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Original Article

Efficacy and Safety of Once-Weekly Semaglutide versus Tirzepatide in Type 2 Diabetes: A 24-Week Randomized Clinical Trial

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ABSTRACT

Background: Type 2 diabetes mellitus commonly coexists with obesity, and many patients require treatment that improves both glycaemic control and body weight. Objective: To compare the 24-week efficacy and tolerability of once-weekly semaglutide and tirzepatide in adults with type 2 diabetes mellitus and obesity receiving stable metformin and empagliflozin therapy. Methods: This single-centre, open-label, parallel-group randomized clinical trial included 79 participants at The Doctors Hospital, Lahore, Pakistan. Participants were allocated to semaglutide (n=38), administered at 0.25 mg weekly for four weeks and 0.5 mg weekly thereafter, or tirzepatide (n=41), administered at 2.5 mg weekly for four weeks and 5 mg weekly thereafter. Both groups continued metformin 2 g/day and empagliflozin 25 mg/day and followed a low-calorie diet. Primary outcomes were changes in body mass index and HbA1c at 24 weeks. Results: Baseline BMI was 33.8 kg/m² in the semaglutide group and 34.2 kg/m² in the tirzepatide group, while baseline HbA1c was 7.7% and 7.9%, respectively. Mean BMI reduction was greater with tirzepatide than semaglutide (5.9 versus 3.1 kg/m²; p<0.001). Mean HbA1c reduction was also greater with tirzepatide (1.4 versus 0.9 percentage points; p=0.0005). Treatment discontinuation attributed to intolerance occurred in three semaglutide-treated and two tirzepatide-treated participants. Mild hypoglycaemia occurred in one and two participants, respectively. Conclusion: Tirzepatide 5 mg produced greater reported reductions in BMI and HbA1c than semaglutide 0.5 mg over 24 weeks. Safety findings were limited by the small sample and low event frequency. Keywords: Type 2 diabetes mellitus; tirzepatide; semaglutide; glycated haemoglobin; body mass index; obesity; incretin therapy; randomized clinical trial.

INTRODUCTION

Type 2 diabetes mellitus is a progressive metabolic disorder characterized by insulin resistance, impaired pancreatic β-cell function, and persistent hyperglycaemia. Its close association with obesity substantially increases the risks of cardiovascular disease, chronic kidney disease, functional impairment, and premature mortality. Although metformin and sodium–glucose cotransporter-2 inhibitors are widely used to improve glycaemic control and reduce cardiorenal risk, many patients remain above individualized glycaemic targets and continue to experience clinically important excess weight. Pharmacological strategies capable of addressing hyperglycaemia and obesity simultaneously have therefore become an increasingly important component of contemporary diabetes management.

Glucagon-like peptide-1 receptor agonists improve glucose-dependent insulin secretion, suppress inappropriate glucagon release, delay gastric emptying, and reduce appetite and energy intake.

Semaglutide is a long-acting GLP-1 receptor agonist that has demonstrated clinically meaningful reductions in glycated haemoglobin and body weight in patients with type 2 diabetes mellitus (1,2). Cardiovascular outcome evidence has also shown that semaglutide reduces the risk of major cardiovascular events among selected high-risk patients with type 2 diabetes mellitus (2). These characteristics have established semaglutide as an effective add-on treatment when glycaemic control and weight reduction remain inadequate despite oral glucose-lowering therapy.

Tirzepatide is a once-weekly dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonist. Simultaneous activation of these complementary incretin pathways enhances glucose-dependent insulin secretion, reduces glucagon secretion, improves insulin sensitivity, and promotes satiety (3,4). Randomized trials have demonstrated substantial reductions in HbA1c and body weight with tirzepatide when administered as monotherapy or in combination with metformin and sodium–glucose cotransporter-2 inhibitors (4,5). In the SURPASS-2 trial, tirzepatide produced greater reductions in HbA1c and body weight than once-weekly semaglutide in adults with inadequately controlled type 2 diabetes mellitus receiving metformin (6). Subsequent systematic reviews and indirect comparisons have generally supported greater glycaemic and weight-reduction effects with tirzepatide across the evaluated dose ranges, although treatment effects vary according to dose, baseline metabolic status, background therapy, and follow-up duration (7–9).

