94); $P < 0.01$; $I^2 = 98\%$ (considerable heterogeneity); Supplementary Figure 1b] and 15% [OR = 32.84 (95% CI: 2.27–474.33); $P = 0.01$; $I^2 = 96\%$ (considerable heterogeneity); Supplementary Figure 1c] as compared to ACG. Data from one study (Rosenstock 2021) involving 234 patients were analyzed to evaluate the impact of tirzepatide on attaining more than 5, 10, and 15% weight loss as compared to those receiving placebo. Patients receiving tirzepatide had significantly higher odds of achieving weight loss more than 5% [OR = 19.23 (95% CI: 9.80–37.73); $P < 0.01$], 10% [OR = 71.14 (95% CI: 9.60–526.86); $P < 0.01$], and 15% [OR = 45.85 (95% CI: 2.74–767.76); $P < 0.01$] as compared to PCG.

Lipid parameters

Data from two studies involving 1026 were analyzed to evaluate the impact of tirzepatide on triglycerides and LDL-C

compared to ACG. Patients receiving tirzepatide did not have significantly different triglycerides [MD-0.60 mmol/L (95% CI: -1.34 to 0.13); P = 0.11; I^2 = 100%; Supplementary Figure 2a] and LDL-C [MD = 0.10 mmol/L (95% CI: -0.08 to 0.28); P = 0.27; I^2 = 98%; Supplementary Figure 2b] as compared to dulaglutide/semaglutide. Data from one study involving 84 patients were analyzed to evaluate the impact of tirzepatide on triglycerides and LDL-C compared to PCG. Patients receiving tirzepatide had significantly lower triglycerides [MD = -1.83 mmol/L (95% CI: -1.93 to -1.73); P < 0.01; Supplementary Figure 2c] and LDL-C [MD = -0.19 mmol/L (95% CI: -0.24 to -0.14); P < 0.01; Supplementary Figure 2d] compared to placebo.

Data from two studies involving 1026 patients were analyzed to evaluate the impact of tirzepatide on HDL-C compared to ACG. Patients receiving tirzepatide had significantly higher HDL-C compared to dulaglutide/semaglutide [MD0.04 mmol/L (95% CI: 0.04–0.04); P < 0.01; I^2 = 0%; Supplementary Figure 2e]. Data from one study involving 84 patients were analyzed to evaluate the impact of tirzepatide on HDL-C compared to PCG. Patients receiving tirzepatide had significantly higher HDL-C as compared to placebo [MD0.03 mmol/L (95% CI: 0.02–0.04); P < 0.01; Supplementary Figure 2f].

Cardiovascular events

Data from one study (del Prato 2021) were analyzed to evaluate the impact of tirzepatide on MACE-4 (transient ischemic attacks, coronary revascularizations, hospitalizations for heart failure, and mortality) and hospitalization for heart failure as compared to active controls. 4-MACE events [RR = 0.83 (95% CI: 0.48–1.44); P = 0.50] and hospitalization for heart failure [RR = 0.51 (95% CI: 0.06–4.22); P = 0.53] were not significantly different in patients receiving tirzepatide as compared to glargine.

Safety

Data from four studies involving 3091 patients were analyzed to evaluate the impact of tirzepatide on treatment emergent adverse event (TAEs) and severe adverse events (SAEs) compared to ACG. The occurrence of TAEs [RR = 1.43 (95% CI: 1.14–1.80); P < 0.01; I^2 = 40% (moderate heterogeneity); Figure 5a;] but not SAEs [RR1.00 (95%CI: 0.64–1.57); P = 1.00; I^2 = 49%(moderate heterogeneity); Figure 5b] was significantly higher in people receiving tirzepatide as compared to active controls.

Data from three studies involving 393 patients were analyzed to evaluate impact of tirzepatide on TAEs and SAEs compared to PCG. Occurrence of TAEs [RR = 2.28 (95% CI: 0.86–6.08); P = 0.10; I^2 = 75% (moderate heterogeneity); Figure 5c] and SAEs [RR = 1.34 (95% CI: 0.36–4.91); P = 0.66; I^2 = 0% (low heterogeneity); Figure 5d] was not significantly different in people on tirzepatide compared to placebo.

Data from four studies involving 3091 patients were analyzed to evaluate the occurrence of hypoglycemia due to tirzepatide compared to ACG. Tirzepatide was associated with significantly lower occurrence of hypoglycemia [RR = 0.32 (95% CI: 0.17–0.60); P < 0.01; I^2 = 78% (moderate heterogeneity); Figure 5e] as compared to those receiving dulaglutide/semaglutide/degludec/glargine (ACG). Data from three studies involving 393 patients were analyzed to evaluate the occurrence of hypoglycemia in patients receiving tirzepatide compared to PCG. Tirzepatide was associated with increased hypoglycemia [RR = 4.22 (95% CI: 1.26–14.15); P = 0.02; I^2 = 0% (low heterogeneity); Figure 5f] as compared to placebo.

