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Original Article

Comparison of the Efficacy of Once Weekly Dose of Trelagliptin Versus Once Daily Dose of Vildagliptin on the Levels of HbA1c in Type-2 Diabetes Patients

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ABSTRACT

Once-weekly dipeptidyl peptidase-4 inhibition represents a potential strategy to reduce dosing burden while maintaining glycaemic efficacy in type 2 diabetes mellitus. **Objectives:** To compare once-weekly trelagliptin with once-daily vildagliptin in adults receiving background metformin, using change in glycated hemoglobin and attainment of glycated hemoglobin below 7%, with secondary assessment of body weight and body mass index. **Methods:** A randomized, open-label, parallel-group clinical trial was conducted at a tertiary care hospital. Adults aged 30 to 60 years with type 2 diabetes mellitus, glycated hemoglobin 7.5% to 9.5% on metformin, were randomized by lottery to trelagliptin 100 mg once weekly or vildagliptin 50 mg once daily for 12 weeks. Independent-samples t testing and chi-square or Fisher's exact testing were applied as appropriate. Prespecified stratified analyses were performed for the efficacy endpoint. **Results:** A total of 102 participants were randomized, and 93 completed follow-ups. Baseline characteristics were comparable. Glycated hemoglobin change was −1.24±0.78% with trelagliptin and −1.52±0.67% with vildagliptin, mean difference 0.28% (95% CI −0.02 to 0.58), p=0.068. Target attainment was 53.2% versus 63.0%, p=0.336. Weight and body mass index changes did not differ significantly, and stratified analyses showed no significant subgroup effects. **Conclusions:** No statistically significant difference was detected between once-weekly trelagliptin and once-daily vildagliptin in glycaemic improvement over 12 weeks in patients. Short-term changes in body weight and body mass index were also not significantly different between the two treatment groups.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) progressive metabolic disorder that affects 11.11% worldwide [1]. While the prevalence in Asia accounts for 8.56%, in Pakistan, approximately 35 million people are affected by diabetes [2, 3]. Management typically begins with lifestyle modifications, but most patients eventually require pharmacological intervention. Type 2 diabetes mellitus is increasingly diagnosed at younger ages in parallel with obesity and sedentary behavior. Glycaemic targets are commonly monitored using glycated haemoglobin (HbA1c), with a widely adopted threshold of 7% [4, 5]. Despite established targets and expanding therapeutic options, a substantial proportion of treated patients do not achieve recommended control, indicating ongoing challenges in routine care. Metformin remains the first-line agent due to its proven efficacy, safety profile, and cardiovascular benefits. When metformin proves insufficient, guidelines recommend adding second-line agents based on patient

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characteristics, comorbidities, and hypoglycemia risk. Available options include dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, and other agents [6, 7]. Suboptimal adherence to antidiabetic medications remains a major challenge in the long-term management of type 2 diabetes and is associated with poorer clinical outcomes. [8]. Dipeptidyl peptidase 4 (DPP 4) inhibitors improve glycaemic control by enhancing incretin-mediated glucose-dependent insulin secretion and reducing inappropriate glucagon release, with low hypoglycemia risk and minimal effect on body weight. Vildagliptin is an established DPP4 inhibitor with documented glycated hemoglobin (HbA1c) lowering efficacy and acceptable tolerability [9]. Trelagliptin is a long-acting DPP-4 inhibitor intended for once-weekly administration and sustained enzyme inhibition across the dosing interval [10]. Comparative trials have yielded heterogeneous HbA1c target attainment findings [11-13]. Some evidence suggests comparable HbA1c reduction versus active comparators, while the adherence advantage and external validity remain uncertain [14, 15]. Although once-weekly dipeptidyl peptidase-4 inhibition is increasingly being considered a useful approach, making treatment easier for type 2 diabetes mellitus patients to follow, studies that directly compare trelagliptin with commonly used daily dipeptidyl peptidase-4 inhibitors are still not sufficient, particularly in patients receiving background metformin therapy in local clinical settings [12, 13].