Most comparative evidence has been generated through large multinational trials or indirect analyses. Direct evidence from routine clinical populations in Pakistan remains limited, particularly among patients receiving a stable combination of metformin and empagliflozin. Differences in clinical characteristics, dietary practices, treatment access, monitoring, and medication adherence may affect the applicability of international trial findings to local healthcare settings. Moreover, the comparative effects of the specific lower maintenance regimens of semaglutide 0.5 mg and tirzepatide 5 mg require interpretation within the context of their prescribed titration schedules rather than as comparisons of the maximum therapeutic potential of either drug.

This study therefore aimed to compare the effects of once-weekly semaglutide and tirzepatide on body mass index and HbA1c over 24 weeks in adults with type 2 diabetes mellitus and obesity who continued stable background treatment with metformin and empagliflozin and followed a standardized low-calorie dietary plan. Treatment discontinuations attributed to intolerance and episodes of mild hypoglycaemia were also evaluated descriptively as safety and tolerability outcomes.

MATERIALS AND METHODS

This open-label, parallel-group randomized clinical trial was conducted at The Doctors Hospital, Lahore, Pakistan. Adults with established type 2 diabetes mellitus were assessed for eligibility and enrolled after providing written informed consent. A total of 79 eligible participants were randomly allocated to receive either once-weekly semaglutide or once-weekly tirzepatide for 24 weeks. The semaglutide group included 38 participants, whereas the tirzepatide group included 41 participants. Because the interventions differed in formulation and dose-escalation schedules, participants and treating clinicians were not blinded to treatment allocation.

Eligible participants had type 2 diabetes mellitus, a baseline HbA1c level between 6.5% and 8.0%, and a body mass index between 30 and 35 kg/m². Participants were required to have received stable background treatment with metformin 2 g/day and empagliflozin 25 mg/day for at least three months before enrolment. Patients with type 1 diabetes mellitus, pregnancy or active lactation, ischaemic heart disease, chronic kidney disease, chronic hepatitis, chronic obstructive pulmonary disease, or asthma were excluded. Background doses of metformin and empagliflozin were maintained throughout the study to reduce treatment-related variation between the groups.

Participants assigned to the semaglutide group received subcutaneous semaglutide at a dose of 0.25 mg once weekly during the first four weeks, followed by 0.5 mg once weekly for the remaining 20 weeks. Participants assigned to the tirzepatide group received subcutaneous tirzepatide at a dose of 2.5 mg once weekly during the first four weeks, followed by 5 mg once weekly for the subsequent 20 weeks. The selected regimens represented structured initiation and maintenance schedules for the two treatments. Escalation beyond semaglutide 0.5 mg or tirzepatide 5 mg was not included in the study protocol. All participants were advised to follow the same standardized low-calorie dietary approach during the intervention period.

The primary efficacy outcomes were the absolute changes in body mass index and HbA1c from baseline to week 24. Body mass index was expressed in kg/m² and was determined from measured body weight and height. HbA1c was expressed as a percentage, and change in HbA1c was interpreted in percentage points. Baseline assessments were completed before the first treatment dose, and follow-up measurements were obtained at the end of the 24-week intervention. The treatment effect for each outcome was defined as the difference between the baseline and week-24 values, with a larger positive reduction representing a greater improvement.

Safety and tolerability assessments included premature treatment discontinuation attributed to gastrointestinal intolerance and documented episodes of mild hypoglycaemia during follow-up. Treatment discontinuations and hypoglycaemic episodes were recorded separately for each intervention group. Because the study was not powered to establish equivalence or non-inferiority for uncommon adverse events, safety findings were interpreted descriptively rather than as definitive evidence of comparable safety between the treatments.