Most common adverse events noted across RCTs were gastrointestinal namely nausea, vomiting, diarrhea and gastro intestinal discomfort. Data from four studies involving 3091 patients were analyzed to evaluate occurrence of nausea, vomiting, and diarrhea in patients receiving tirzepatide compared to ACG. Patients receiving tirzepatide had similar occurrence of nausea [RR = 2.86 (95% CI: 0.56–14.52); P = 0.21; I^2 = 97% (considerable heterogeneity); Supplementary Figure 3a], vomiting [RR = 2.63 (95% CI: 0.62–11.16); P = 0.19; I^2 = 93% (considerable heterogeneity); Supplementary Figure 3b], and diarrhea [RR = 2.52 (95% CI: 0.92–6.92); P = 0.07; I^2 = 93; Supplementary Figure 3c] as compared to active controls. Data from three studies involving 594 patients were analyzed to evaluate occurrence of nausea, vomiting and diarrhea in patients receiving tirzepatide compared to PCG. Patients receiving tirzepatide had significantly higher nausea [RR = 3.02 (95% CI: 1.51–6.05); P < 0.01; I^2 = 0% (low heterogeneity); Supplementary Figure 3d], vomiting [RR = 3.63 (95% CI: 1.13–11.67); P = 0.03; I^2 = 0% (low heterogeneity); Supplementary Figure 3e], and diarrhea [RR = 3.17 (95% CI: 1.64–6.15); P < 0.01; I^2 = 31%; Supplementary Figure 3f] as compared to placebo.

Data from two studies (Frias 2018a and Frias 2021) involving 1043 were analyzed to evaluate the impact of tirzepatide on liver enzyme ALT compared to ACG. Patients receiving tirzepatide had lower ALT as compared to dulaglutide/semaglutide [MD = -4.34 U/L (95% CI: -9.14 to 0.46); P = 0.08; I^2 = 99%], which approached statistical significance. Data from one study (Frias 2018b) involving 102 patients were analyzed to evaluate the impact of tirzepatide on ALT compared to PCG. Patients receiving tirzepatide had significantly lower ALT compared to placebo [MD = -4.80U/L (95% CI: -5.52 to -4.08); P < 0.01].

Insulin resistance and glucagon

Data from two studies (Frias 2018a and Frias 2021) involving 1028 patients were analyzed to evaluate the impact on IR as estimated using homeostatic model of insulin resistance (HOMA-IR) compared to ACG. Patients receiving tirzepatide had significantly lower IR compared to dulaglutide/semaglutide [MD-0.44 (95% CI: -0.75 to -0.14); P < 0.01; I^2 = 99%]. Data from one study (Frias 2018b) involving 86 patients were analyzed to evaluate the impact of treatment on HOMA-IR compared to PCG. Patients receiving tirzepatide had significantly lower IR compared to placebo [MD = -0.70 (95%CI: -0.78 to -0.62); P < 0.01].

