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Comparison of Efficacy of Once-Weekly Trelagliptin versus Once-Daily Vildagliptin on Glycemic Control in Patients with Type 2 Diabetes: A Randomized Controlled Trial

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ABSTRACT

Background and Objective: The comparative efficacy of once-weekly trelagliptin versus once-daily vildagliptin in glycemic control among patients with type 2 diabetes remains insufficiently explored. This study aimed to evaluate the efficacy of these two DPP-4 inhibitors in improving glycemic outcomes in individuals inadequately controlled on metformin. **Material and Methods:** A randomized controlled trial was conducted at Department of General Medicine, PNS Hafeez Hospital Islamabad. Adults aged 30–60 years with type 2 diabetes and baseline HbA1c of 7.5–9.5% were enrolled using non-probability consecutive sampling. Participants were randomized via lottery to receive either trelagliptin 100 mg once weekly or vildagliptin 50 mg once daily for three months. Baseline demographics, comorbidities, and laboratory values were recorded. The primary outcome was the proportion of patients achieving HbA1c <7% at three months; secondary outcomes included mean reduction in HbA1c. Data were analyzed using t-tests and chi-square tests, with stratification for potential confounders. **Results:** Of 102 participants, both groups were similar in baseline characteristics. At three months, the mean HbA1c was 7.6 ± 0.7% in the trelagliptin group and 7.3 ± 0.6% in the vildagliptin group ($p < 0.05$). Mean reduction in HbA1c was 0.8 ± 0.3% for trelagliptin and 1.0 ± 0.4% for vildagliptin ($p < 0.01$). Achievement of HbA1c <7% occurred in 19 (37.3%) versus 28 (54.9%) participants, respectively ($p < 0.1$). No statistically significant differences were observed in subgroup analyses. **Conclusion:** Vildagliptin provided greater improvement in glycemic control compared to trelagliptin. Both agents were safe and effective in routine clinical practice.

INTRODUCTION

The worldwide burden of diabetes mellitus (DM) has been steadily increasing, with an estimated global prevalence of 8.3% in 2014, affecting about 387 million people, and projections indicating a rise to 592 million by 2035 [1]. Type 2 diabetes mellitus (T2DM) accounts for the majority of cases, and its management primarily relies on lifestyle modification, with pharmacological treatment including metformin, introduced when lifestyle measures are insufficient. Guidelines from the ADA and EASD recommend a stepwise addition of other antidiabetic drugs tailored to individual patient needs [2,3]. However, achieving the target HbA1c of less than 7.0% remains challenging, as only 57.3% of patients meet this goal. Suboptimal glycemic control is often linked to poor medication adherence, which tends to be lower in diabetes patients than in those with other chronic illnesses, adversely affecting outcomes [4].

A randomized clinical trial reported that a higher proportion of patients achieved optimal HbA1c levels with daily vildagliptin compared to once-weekly trelagliptin [5]. Another 12-week study found no significant difference in HbA1c reduction between patients maintained on daily DPP-4 inhibitors and those switched to weekly trelagliptin [6]. Additionally, research comparing once-weekly omarigliptin to once-daily sitagliptin found similar rates of patients achieving target HbA1c in both groups [7]. Collectively, these studies indicate that while efficacy may differ between regimens, both once-weekly and daily DPP-4 inhibitors are effective options for glycemic management in type 2 diabetes.

Trelagliptin, with its once-weekly dosing facilitated by an innovative molecular design, presents a unique opportunity to address this issue. Although studies suggest a favorable profile for weekly Trelagliptin, the question of its universal efficacy and safety remains. [6,8] Also, existing research, such as the meta-analysis by Dutta et al. (2022), has not definitively established superior

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adherence with Trelagliptin, nor has it resolved the debate over adherence and glycaemic control. [9] The proposed study aims to close these knowledge gaps by establishing a definitive comparison of Trelagliptin efficacy against daily DPP-4 inhibitors, focusing specifically on its impact on HbA1c levels. This research will be the first of its kind in our region, addressing a significant gap in the literature which previously comprised mostly small-scale studies reported from Japan. By conducting this study with a larger sample size and within a different demographic, it will provide valuable insights into evidence-based management of T2DM.

MATERIAL AND METHODS

This randomized controlled trial was conducted in the Department of General Medicine at PNS Hafeez hospital Islamabad, spanning a period of 4 months (January 2025 to May 2025). Ethical clearance was obtained from the Institutional Review Board (491/16, Dated: 23/10/24), and the study protocol was registered with the clinical trial registry (NCT06913101). A non-probability consecutive sampling technique was employed to recruit eligible participants, ensuring a pragmatic and representative selection from the patient population attending the department. Written informed consent was obtained from all participants after a thorough explanation of the study objectives, procedures, potential risks, and benefits. Baseline demographic and clinical characteristics, including age, gender, comorbidities, and laboratory investigations were recorded at the time of enrollment to confirm eligibility and to characterize the study population.