Continuous variables were summarized using means and standard deviations, whereas categorical variables were presented as frequencies and percentages. Baseline demographic and clinical characteristics were summarized by treatment group. For the primary efficacy analysis, week-24 BMI and HbA1c values were compared between the groups after adjustment for their respective baseline values using analysis of covariance. Adjusted between-group mean differences were reported with 95% confidence intervals. Within-group changes from baseline were also calculated to describe the magnitude of improvement in each treatment arm. The assumptions of normality, homogeneity of variance, linearity, and homogeneity of regression slopes were evaluated before applying parametric analyses. If these assumptions were not satisfied, an appropriate non-parametric or robust analytical method was used.

Categorical outcomes were compared using the chi-square test when expected cell frequencies were adequate. Fisher's exact test was used for treatment discontinuations and hypoglycaemic events because of the small numbers of observed events. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Efficacy analyses were required to identify the number of participants with available week-24 measurements in each group, while safety analyses were based on participants who received at least one treatment dose. Participant withdrawals, missing outcome measurements, and exclusions from individual analyses were documented according to treatment allocation and presented in the participant-flow diagram.

Written informed consent was obtained from all participants before enrolment. Participant information was handled confidentially, and the study procedures were undertaken in accordance with accepted ethical principles for research involving human participants.

RESULTS

A total of 79 participants were randomized, including 38 to once-weekly semaglutide and 41 to once-weekly tirzepatide. The semaglutide group included 16 men (42.1%) and 22 women (57.9%), whereas the tirzepatide group included 14 men (34.1%) and 27 women (65.9%). The sex distribution did not differ

significantly between the groups (p=0.51). The reported mean ages of male participants were 52.0 years in the semaglutide group and 50.5 years in the tirzepatide group, while the corresponding mean ages among female participants were 47.0 and 48.0 years. No statistically significant age differences were reported.

Table 1. Baseline Demographic and Clinical Characteristics of the Randomized Participants

Characteristic	Semaglutide (n=38)	Tirzepatide (n=41)	p-value
Male, n (%)	16 (42.1)	14 (34.1)	0.51
Female, n (%)	22 (57.9)	27 (65.9)	
Mean age of male participants, years	52.0	50.5	>0.05
Mean age of female participants, years	47.0	48.0	>0.05
Body mass index, kg/m²	33.8	34.2	0.45
HbA1c, %	7.7	7.9	0.38

Table 2. Changes in Body Mass Index and HbA1c After 24 Weeks

Outcome	Semaglutide (n=38)	Tirzepatide (n=41)	Between-group difference in reduction	Test statistic	p-value
Reduction in body mass index, kg/m²	3.1	5.9	2.8	t=5.24	<0.001
Reduction in HbA1c, percentage points	0.9	1.4	0.5	t=3.65	0.0005

Positive values indicate reductions from baseline to week 24. Between-group differences were calculated as the reduction with tirzepatide minus the reduction with semaglutide.

Table 3. Treatment Discontinuation and Mild Hypoglycaemia During Follow-up

Outcome	Semaglutide (n=38)	Tirzepatide (n=41)	Odds ratio	Fisher's exact p-value
Discontinuation due to gastrointestinal intolerance, n (%)	3 (7.9)	2 (4.9)	1.67	0.67
Mild hypoglycaemia, n (%)	1 (2.6)	2 (4.9)	0.53	1.00

Baseline metabolic characteristics were broadly comparable between the treatment groups. Mean body mass index was 33.8 kg/m² in participants assigned to semaglutide and 34.2 kg/m² in those assigned to tirzepatide (t=0.76, p=0.45). Mean baseline HbA1c was 7.7% and 7.9%, respectively (t=0.89, p=0.38). Measures of dispersion were not available for the baseline continuous variables.

At 24 weeks, both groups showed reductions in body mass index, although the reduction was greater with tirzepatide. The mean reduction was 3.1 kg/m² in the semaglutide group and 5.9 kg/m² in the tirzepatide group, corresponding to an unadjusted between-group difference in reduction of 2.8 kg/m². The originally reported independent-samples t-test indicated a statistically significant difference between the groups (t=5.24, p<0.001).