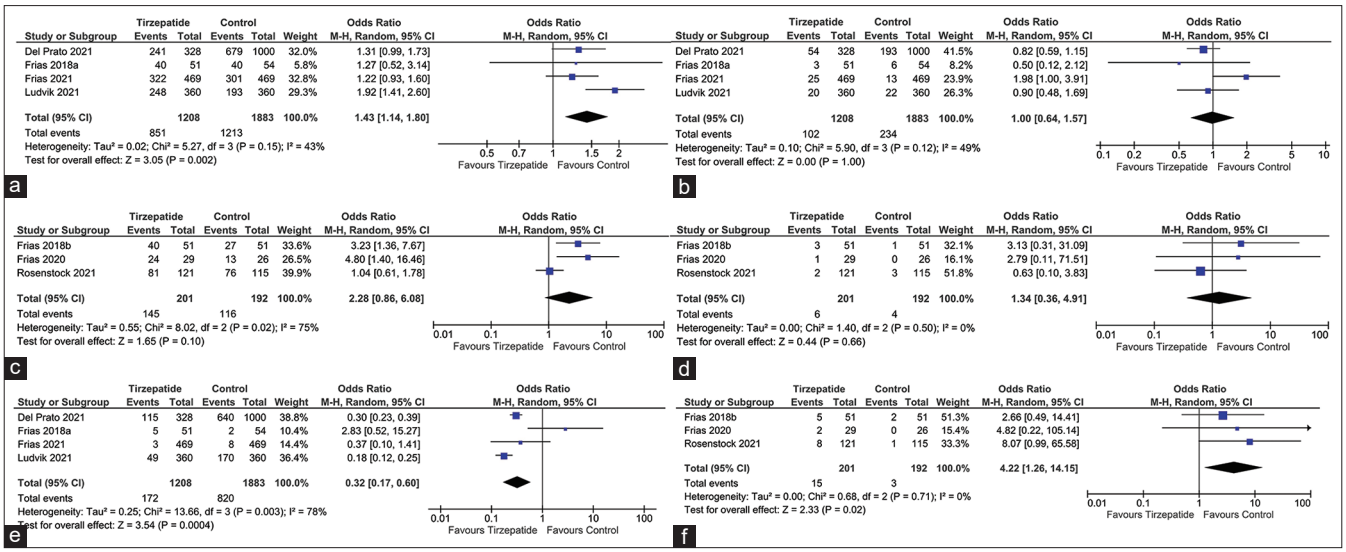

Figure 5: Forest plot highlighting the side-effect profile of the use of tirzepatide (a) total adverse events (TAEs) as compared to ACG; (b) severe adverse events (SAEs) as compared to ACG; (c) TAEs as compared to PCG; (d) SAEs as compared to PCG; (e) hypoglycemia as compared to ACG; and (f) hypoglycemia as compared to PCG

Data from two studies (Frias 2018a and Frias 2021) involving 1028 patients were analyzed to evaluate the impact on fasting glucagon compared to ACG. Patients receiving tirzepatide had lower glucagon when compared to dulaglutide/semaglutide [MD = -3.37 pmol/L (95% CI: -6.99 to 0.25); $P = 0.07$; $I^2 = 95\%$], which approached statistical significance. Data from one study (Frias 2018b) involving 86 patients were analyzed to evaluate the impact of treatment on glucagon as compared to PCG. Patients receiving tirzepatide had significantly lower glucagon when compared to placebo [MD = -3.20 (95%CI: -3.60 to -2.80); $P < 0.01$].

The funnel plot evaluating the presence of publication bias has been elaborated in Supplementary Figure 4.

Discussion

This is the first Cochrane meta-analysis to analyze and highlight the glycemic efficacy, weight loss properties, impact of different parameters of metabolic syndrome, tolerability, and side effect, and profile of tirzepatide in T2DM. Our meta-analysis follows a recently published meta-analysis involving smaller numbers of patients with fewer RCTs (2783 patients; four RCTs) published Bhagavathula *et al.*[21] Bhagavathula *et al.* did a pooled analysis of data of patients receiving tirzepatide 5, 10, and 15 mg/day and documented greater lowering of HbA1c (-1.94%, 95% CI: -2.02 to -1.87), fasting glucose (-54.72 mg/dL, 95% CI: -62.05 to -47.39), and weight (-8.47%, 95% CI: -9.66 to -7.27).[21] We instead focused on the detailed analysis of patients receiving 10 mg of tirzepatide per day as that was observed to be the most acceptable dose across trials.

Tirzepatide at 10 mg/12 mg per week was found to be superior to dulaglutide, semaglutide, degludec, and glargine insulin with regards to glycemic efficacy (HbA1c, FPG, PPG reduction, and percentage of patients achieving HbA1c <7, <6.5, and <5.7%) as well as reduction in obesity (body weight, BMI, waist circumference reduction, percentage of people achieving >5, 10%, and 15% weight loss). These results suggest that tirzepatide may be the most potent agent developed till date to tackle diabesity. Tirzepatide is an imbalanced dual agonist in favor of GIPR over GLP-1R activity. It shows equal affinity for the GIPR compared with native GIP but binds the GLP-1R with approximately 5-fold weaker affinity than native GLP-1.[2] This imbalanced activity of this novel multiincretin may explain the unprecedented impact on glycemic control, weight loss, and other pleotropic benefits of tirzepatide. Tirzepatide has the same potency and affinity as endogenous GIP but is comparatively weaker at the GLP-1R. The strong GIPR-induced glucose lowering shown in different mechanistic studies of GLP1R-null mice, along with the synergistic GLP-1R agonism, explains the excellent glycemic benefits with tirzepatide[5] Tirzepatide contains a C20 unsaturated di-acid acyl chain contributes to albumin binding and the overall properties of the molecule, enhancing its half-life enabling once-weekly dosing.[22]

Our meta-analysis showed that the impact on lipid parameter by tirzepatide is largely similar to that seen with dulaglutide and semaglutide, except of a significantly greater improvement in serum HDL-C levels with tirzepatide. A greater reduction in IR and glucagon levels were noted with tirzepatide as compared to dulaglutide and semaglutide. These may also contribute to the better glycemic and metabolic outcomes with tirzepatide when compared to the GLP1R analogues.

Patients receiving tirzepatide have increased occurrence of treatment emergent side effects both compared to active controls and placebo controls. The occurrences of SAEs were not different with tirzepatide as compared to active or placebo controls. Gastrointestinal side effects were predominant type

of side effects noted with tirzepatide, which is similar to GLP-1R analogues. It has been suggested in some studies that the significantly lower GLP-1R affinity of tirzepatide as compared to the GLP-1R analogues dulaglutide or semaglutide may explain marginally lower gastrointestinal side effects with this molecule. The reported antiemetic effect of GIP agonism may also contribute to the better gastrointestinal tolerability of tirzepatide.[21] How much of this translates into clinical evidence remains to be documented. The impressive impact on glycemia, weight loss, with lower risk of hypoglycemia from this meta-analysis suggests that tirzepatide will soon be approved for clinical use across the globe. Tirzepatide is a welcome armamentarium in the war against diabesity and should help in diabetes reversal in the real-world scenario. The side-effect profile especially gastrointestinal tolerance and monthly cost of therapy would have an important impact on the acceptability of this molecule in clinical practice, especially in the developing world. It must be realized that most of the evidence generated in this meta-analysis is of moderate to poor grade, due to significant associated data heterogeneity and publication bias. Hence, the need for better higher quality data on the use of tirzepatide in diabesity remains.