In addition, regional variation in medication adherence, healthcare access, and routine prescribing practices may influence therapeutic effectiveness, thereby limiting the generalizability of findings from previously published studies. Therefore, the study aimed to compare the efficacy of once-weekly trelagliptin and once-daily vildagliptin over 12 weeks in adults with type 2 diabetes mellitus inadequately controlled on metformin, in terms of the proportion of patients achieving an HbA1c level below 7%, as well as mean changes in HbA1c levels, body weight, and body mass index, conducted as a randomized clinical trial.

METHODS

This randomized, open-label, parallel group clinical trial (NCT06889909) was conducted in the Department of General Medicine, Lahore General Hospital, Lahore, from June 2025 to January 2026. The study was started after attaining ethical approval (2025/ERC/67; dated 6th January 2025) and informed consent from all the eligible participants. Initially, 116 patients were enrolled through non-probability consecutive sampling for eligibility assessment after incorporating a 20% attrition allowance, based on an assumed 33.3% achievement of glycated hemoglobin below 7% with trelagliptin and 61.1% with vildagliptin at 12 weeks, using a 95% confidence level and 80% power [13]. After application of the prespecified eligibility criteria, 14 patients were excluded, including those with insulin use or oral antidiabetic drugs other than metformin within the preceding 3 months (n=5), significant cardiovascular disease (n=2), and chronic kidney disease stage 3 or higher or hepatic dysfunction (n=7). The remaining 102 participants fulfilled the inclusion criteria and were randomized using a lottery method, with 51 allocated to once weekly trelagliptin and 51 allocated to once daily vildagliptin. Adult patients previously diagnosed with T2DM with inadequate glycemic control (glycated hemoglobin was required to be between 7.5% and 9.5%), taking metformin of either sex aged between 30 and 60 years were included in the study. Exclusion criteria in addition to the above were patients with type 1 diabetes mellitus, diabetic ketoacidosis, myocardial infarction within 6 months, unstable angina, or uncontrolled hypertension, pancreatic dysfunction, pregnancy, lactation, planned pregnancy, or urgent need for insulin for acute metabolic decompensation or infection. Group A received trelagliptin 100 mg once weekly, administered before breakfast on the same weekday throughout follow-up. Group B received vildagliptin 50 mg once daily [11]. Participants continued their established metformin regimen throughout the 12-week intervention period, and changes in metformin dose were not permitted unless clinically necessary. Any modification or discontinuation of metformin was recorded during follow-up. No other glucose-lowering agents were permitted during the intervention period. Metformin was permitted as concomitant therapy, while other glucose-lowering agents were not allowed during the intervention period. Baseline variables included age, sex, body mass index, comorbidities, and screening investigations, including liver function tests, renal function tests, serum electrolytes, and fundoscopy to document retinal status. The primary outcome was the proportion of patients achieving glycated hemoglobin below 7% at 12 weeks. The secondary outcomes include mean change in glycated hemoglobin, weight, and body mass index from baseline to 12 weeks (Figure 1).

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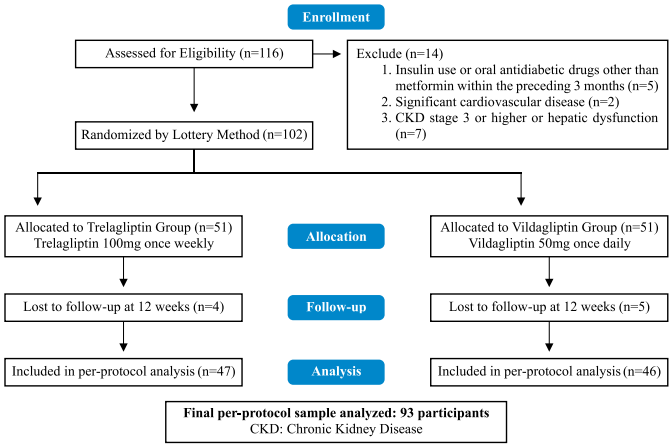