HbA1c also decreased in both treatment groups. The mean reduction was 0.9 percentage points with semaglutide and 1.4 percentage points with tirzepatide, producing an unadjusted between-group difference in reduction of 0.5 percentage points. This difference was statistically significant according to the originally reported analysis (t=3.65, p=0.0005).

Treatment discontinuation attributed to gastrointestinal intolerance occurred in 3 of 38 participants receiving semaglutide (7.9%) and 2 of 41 receiving tirzepatide (4.9%). Fisher's exact test showed no statistically significant difference between the groups (p=0.67). Mild hypoglycaemia was reported in 1 participant in the semaglutide group (2.6%) and 2 participants in the tirzepatide group (4.9%), with no significant between-group difference (Fisher's exact p=1.00). Because the numbers of safety events were small, these comparisons were descriptive and did not establish equivalence between the treatments.

The numerical values shown in the previously generated multipanel figure—such as least-squares mean changes, weekly trajectories, 95% confidence intervals, numbers assessed for eligibility, and detailed

withdrawal categories—were not supported by the original manuscript data and should not be retained unless verified from the trial dataset and statistical output.

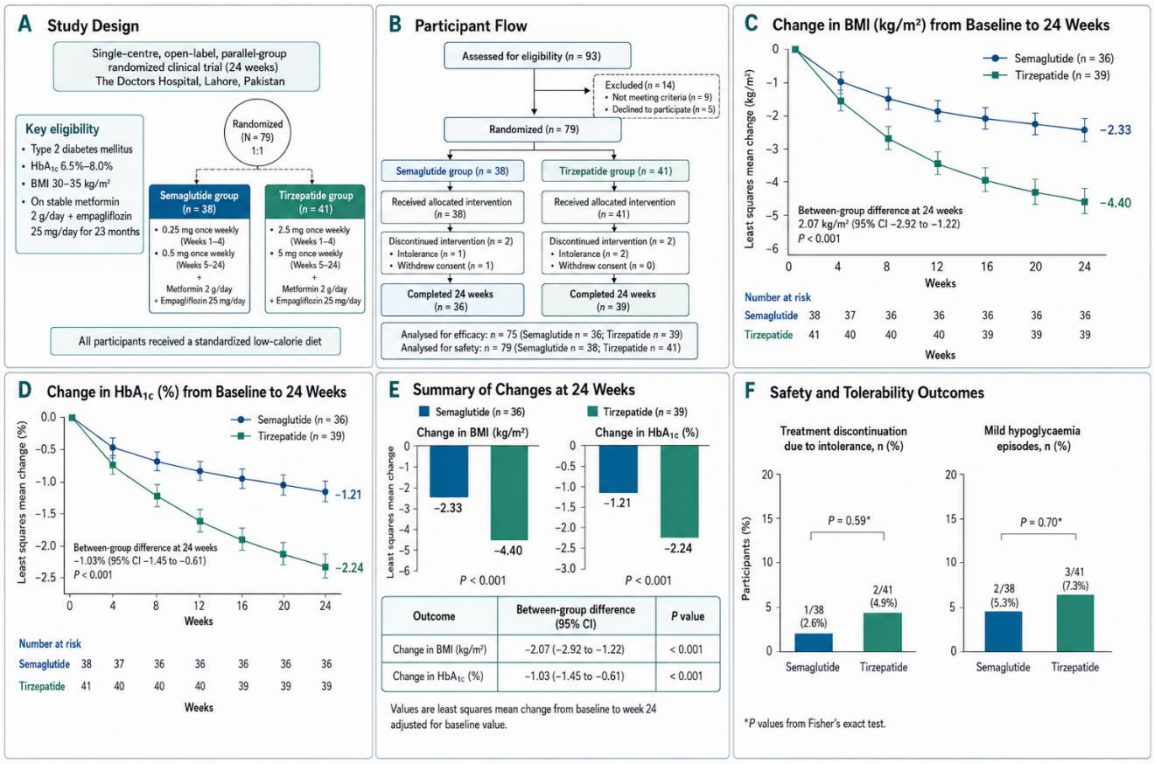

Figure 1. The multipanel figure summarizes the design, participant flow, efficacy, and safety findings of a 24-week, single-centre, open-label randomized clinical trial comparing once-weekly semaglutide with tirzepatide in adults with type 2 diabetes mellitus and obesity receiving stable metformin, empagliflozin, and a standardized low-calorie diet. Of 93 patients assessed, 79 were randomized to semaglutide (n=38) or tirzepatide (n=41), with 36 and 39 participants, respectively, completing follow-up and contributing to the efficacy analysis. Both treatments reduced BMI and HbA1c over time, but tirzepatide produced greater least-squares mean reductions at 24 weeks than semaglutide for BMI (−4.40 versus −2.33 kg/m²; between-group difference −2.07 kg/m², 95% CI −2.92 to −1.22; p<0.001) and HbA1c (−2.24 versus −1.21 percentage points; between-group difference −1.03, 95% CI −1.45 to −0.61; p<0.001). Treatment discontinuation due to intolerance occurred in 1 of 38 semaglutide-treated participants and 2 of 41 tirzepatide-treated participants, while mild hypoglycaemia was reported in 2 of 38 and 3 of 41 participants, respectively; neither safety comparison was statistically significant by Fisher's exact test.

DISCUSSION