To conclude, it may be said that though this meta-analysis provides us with exciting data on impressive glycemic efficacy and weight loss properties of tirzepatide over 1-year clinical use. Need for more long-term efficacy and safety data of higher grade remains with regard to use of tirzepatide in diabesity.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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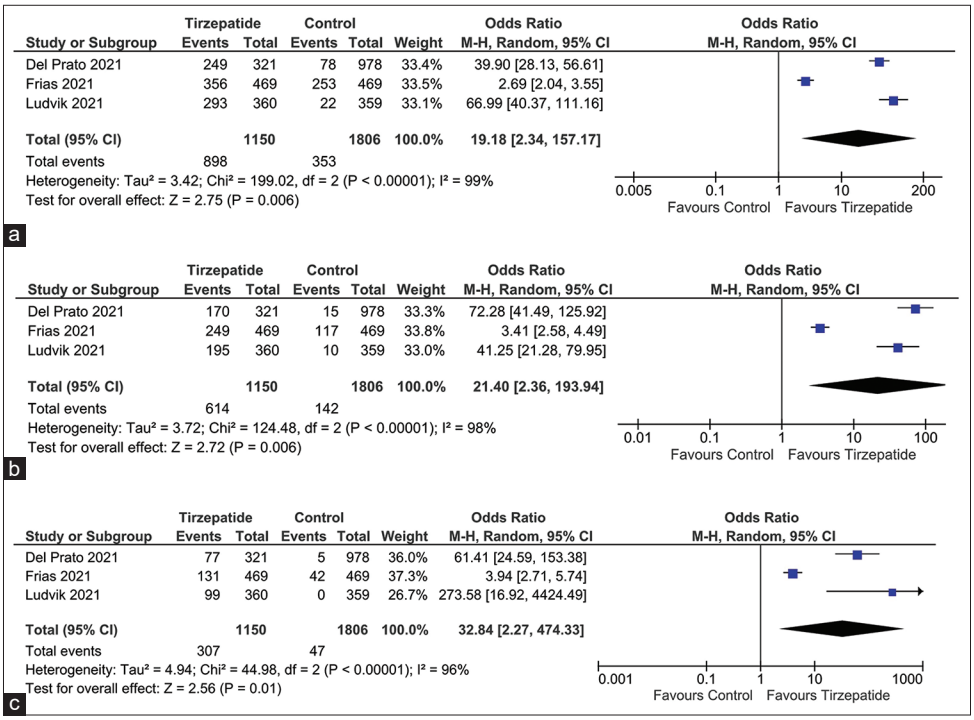
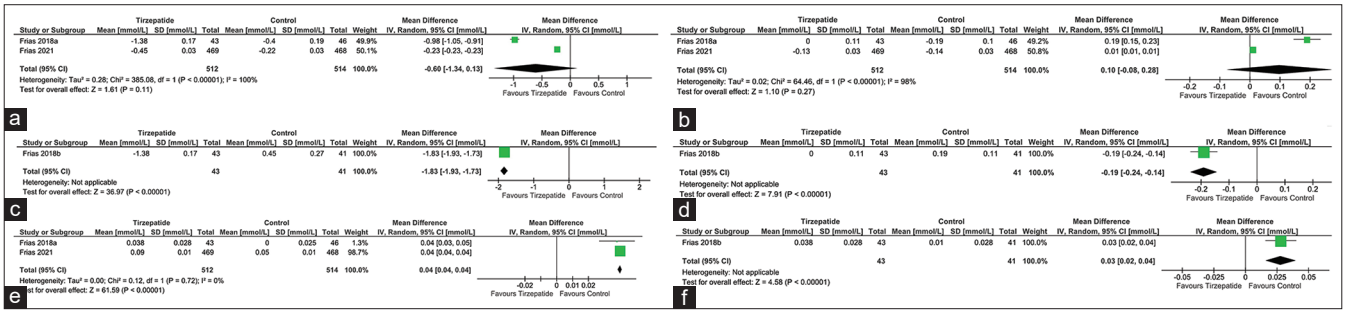
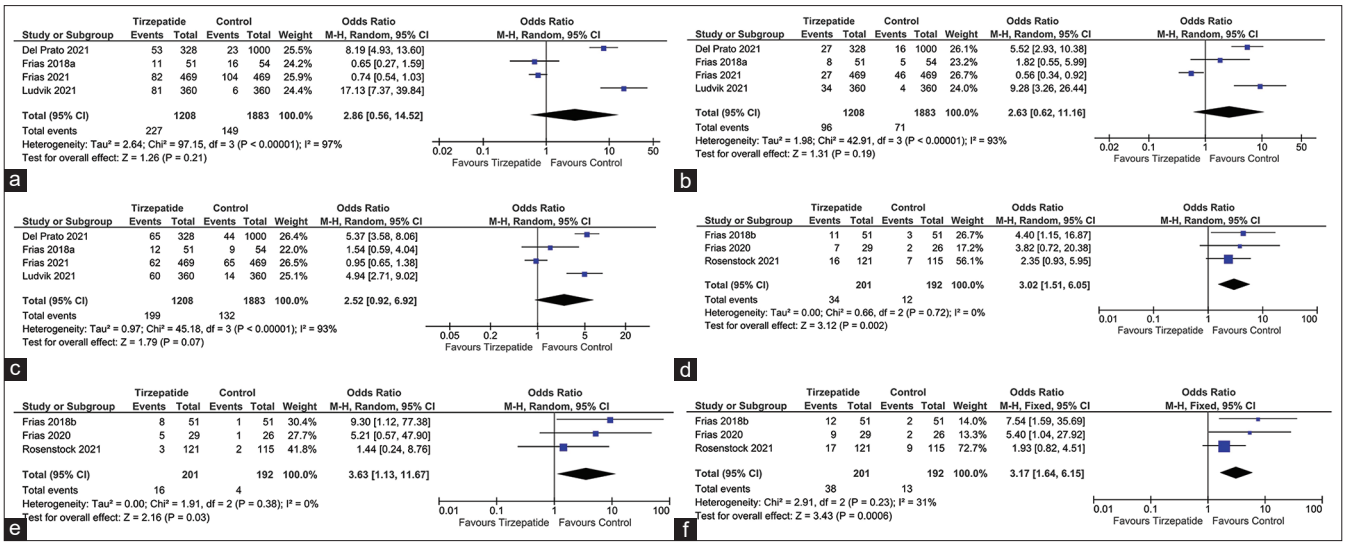
Supplementary file