Figure 1: Consort flow diagram

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 26.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. The corresponding W statistics and p-values for the variables included in the analyses are provided in Supplementary Table X. Continuous variables satisfying the normality assumption were summarized as mean ± standard deviation and compared between groups using the independent-samples t-test. Therefore, these variables were reported in the form of mean/standard deviation, and between-group comparisons were performed using the independent samples t-test. Categorical variables were summarized as frequencies with percentages and compared using the chi-square test, with the Fisher exact test applied when expected cell counts were small. Outcome analyses were performed using the per-protocol population, comprising participants who completed the 12-week follow-up. Of the 102 randomized participants, 9 (8.8%) were lost to follow-up and were therefore excluded from the primary per-protocol efficacy analysis. Because outcome data were unavailable for these participants, no imputation-based intention-to-treat analysis was performed. Prespecified subgroup analyses for the efficacy endpoint were undertaken after stratification by age group, sex, body mass index category, and duration of diabetes. All statistical tests were two-sided, and a p-value below 0.05 was considered statistically significant.

RESULTS

At baseline, 102 participants were enrolled in the study. A total of 9 participants were lost to follow-up at 3 months, including 4 participants from the trelagliptin group and 5 participants from the vildagliptin group. Baseline age, age-group distribution, sex distribution, diabetes duration category, body mass index category, and metformin dose were comparable between treatment groups, with no statistically significant between-group differences (all p > 0.050)(Table 1).

Table 1: Baseline Characteristics by Treatment Group (n=102)

Variables	Trelagliptin, (n = 51)	Vildagliptin, (n = 51)	Test Statistic	p-value
Age (Years), M (SD)	48.13 (5.70)	48.73 (5.79)	t (100) = −0.53	0.597
Age Group, n (%)				
30–45 Years	17 (33.3)	15 (29.4)	χ^2 (1) = 0.18	0.670
46–60 Years	34 (66.7)	36 (70.6)		
Sex, n (%)				
Male	32 (62.7)	32 (62.7)	χ^2 (1) = 0.00	1.000
Female	19 (37.3)	19 (37.3)		
Duration of Diabetes Category, n (%)				
≤ 5 Years	25 (49.0)	19 (37.3)	χ^2 (1) = 1.44	0.230
> 5 Years	26 (51.0)	32 (62.7)		
Body Mass Index Category, n (%)				
Normal (18.5–24.9)	20 (39.2)	17 (33.3)	χ^2 (2) = 0.44	0.805
Overweight (25.0–29.9)	22 (43.1)	25 (49.0)		
Obese (≥ 30.0)	9 (17.6)	9 (17.6)		
Metformin dose, M (SD)	921.57 (293.64)	965.69 (295.89)	t (100) = −0.76	0.452

Baseline analyses included 102 participants, 51 per group. At 12 weeks, data were available for 47 in the trelagliptin arm and 46 in the vildagliptin arm. No between-group differences were observed for weight, body mass index, or glycated hemoglobin at baseline or follow-up. The change in glycated hemoglobin was −1.24 ± 0.78% with trelagliptin and −1.52 ± 0.67% with vildagliptin, mean difference 0.28% (95% CI −0.02 to 0.58), p=0.068. Although this p-value did not reach the conventional 5% significance threshold, it represents a borderline statistical trend favouring vildagliptin over trelagliptin. Both groups experienced a mean reduction in weight from baseline to 12 weeks (−1.01 ± 1.42 kg for trelagliptin and −1.29 ± 1.48 kg for vildagliptin). The between-group difference in weight change was 0.28 kg (95% CI −0.31 to 0.88), p=0.348, indicating that the magnitude of weight loss was similar between the two regimens. Body mass index change differed by 0.12 kg/m^2 (95% CI −0.09 to 0.33), p=0.269. Absolute values at 12 weeks remained comparable (Table 2).