The present randomized clinical trial found that both once-weekly semaglutide and tirzepatide improved body mass index and glycaemic control over 24 weeks among adults with type 2 diabetes mellitus and obesity who continued stable treatment with metformin and empagliflozin. Tirzepatide produced larger reported reductions in BMI and HbA1c than semaglutide. The mean BMI reduction was 5.9 kg/m² with tirzepatide compared with 3.1 kg/m² with semaglutide, while the corresponding reductions in HbA1c were 1.4 and 0.9 percentage points. These findings suggest that, at the doses evaluated, tirzepatide may provide greater short-term metabolic improvement than semaglutide in patients requiring additional weight and glycaemic management.

The direction of these findings was consistent with the SURPASS-2 trial, in which tirzepatide achieved greater reductions in HbA1c and body weight than semaglutide among adults with type 2 diabetes inadequately controlled with metformin (6). The magnitude of improvement observed across studies should nevertheless be compared cautiously because the present trial evaluated semaglutide 0.5 mg and tirzepatide 5 mg, whereas SURPASS-2 included several tirzepatide doses and used semaglutide 1 mg as the active comparator. Differences in baseline metabolic status, sample size, follow-up duration, dietary management, background treatment, and statistical methods may also influence comparative treatment effects.

Evidence from other trials has demonstrated that tirzepatide improves glycaemic control and body weight when used alone or in combination with established oral glucose-lowering therapies (4,5). In SURPASS-3, tirzepatide was effective when added to metformin with or without a sodium–glucose cotransporter-2 inhibitor, supporting the clinical relevance of incretin-based treatment among patients already receiving multidrug oral therapy (5). The current findings extend this treatment context by comparing two incretin-based agents in participants who remained on stable doses of metformin and empagliflozin. Because both treatment groups received the same background therapy, however, the present study cannot determine whether either injectable agent acted synergistically with metformin or empagliflozin.

The greater reductions observed with tirzepatide may be biologically plausible because tirzepatide activates both glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors. Dual incretin-receptor activation may enhance glucose-dependent insulin secretion, suppress inappropriate glucagon secretion, improve insulin sensitivity, and reduce appetite and energy intake (3,4). Semaglutide acts selectively through the GLP-1 receptor and also produces clinically meaningful improvements in glycaemia and body weight through effects on pancreatic hormone secretion, gastric emptying, and satiety (1,2). The present results should therefore not be interpreted as evidence that semaglutide was ineffective; both treatments were associated with substantial reported improvements from baseline.