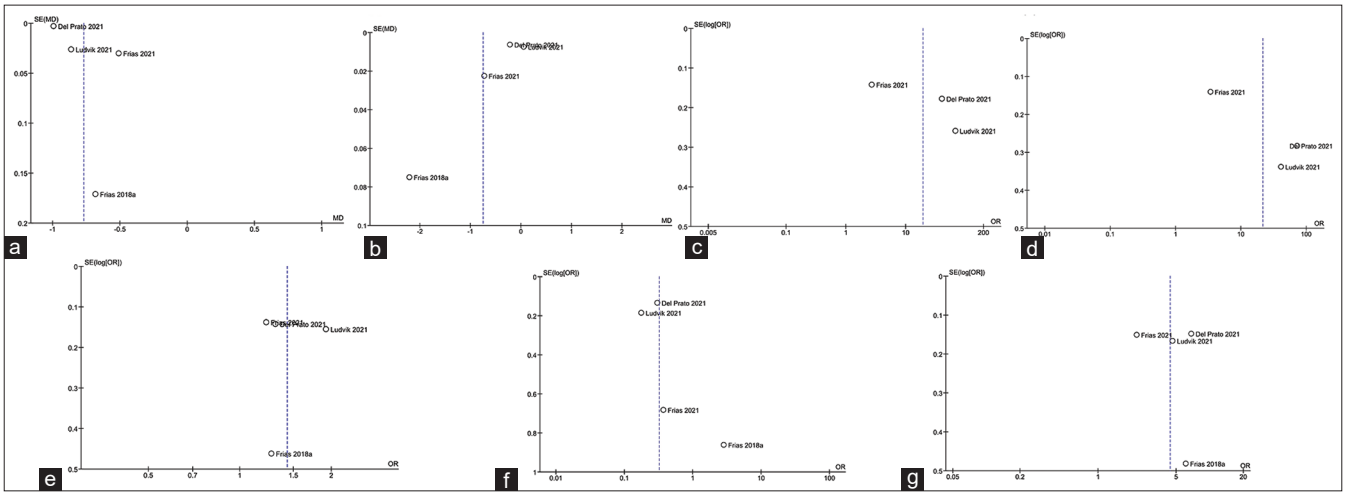
Supplementary Figure 1: Percentage of people having weight loss (a) >5% as compared to ACG; (b) >10% as compared to ACG; (c) >15% as compared to ACG



Supplementary Figure 2: Forest plot highlighting the impact of tirzepatide on (a) triglycerides as compared to ACG; (b) LDL-C as compared to ACG; (c) triglycerides as compared to PCG; (d) LDL-C as compared to PCG; (e) HDL-C compared to ACG; and (f): HDL-C as compared to PCG