The study included 102 adults aged 30 to 60 years of either gender who had been diagnosed with type 2 diabetes mellitus according to American Diabetes Association criteria and presented with HbA1c levels between 7.5% and 9.5% at screening. Patients were excluded if they had a history of type 1 diabetes mellitus or diabetic ketoacidosis, had used insulin or antidiabetic agents other than metformin within three months before recruitment, had significant cardiovascular, hepatic, renal, or pancreatic dysfunction, were pregnant or lactating, had participated in other clinical trials within the preceding 30 days, had hypersensitivity to study drugs, or had any medical or psychological conditions that could prevent study completion. Randomization was performed using a lottery method to assign participants equally into two groups, which helped minimize allocation bias. Group A received trelagliptin 100 mg once weekly before breakfast on the same day each week, while Group B was given vildagliptin 50 mg once daily. Both treatments continued for three months.

Data Collection and Outcome Assessment

Throughout the study period, participants attended scheduled follow-up visits where medication adherence, potential adverse events, and any changes in other medications were documented. The primary outcome measure focused on glycemic control, with efficacy defined as the proportion of participants achieving an HbA1c level below 7% after three months of treatment. The mean reduction in HbA1c from baseline to three months was also calculated for each group. Operational definitions of type 2 diabetes mellitus, efficacy, and mean HbA1c reduction were applied uniformly according to internationally recognized criteria. All laboratory investigations were conducted at the hospital's accredited laboratory with quality assurance protocols in place to ensure reliable data. All data were captured using a structured form developed specifically for this study, which helped maintain consistency in data collection across all participants and visits.

Statistical analyses were performed using SPSS version 26.0. Continuous variables were expressed as means and standard deviations and compared between groups using the independent t-test. Categorical variables were documented as frequencies and percentages, with intergroup comparisons conducted using the Chi-square test. Stratification was undertaken to control for confounding variables including age, gender, duration of diabetes, and body mass index. Post-stratification analyses employed the Chi-square test for categorical outcomes. Statistical significance was set at a p-value of less than 0.05 for all comparisons.

RESULTS

Both groups were similar in age, gender distribution, body mass index, and duration of diabetes. There were no significant differences in baseline characteristics, indicating that the groups were well matched before treatment began (Table 1).

Table 1

Comparison of Baseline Demographic and Clinical Characteristics between Trelagliptin and Vildagliptin Groups. (n=102)

Variable	Trelagliptin Group (n=51)	Vildagliptin Group (n=51)	p-value
Mean age (years)	48.2 ± 7.1	47.6 ± 6.9	0.663
Male gender, n (%)	29 (56.9)	28 (54.9)	0.841
Mean BMI (kg/m^2)	28.1 ± 3.2	27.9 ± 3.0	0.751
Duration of diabetes (years)	5.8 ± 2.4	6.0 ± 2.3	0.673
Hypertension, n (%)	22 (43.1)	21 (41.2)	0.838
Dyslipidemia, n (%)	18 (35.3)	17 (33.3)	0.830
Baseline HbA1c (%)	8.4 ± 0.5	8.3 ± 0.6	0.345

After three months of treatment, average HbA1c levels decreased in both groups, with a greater reduction seen in those receiving vildagliptin compared to trelagliptin. More participants in the vildagliptin group reached the target HbA1c of less than 7%. These results indicate that vildagliptin led to slightly better improvement in blood sugar control over the study period (Table 2).

Table 2

Comparison of Glycemic Outcomes at Three Months

Outcome	Trelagliptin Group (n=51)	Vildagliptin Group (n=51)	p-value
Mean HbA1c at 3 months (%)	7.6 ± 0.7	7.3 ± 0.6	0.02
Mean reduction in HbA1c (%)	0.8 ± 0.3	1.0 ± 0.4	<0.005
HbA1c <7% at 3 months, n (%)	19 (37.3)	28 (54.9)	<0.1

The stratified analysis showed that, among participants under 50 years of age, a higher proportion in the vildagliptin group achieved HbA1c less than 7% compared to the trelagliptin group, but the difference was not statistically significant (p = 0.218). Similarly, for those

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aged 50 years or older, more participants in the vildagliptin group met the target, though the difference was not significant (p = 0.165). Among males and females, higher percentages achieved the goal with vildagliptin than with trelagliptin, but again, these differences were not statistically meaningful (p = 0.189 and p = 0.270, respectively). For those with a diabetes duration of less than five years, as well as those with a longer duration, and in both BMI categories, the vildagliptin group consistently showed higher success rates; however, none of these subgroup differences reached statistical significance (p values ranged from 0.165 to 0.357) (Table 3).

Table 3

Stratified Analysis of Efficacy (HbA1c <7% at 3 Months) by Baseline Characteristics

Variable	Category	Trelagliptin Group n/N (%)	Vildagliptin Group n/N (%)	p-value*
Age (years)	<50	10/24 (41.7%)	16/28 (57.1%)	0.218
	≥50	9/27 (33.3%)	12/23 (52.2%)	0.165
Gender	Male	11/29 (37.9%)	15/28 (53.6%)	0.189
	Female	8/22 (36.4%)	13/23 (56.5%)	0.270
Duration of Diabetes (yrs)	<5	10/22 (45.5%)	14/22 (63.6%)	0.270
	≥5	9/29 (31.0%)	14/29 (48.3%)	0.165
BMI (kg/m^2)	<27	8/21 (38.1%)	12/22 (54.5%)	0.357
	≥27	11/30 (36.7%)	16/29 (55.2%)	0.189

DISCUSSION

The observed mean reduction in HbA1c after three months was 0.8 ± 0.3% in the trelagliptin group and 1.0 ± 0.4% in the vildagliptin group, with a statistically significant difference favoring vildagliptin (p < 0.01). A greater proportion of patients receiving vildagliptin achieved the target HbA1c of less than 7% compared to those on trelagliptin (54.9% vs. 37.3%, respectively).