Table 2: Between-Group Comparisons of Anthropometric and Glycemic Outcomes at Baseline and 3 Months

Outcomes	Trelagliptin (mean ± SD)	Vildagliptin (mean ± SD)	Mean Difference, 95% CI (Trelagliptin Minus Vildagliptin)	t (df)	p-value	Effect Size (Cohen's d)
Weight at Baseline (kg)	77.92 ± 10.09	75.96 ± 9.88	1.96 [−1.96 to 5.88]	0.99 (100)	0.324	–
Weight at 12 Weeks (kg)	77.39 ± 10.35	74.60 ± 9.42	2.80 [−1.28 to 6.87]	1.36 (91)	0.177	–
Change in Weight (kg)	−1.01 ± 1.42	−1.29 ± 1.48	0.28 [−0.31 to 0.88]	0.94 (91)	0.348	0.19

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Body Mass Index at Baseline (kg/m^2)	26.14 ± 3.21	26.59 ± 3.09	−0.45 [−1.69 to 0.79]	−0.72 (100)	0.475	–
Body Mass Index at 12 Weeks (kg/m^2)	25.96 ± 3.23	26.19 ± 3.10	−0.22 [−1.53 to 1.08]	−0.34 (91)	0.733	–
Change in Body Mass Index (kg/m^2)	−0.35 ± 0.50	−0.46 ± 0.52	0.12 [−0.09 to 0.33]	1.11 (91)	0.269	0.24
Glycated Hemoglobin at Baseline (%)	8.41 ± 0.49	8.51 ± 0.49	−0.11 [−0.30 to 0.09]	−1.09 (100)	0.278	–
Glycated Hemoglobin at 12 Weeks (%)	7.14 ± 0.66	7.01 ± 0.63	0.14 [−0.13 to 0.40]	1.01 (91)	0.313	–
Change in Glycated Hemoglobin (%)	−1.27 ± 0.78	−1.50 ± 0.67	0.28 [−0.02 to 0.58]	0.94 (91)	0.068	0.38

The proportion achieving HbA1c below 7% at 3 months did not differ significantly between groups, χ^2 (1) = 0.93, p=0.336. HbA1c target attainment was 53.2% with trelagliptin and 63.0% with vildagliptin (Table 3).

Table 3: Primary Efficacy Outcome at 3 Months: HbA1c < 7%

Outcomes	Trelagliptin, (n = 47)	Vildagliptin, (n = 46)	χ^2 (df)	p-value
HbA1c < 7%, n (%)	25 (53.2)	29 (63.0)	0.93 (1)	0.336
HbA1c ≥ 7%, n (%)	22 (46.8)	17 (37.0)		

No statistically significant between-group differences in efficacy were detected within age, sex, body mass index categories, or diabetes duration strata (all p ≥ 0.050) (Table 4).

Table 4: Efficacy Stratified by Baseline Characteristics: HbA1c < 7% At 3 Months

Stratum	Vildagliptin Yes / Total, n (%)	Trelagliptin Yes / Total, n (%)	p-value
Age 30–45 years	12/17 (70.6)	12/15 (80.0)	0.539
Age 46–60 years	13/30 (43.3)	17/31 (54.8)	0.369
Male	17/29 (58.6)	20/27 (74.1)	0.222
Female	8/18 (44.4)	9/19 (47.4)	0.858
BMI Normal (18.5–24.9)	9/17 (52.9)	7/14 (50.0)	0.870
BMI Overweight (25.0–29.9)	10/21 (47.6)	15/24 (62.5)	0.316
BMI Obese (≥ 30.0)	6/9 (66.7)	7/8 (87.5)	0.312
Diabetes duration ≤ 5 years	14/22 (63.6)	10/16 (62.5)	0.943
Diabetes duration > 5 years	11/25 (44.0)	19/30 (63.3)	0.152