Supplementary Figure 3: Forest plot highlighting the gastrointestinal side-effect profile of the use of tirzepatide (a): nausea as compared to ACG; (b) vomiting as compared to ACG; (c) diarrhea as compared to ACG; (d) nausea as compared to PCG; (e) vomiting as compared to PCG; and (f): diarrhea as compared to PCG



Supplementary Figure 4: Evaluating the presence of publication bias for (a) HbA1c ACG; (b) fasting glucose ACG; (c) weight loss >5% ACG; (d) weight loss >10% ACG; (e): treatment emergent adverse events ACG; (f) hypoglycemia ACG; and (g) HbA1c <6.5% ACG

Supplementary Table 1: Characteristics of patients in the six different randomized controlled trials evaluated in this meta-analysis on use of tirzepatide in type-2 diabetes

Study details	Number of patients in tirzepatide and control groups	Patient characteristics and nature of controls	Duration of study (weeks)	Outcomes evaluated in the study
Frias *et al*.[12] 2018	Placebo 51 Tirzepatide 1 mg, 52 patients Tirzepatide 5 mg, 55 patients Tirzepatide 10 mg, 51 patients Tirzepatide 15 mg, 53 patients Dulaglutide 1.5 mg, 54 patients	People with type 2 diabetes (T2DM) for at least 6 months, inadequately controlled diabetes on diet, exercise±metformin and BMI 23-50 kg/m^2 Controls (in Dulaglutide or placebo) were similar to patients in Tirzepatide group	26 weeks	Primary outcome: Change in HbA1c from baseline to 26 weeks Secondary outcome: Change in Hba1c from baseline to 12 weeks; change in mean body weight, fasting plasma glucose, and waist circumference from baseline to weeks 12 and 26; >5% and >10% weight loss; patients reachingHbA1c target (6.5% and 7%); and change in lipid parameters from baseline to 26 weeks
Frias *et al*.[13] 2020	Placebo 26 Tirzepatide 12 mg, 29 patients Tirzepatide 15 mg, 56 patients	People with T2DM for at least 6 months, inadequately controlled T2DM on diet, exercise±metformin and BMI 23-45 kg/m^2. Controls were similar to patients in Tirzepatide group	12 weeks	Primary outcome: Change in HbA1c from baseline to 12 weeks Secondary outcomes: change in mean body weight, fasting blood glucose (FBG), and waist circumference; treatment-emergent AEs (TAEs), serious AEs (SAEs), incidence of nausea, vomiting, and diarrhea, discontinuation of study drug because of AEs, and incidence and rate of hypoglycemia
Frias *et al*.[14] 2021	Tirzepatide 5 mg, 55 patients Tirzepatide 10 mg, 52 patients Tirzepatide 15 mg, 53 patients Semaglutide 1 mg, 54 patients	T2DM patients ≥18 year age, inadequately controlled with metformin at ≥1500 mg/day; HbA1c 7.0-10.5%, BMI ≥25kg/m^2, and stable weight (±5%) during previous 3 months. Controls were similar to patients in Tirzepatide group	40 weeks	Primary outcome: Change in HbA1c from baseline to 40 weeks Secondary outcomes: change in body weight from baseline to week 40; and HbA1c <7.0% <5.7%; <6.5%; weight loss >5%, >10%, or >15%; the mean change from baseline in the fasting serum glucose level and in the daily, patient-measured, mean seven-point blood glucose profiles; BMI and waist circumference; lipid levels; insulin resistance; and the fasting glucagon level adjusted for the fasting serum glucose level, TAEs and SAEs
Rosenstock *et al*.[15] 2021	Tirzepatide 5 mg, 121 patients Tirzepatide 10 mg, 121 patients Tirzepatide 15 mg, 121 patients Placebo, 115 patients	T2DM patients ≥18 years age, T2DM inadequately controlled with diet and exercise alone. Never taken injectable therapy for T2DM, had HbA1c 7·0–9·5%, BMI≥23 kg/m², stable weight during previous 3 months with agreement not to initiate diet or exercise program during study with intent of reducing weight other than lifestyle and dietary measures for diabetes	40 weeks	Primary outcome: Change in HbA1c from baseline to 40 weeks Secondary outcomes: change in body weight from baseline to week 40; HbA1c <7.0% <5.7%; <6.5% or less; weight loss of >5%, >10%, or >15%; mean change from baseline in fasting glucose and daily, patient-measured, mean seven-point blood glucose profiles; BMI, mean change from baseline in daily mean seven-point self-monitored blood glucose (SMBG) profiles at 40 weeks, TAEs and SAEs
Ludvik *et al*.[16] 2021	Tirzepatide 5 mg, 358 patients Tirzepatide 10 mg, 360 patients Tirzepatide 15 mg, 359 patients Degludec, 360 patients	T2DM ≥18 years, insulin naïve, HbA1c 7·0-10·5%, on metformin alone or with SGLT2 inhibitor for >3 months before screening, BMI >25 kg/m^2, and stable weight (no change outside of 5%) during previous 3 months	52 weeks	Primary outcome: Change in HbA1c from baseline to 52 weeks Secondary outcomes: change in weight from baseline to week 52; HbA1c <7.0% <5.7%; <6.5% or less; weight loss of >5%, >10%, or >15%; mean change from baseline in fasting glucose and daily patient-measured, mean seven-point blood glucose profiles; BMI and change from baseline in daily mean seven-point SMBG profiles, TAEs and SAEs
Del Prato *et al*.[17] 2021	Tirzepatide 5 mg, 329 patients Tirzepatide 10 mg, 328 patients Tirzepatide 15 mg, 338 patients Glargine, 1000 patients	T2DM patients aged ≥18 years, HbA1c 7·5-10·5%, on metformin, sulfonylurea, or SGLT-2] inhibitor either alone or in any combination, BMI >25 kg/m² and stable weight during the previous 3 months, at	52 weeks	Primary outcome: Change in HbA1c from baseline to 52 weeks Secondary outcomes: change in weight from baseline to week 52; HbA1c <7.0% <5.7%; <6.5% or less; weight loss of >5%, >10%, or>15%; mean change from baseline in fasting glucose and daily