The current findings are broadly consistent with results from pivotal trials evaluating DPP-4 inhibitors in similar populations. Several studies have reported modest reductions in HbA1c with trelagliptin. In a phase 3, double-blind, non-inferiority trial among Japanese patients with T2DM, trelagliptin demonstrated a mean HbA1c reduction of -0.33%, which was non-inferior to alogliptin (-0.45%), and both agents displayed comparable safety profiles [10]. Other open-label and exploratory trials have reported that trelagliptin improves glycemic variability and achieves glycemic control without increased risk of hypoglycemia, confirming its safety and tolerability [11]. These values are slightly lower than the mean reductions observed in the present study, which may be attributable to differences in baseline HbA1c, study duration, ethnicity, and background therapy.

The efficacy of vildagliptin has also been investigated in large multicenter trials, with mean HbA1c reductions typically in the range of -0.5% to -1.3% over 12 to 24 weeks [12–15]. A Chinese multicenter trial (n=277), vildagliptin was associated with a mean reduction of -0.65% and demonstrated comparable efficacy to other DPP-4 inhibitors [15]. This aligns with the observed reduction in the current study, reinforcing the conclusion that vildagliptin remains an effective glucose-lowering agent across diverse populations. Notably, previous literature indicates that DPP-4 inhibitors, including both trelagliptin and vildagliptin, are generally well tolerated, with minimal risk of hypoglycemia and weight neutrality [11,15].

Comparison of proportions achieving glycemic targets in this study highlights a modest advantage for vildagliptin over trelagliptin, although the difference did not reach conventional statistical significance (p < 0.1). This trend mirrors findings reported by Meguro et al., where 33.3% of patients on trelagliptin and 61.1% of those on vildagliptin achieved an HbA1c of less than 7.0% [5]. While both agents demonstrated robust efficacy, daily vildagliptin appeared to facilitate target achievement in a greater proportion of patients. Similar patterns have been noted in large studies of once-weekly versus once-daily DPP-4 inhibitors, with some demonstrating non-inferiority and others indicating potential advantages for daily dosing regimens [7]. However, a 12-week randomized study by Oita et al. observed no significant difference in mean HbA1c change between those who switched to weekly trelagliptin and those who continued daily DPP-4 inhibitor therapy, supporting the equivalence of these agents in appropriately selected patients [6].

Subgroup analyses in the current study did not reveal statistically significant differences in efficacy based on age, gender, duration of diabetes, or BMI, a finding corroborated by the subgroup evaluations reported in several prior studies [11,14,15]. For instance, research involving special populations such as the elderly or those with renal impairment found that trelagliptin and vildagliptin produced similar improvements in glycemic control and maintained favorable safety profiles [12,14]. Furthermore, trials comparing trelagliptin to other glucose-lowering agents such as dulaglutide found that, although dulaglutide induced a greater reduction in HbA1c, trelagliptin exhibited similar effects on beta-cell function and maintained safety [14,15].

The difference in mean HbA1c reduction between groups in the present study, while statistically significant, must be interpreted in the context of patient adherence, dosing frequency, and patient preference. Weekly dosing regimens such as trelagliptin are postulated to enhance adherence, particularly in populations prone to medication fatigue, although meta-analyses have yet to definitively establish superior adherence with once-weekly formulations [12,16]. As such, individualization of therapy remains paramount, balancing efficacy, safety, convenience, and patient preference. Both agents were well tolerated in this study, with no severe adverse events or discontinuations attributed to study medication. This is consistent with the extensive safety data for DPP-4 inhibitors, which have established a favorable profile with low rates of hypoglycemia and metabolic side effects [16,17].

This study was limited by its single-center design, relatively short follow-up period, and moderate sample size, which may affect the generalizability of the results. However, strengths include rigorous randomization, comprehensive stratified analysis, and direct comparison of two clinically relevant DPP-4 inhibitors. Future multicenter trials with longer follow-up are needed to assess the durability of glycemic control and long-term safety outcomes. Incorporating patient adherence, quality of life, and cardiovascular endpoints will further inform

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the optimal use of once-weekly versus daily regimens in diverse population.

CONCLUSION

Both once-weekly trelagliptin and once-daily vildagliptin were effective and well tolerated in improving blood sugar control in individuals with type 2 diabetes. Although both treatments provided meaningful benefits, daily vildagliptin led to better glycemic outcomes for a greater number of patients. These findings support the continued use of DPP-4 inhibitors in clinical practice and emphasize the importance of individualizing therapy based on patient needs and treatment preferences.

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