DISCUSSION

This randomized, open-label, parallel-group trial conducted among adults with type 2 diabetes inadequately controlled on metformin demonstrated clinically meaningful improvement in glycaemic control with both once-weekly trelagliptin and once-daily vildagliptin over 12 weeks. The mean reduction in HbA1c exceeded 1% in both treatment arms. The between-group difference did not reach statistical significance (p=0.068); however, this borderline value suggests a trend that cannot be dismissed. This near-significant trend warrants cautious interpretation and indicates that a modest advantage for vildagliptin may exist, although the current sample size and follow-up duration were insufficient to confirm it definitively. Furthermore, the confidence interval included the null value, indicating that a clear superiority signal could not be established within the available sample and follow-up duration. Although the difference in HbA1c change between treatment groups was not statistically significant, these findings should not be interpreted as establishing comparability between the two treatments. Similarly, attainment of glycated hemoglobin below 7% occurred in over half of participants in both arms without a statistically significant difference, and prespecified stratified analyses by age, sex, body mass index category, and diabetes duration did not identify effect modification for the efficacy endpoint. Comparable glycaemic efficacy between once-weekly trelagliptin and daily dipeptidyl peptidase 4 inhibitors has been consistently reported in active controlled trials. In an Indian non-inferiority trial, trelagliptin 100 mg once weekly achieved glycated hemoglobin reduction similar to vildagliptin 50 mg twice daily, with target attainment of glycated hemoglobin below 7% in nearly half of participants, and a small between-group difference supported by confidence intervals compatible with clinical equivalence [15]. Concordant findings were observed in a phase 3 non-inferiority study comparing trelagliptin 100 mg once weekly with alogliptin 25 mg once daily, where both active regimens reduced glycated hemoglobin relative to placebo, and the difference between active therapies remained modest, supporting non-inferiority of weekly dosing [16]. Similarly, Nazeer *et al.* reported HbA1c <7% attainment in 37.3% and 54.9% of participants receiving trelagliptin and vildagliptin, respectively, whereas the corresponding proportions in the present study were higher in both groups but remained numerically in favor of vildagliptin [11]. The present findings differ by demonstrating no statistically significant between-group difference despite similar follow-up and background metformin use, suggesting that adherence, baseline metabolic profiles, clinical setting, and statistical power may contribute to observed heterogeneity across studies [14]. Both arms in the present trial achieved reductions that appear larger than typical class-level effects reported in many dipeptidyl peptidase 4 inhibitor trials, a pattern plausibly related to higher baseline glycated hemoglobin and restricted concomitant therapy [10, 15]. Differences in baseline therapy and disease context are important when interpreting between-study contrasts. Several comparator trials evaluated treatment-naïve participants managed with diet and exercise alone, whereas the present trial enrolled individuals already receiving metformin with glycated hemoglobin restricted to 7.5% to 9.5%, a profile that may yield larger absolute reductions because higher baseline glycated hemoglobin