Contd...

Supplementary Table 1: Contd...

Study details	Number of patients in tirzepatide and control groups	Patient characteristics and nature of controls	Duration of study (weeks)	Outcomes evaluated in the study
		increased risk of cardiovascular events (known coronary, peripheral arterial, or cerebrovascular disease, or aged 50 years or older with history of chronic kidney disease and an estimated glomerular filtration rate (eGFR) <60 mL/min/1·73 m^2 or history of congestive heart failure		patient-measured, mean seven-point blood glucose profiles; BMI and change from baseline in daily mean seven-point SMBG profiles, TAEs and SAEs. Comparison was done relative to four-component composite endpoint of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina (MACE-4)

T2DM: type-2 diabetes; MAGE: mean average glucose excursion; OAD: oral antidiabetes medication; GFR: glomerular filtration rate; SGLT: sodium-glucose cotransporter; MACE-4, transient ischemic attacks, coronary revascularizations, hospitalizations for heart failure, and mortality

Supplementary Table 2: Study details of the three *post-hoc* analysis data of the study done by Frias *et al*. (2018) evaluated in this meta-analysis

Study details	Number of patients in tirzepatide and control groups	Patient characteristics and nature of controls	Duration of study (weeks)	Outcomes evaluated in the study and reasons for exclusion
Wilson *et al*.[6]	Placebo 51 Tirzepatide 1 mg, 52 patients Tirzepatide 5 mg, 55 patients Tirzepatide 10 mg, 51 patients Tirzepatide 15 mg, 53 patients Dulaglutide 1.5 mg, 54 patients	People with type 2 diabetes for at least 6 months WITH inadequately controlled diabetes on diet, exercise±metformin AND body mass index (BMI) of 23-50 $kg.m^2$ Controls (in Dulaglutide or placebo) were similar to subjects in Tirzepatide group	26 weeks	Change in serum lipoprotein profile, apolipoprotein (apo) A-I, B and C-III and preheparin lipoprotein lipase from baseline to at 4, 12, and 26 weeks; change in lipoprotein particle profile at baseline and 26 weeks
Hartmen *et al*.[18]	Placebo 51 Tirzepatide 1 mg 52 Tirzepatide 5 mg 55 Tirzepatide 10 mg 51 Tirzepatide 15 mg 53 Dulaglutide 1.5 mg 54	People with type 2 diabetes for at least 6 months WITH inadequately controlled diabetes on diet, exercise±metformin AND body mass index (BMI) of 23-50 $kg.m^2$ Controls (in Dulaglutide or placebo) were similar to subjects in Tirzepatide group.	26 weeks	Changes from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), keratin-18 (K-18), procollagen III (Pro-C3), and adiponectin
Thomas *et al*.[19]	Placebo 51 Tirzepatide 1 mg, 52 patients Tirzepatide 5 mg, 55 patients Tirzepatide 10 mg, 51 patients Tirzepatide 15 mg, 53 patients Dulaglutide 1.5 mg, 54 patients	People with type 2 diabetes for at least 6 months WITH inadequately controlled diabetes on diet, exercise±metformin AND body mass index (BMI) of 23-50 $kg.m^2$ Controls (in Dulaglutide or placebo) were similar to subjects in Tirzepatide group	26 weeks	Change in biomarkers of beta-cell function and insulin resistance (IR) and evaluate weight loss contributions to IR improvements at 26 weeks
Pirro *et al*.[20]	Placebo 51 Tirzepatide 1 mg, 52 patients Tirzepatide 5 mg, 55 patients Tirzepatide 10 mg, 51 patients Tirzepatide 15 mg, 53 patients Dulaglutide 1.5 mg, 54 patients	People with type 2 diabetes for at least 6 months WITH inadequately controlled diabetes on diet, exercise±metformin AND body mass index (BMI) of 23-50 $kg.m^2$ Controls (in Dulaglutide or placebo) were similar to subjects in Tirzepatide group	26 weeks	Branched-chain amino acids, direct catabolic products glutamate, 3-hydroxyisobutyrate, branched-chain ketoacids, and indirect byproducts such as 2-hydroxybutyrate decreased compared to baseline and placebo. The decrease in the above metabolites was greater in the Tirzepatide group as compared to dulaglutide