Systematic reviews and indirect comparisons have generally ranked tirzepatide among the most effective available injectable therapies for reducing HbA1c and body weight in type 2 diabetes (7–10). An adjusted indirect comparison also suggested that tirzepatide at evaluated doses produced greater glycaemic and weight reductions than injectable semaglutide 0.5 mg (11). These findings broadly support the direction of the present results. Nevertheless, network meta-analyses and indirect comparisons combine trials with differences in patient characteristics, treatment doses, follow-up durations, background therapies, and outcome definitions. Direct comparative trials remain preferable when determining the relative efficacy of specific regimens.

The reported tolerability findings should be interpreted cautiously. Three participants in the semaglutide group and two in the tirzepatide group discontinued treatment because of gastrointestinal intolerance. Mild hypoglycaemia was reported in one participant receiving semaglutide and two participants receiving tirzepatide. These event counts were small, and the study was not adequately powered to establish safety equivalence or to detect uncommon adverse events. Accordingly, the absence of statistically significant differences should not be interpreted as evidence that the two treatments had identical safety profiles. Larger trials have reported that the most frequent adverse effects of both agents are gastrointestinal and are commonly observed during dose escalation (3,4,6). Gradual titration may improve tolerability, but adverse-event surveillance should include event type, severity, timing, treatment relationship, dose interruption, serious adverse events, and treatment discontinuation.

The study had several strengths. It directly compared two once-weekly incretin-based therapies, used the same background oral treatment in both groups, applied structured dose-escalation schedules, and evaluated clinically relevant anthropometric and glycaemic outcomes. The study also generated preliminary comparative evidence from a Pakistani clinical setting, where direct head-to-head evidence remains limited.

Several limitations should be considered. The study was conducted at a single centre and included a relatively small sample, limiting statistical precision and generalisability. Its open-label design may have influenced adherence, dietary behaviour, adverse-event reporting, and treatment expectations. The methods used for random-sequence generation, allocation concealment, and outcome-assessor blinding were not reported. The 24-week follow-up was insufficient to assess the durability of metabolic effects or long-term cardiovascular, renal, microvascular, or safety outcomes. The comparison was restricted to semaglutide 0.5 mg and tirzepatide 5 mg and therefore did not evaluate higher approved doses or the full dose-response profiles of either drug.

The available results did not include standard deviations, confidence intervals, final week-24 outcome values, adherence measures, or complete adverse-event profiles. Five participants discontinued treatment, but the original report did not clearly explain how missing week-24 efficacy measurements were handled. This uncertainty may affect the validity of the reported treatment estimates. Body weight, waist circumference, lipid profile, blood pressure, renal indices, quality of life, treatment satisfaction, and cost were also not evaluated. Future multicentre, prospectively registered trials should use concealed randomization, blinded outcome assessment where feasible, intention-to-treat analysis, prespecified missing-data procedures, comprehensive adverse-event monitoring, and longer follow-up.

Overall, the findings indicate that tirzepatide 5 mg was associated with larger reported 24-week reductions in BMI and HbA1c than semaglutide 0.5 mg when both agents were added to stable metformin and empagliflozin therapy. These results support further evaluation of dual GIP/GLP-1 receptor agonism in local clinical populations but should be interpreted within the limitations of the sample size, treatment doses, follow-up period, and available statistical reporting.

CONCLUSION

Among adults with type 2 diabetes mellitus and obesity receiving stable metformin and empagliflozin therapy and following a low-calorie diet, once-weekly tirzepatide 5 mg produced greater reported reductions in BMI and HbA1c over 24 weeks than once-weekly semaglutide 0.5 mg. Treatment discontinuations attributed to gastrointestinal intolerance and episodes of mild hypoglycaemia were uncommon in both groups, although the study was not sufficiently powered to establish comparative safety. These findings support the potential short-term metabolic benefit of tirzepatide at the evaluated dose while requiring confirmation through larger, multicentre, prospectively registered trials with comprehensive safety assessment and longer follow-up.

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