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is typically associated with greater absolute improvement after treatment intensification [15]. In addition, the vildagliptin regimen used in the present trial was once daily, whereas much of the comparative evidence base uses twice-daily dosing to sustain enzyme inhibition throughout the dosing interval, which may influence relative efficacy estimates across trials and settings [10, 15]. Pharmacokinetic and pharmacodynamic evidence support the biological plausibility of sustained weekly efficacy with trelagliptin. Trelagliptin has demonstrated prolonged dipeptidyl peptidase 4 inhibition extending to 168 hours after dosing, indicating maintenance of clinically relevant enzyme suppression across the full dosing interval and providing a mechanistic basis for once-weekly administration [17]. Evidence from randomized trials and meta-analysis suggests that once-weekly trelagliptin provides glycaemic efficacy comparable to that of daily DPP-4 inhibitor therapy [18]. This sustained inhibitory profile is consistent with the observation that weekly therapy can achieve glycated hemoglobin lowering comparable to daily regimens when adherence is preserved, and background therapy remains stable [18]. Beyond integrated glycaemia, short-term indices of glycaemic variability also support durable control with weekly inhibition. In a randomized pilot comparison of trelagliptin versus alogliptin, improvements were observed in continuous glucose monitoring-derived variability metrics, including reductions in the standard deviation of 24-hour glucose and the mean amplitude of glycaemic excursions, suggesting glucose-stabilizing effects across days following dosing. Such mechanistic data complement clinical endpoints because glycated hemoglobin reflects average glycaemia over preceding weeks and is not designed to capture day-to-day peaks and troughs [19]. Weight and body mass index changed minimally and did not differ between regimens during the 12 week follow up, consistent with the weight-neutral profile of dipeptidyl peptidase 4 inhibitors, for which relevant weight loss is not expected without lifestyle intensification or weight-reducing add-on therapy [14]. In a phase 3 non-inferiority trial of trelagliptin 100 mg weekly versus alogliptin 25 mg daily, mean weight and body mass index changes remained modest over 24 weeks, supporting the view that these agents improve glycaemia without a direct effect on adiposity [15]. Similar patterns were reported in head-to-head evaluation against vildagliptin, with small anthropometric shifts over 16 weeks in both arms [16]. Although the present trial evaluated glycaemic and anthropometric endpoints, interpretation is supported by safety and patient-reported evidence for once-weekly trelagliptin. A safety synthesis reported low hypoglycemia frequency, particularly in monotherapy, and predominantly mild adverse events, consistent with class expectations for dipeptidyl peptidase-4 inhibitors [14]. In a randomized comparison of weekly trelagliptin and daily alogliptin, overall health-related quality-of-life scores did not differ significantly, indicating that dosing frequency alone does not guarantee superior patient experience [20]. Preference findings from the TRINITY programme similarly showed heterogeneous choices, with some participants favoring daily regimens despite comparable satisfaction, supporting individualized prescribing [13]. Switching and observational studies have reported stable glycated hemoglobin after conversion from daily inhibitors to weekly trelagliptin, with signals of adherence in selected settings [21].

Clinically, comparable short-term efficacy permits selection based on adherence risk, cost, and feasibility of comparator dosing. Strengths include randomized allocation and restriction of background therapy to metformin. Limitations include the single-centre, open-label design, 12-week follow-up, attrition, and per-protocol analysis. The open-label design may have introduced performance and detection bias, while loss to follow-up of 9 participants (8.8%) may have introduced attrition bias. Although 12 weeks was sufficient to assess short-term HbA1c changes, it was insufficient to determine the durability of treatment effects over the longer term.. Additional limitations include the underpowered subgroup analyses presented in Table 4; the small numbers in each stratum mean that these findings are exploratory and hypothesis-generating rather than confirmatory, and they should not be used to guide treatment decisions in specific patient subsets without further validation. Longer trials incorporating adherence metrics, continuous glucose monitoring, and cost-effectiveness are warranted, including evaluation in comorbidity groups. However, these subgroup analyses should be interpreted with caution, as the small sample sizes within each stratum provide limited statistical power to detect genuine subgroup effects.

CONCLUSIONS

Patients with type 2 diabetes mellitus on metformin, once-weekly trelagliptin, and once-daily vildagliptin showed similar efficacy, with no significant difference in the proportion of patients achieving HbA1c below 7% at 12 weeks. The reduction in HbA1c was also comparable between the two groups. Similarly, improvement in anthropometric measures was also comparable between regimens. These findings suggest that once-weekly trelagliptin may provide a short-term glycemic response comparable to once-daily vildagliptin in patients receiving metformin; however, longer-term studies are required to establish the durability of this effect.

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Authors' Contribution

Conceptualization: BH
Methodology: BH, EU, FS, JM, MIJ
Formal analysis: BH, EU, FS, JM, NB, MIJ
Writing and Drafting: BH, NB
Review and Editing: BH, EU, FS, JM, NB, MIJ

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflict of Interest

All the authors declare no conflict of interest.

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