T2DM: type-2 diabetes; OAD: oral antidiabetes medication; GFR: glomerular filtration rate

Supplementary Table 3: Risk of bias assessment table

Del Prato 2021	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Open-label, parallel-group, phase 3 randomized controlled study
Allocation Concealment (Selection Bias)	Low Risk	Participants were randomly assigned (1:1:1:3), by the Eli Lilly and Company computer-generated random sequence using an interactive web response system to receive tirzepatide or glargine.
Blinding Of Participants & Personal (Performance Bias)	High Risk	Open labelled study
Blinding Of Outcome Assessment (Detection Bias)	High Risk	Open labelled study
Incomplete Outcome Data (Attrition Bias)	Low Risk	1335 patients were randomized to receive either tirzepatide 10mg/d or glargine insulin, of which 1194 patients completed the study. Hence attrition was 114 patients (10.56%)
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	The study was funded by Eli Lilly and Company.
Frias 2018	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Randomized double blinded active control, parallel group study
Allocation Concealment (Selection Bias)	Low Risk	Stratified block randomization was done
Blinding Of Participants & Personal (Performance Bias)	Low Risk	Yes, double blinded RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Yes, double blinded RCT
Incomplete Outcome Data (Attrition Bias)	Low RIsk	318 patients were randomized, of which data from 283 patients were analysed after 26 weeks follow-up (attrition rate 11%). An attrition rate of more than 15% was considered to be significant
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	The study was funded by Eli Lilly and company
Frias 2020	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Randomized, double-blind, multicentre, parallel group, active trial
Allocation Concealment (Selection Bias)	Low Risk	Stratified block randomization was done
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	111 patients were randomized, of which 95 patients completed the study. Hence attrition rate was 14.41%
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Risk	The study was funded by Eli Lilly and company.
Frias 2021	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Active-control, randomized, double-blind, parallel-group, clinical trial
Allocation Concealment (Selection Bias)	Low risk	Stratified Randomization
Blinding Of Participants & Personel (Performance Bias)	Low Risk	Double blind RCT
Blinding Of Outcome Assessment (Detection Bias)	Low Risk	Double blind RCT
Incomplete Outcome Data (Attrition Bias)	Low Risk	1678 out of 1879 patients completed the study (attrition rate 10.69%)
Selective Reporting (Reporting Bias)	Low Risk	All Pre-Specified Outcomes Were Reported
Other Biases	High Rsk	Three authors employed by the sponsor contributed to the trial design, and two authors employed by the sponsor were responsible for the statistical analyses. The last author (who was employed by the sponsor) provided medical oversight during the trial. The study was funded and supported by Eli Lilly
Ludvik 2021	Risk Of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Open-label, parallel-group, multicenter, multiethnic, phase 3 randomized controlled study
Allocation Concealment (Selection Bias)	Low risk	Assignment to treatment group was determined by a computer-generated random sequence using the Eli Lilly and Company interactive web response system.
Blinding Of Participants & Personal (Performance Bias)	High Risk	Open labelled study
Blinding Of Outcome Assessment (Detection Bias)	High Risk	Open labelled study
Incomplete Outcome Data (Attrition Bias)	Low risk	726 patients were randomized to receive either tirzepatide 10mg/d or degludec insulin, of which 652 patients completed the study. Hence attrition was 74 patients (10.19%)
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	The study was funded by Eli Lilly and Company.
Rosenstock 2021	Risk Of Bias	Author Judgement

Supplementary Table 3: Contd...

Del Prato 2021	Risk of Bias	Author Judgement
Random Sequence Generation (Selection Bias)	Low Risk	Open-label, parallel-group, multicenter, multiethnic, phase 3 randomized placebo- controlled study of 4o week duration
Allocation Concealment (Selection Bias)	Low risk	Assignment to treatment group was determined by a computer-generated random sequence using the Eli Lilly and Company interactive web response system.
Blinding Of Participants & Personal (Performance Bias)	High Risk	Open labelled study
Blinding Of Outcome Assessment (Detection Bias)	High Risk	Open labelled study
Incomplete Outcome Data (Attrition Bias)	Low risk	236 patients were randomized to receive either tirzepatide 10mg/d or placebo, of which 211 patients completed the study. Hence attrition was 25 patients (10.59%)
Selective Reporting (Reporting Bias)	Low Risk	All pre-specified outcomes were reported
Other Biases	High Risk	The study was funded by Eli Lilly and Company.