IJPSR (2026), Volume 17, Issue 5 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 18 December 2025; received in revised form, 30 December 2025; accepted, 31 December 2025; published 01 May 2026

COMPARATIVE EFFICACY AND SAFETY OF GLIMEPIRIDE–METFORMIN VERSUS TENELIGLIPTIN–METFORMIN IN TYPE 2 DIABETES MELLITUS: A PROSPECTIVE RANDOMIZED STUDY

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Keywords:

Type 2 diabetes mellitus, Metformin, Glimepiride, Teneligliptin; HbA1c, Oral hypoglycemic agents

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ABSTRACT: Background: Diabetes mellitus (DM) is one of the most prevalent chronic metabolic disorders worldwide. Optimal glycaemic control often requires combination therapy using oral hypoglycemic agents with complementary mechanisms of action. **Objectives:** To compare the efficacy and safety of Glimepiride Metformin and Teneligliptin Metformin combinations in patients with T2DMinadequately controlled on monotherapy. **Materials and Methods:** This prospective, open-label, parallel, randomized single-centre study included 204 patients with uncontrolled type 2 DM, randomized equally into two groups. Group A received Glimepiride 2 mg once daily plus Metformin 1 g twice daily, while Group B received Teneligliptin 20 mg once daily plus Metformin 1 g twice daily. Fasting blood sugar (FBS) and post-prandial blood sugar (PPBS) were measured at baseline, 3 and 6 months, and glycated haemoglobin (HbA1c) at baselineand 6 months. Adverse events were recorded. Data were analyzed using chi-square and unpaired t-tests. **Results:** Baseline parameters were comparable between groups. At 6 months, differences in mean FBS and mean PPBSin Group A and Group B respectively were not statistically significant. Mean HbA1c was significantly lower in Group B (6.61 ± 0.34 %) compared to Group A (6.75 ± 0.44 %) ($p = 0.018$). Adverse effects were mild, with lower frequency of symptomatic hypoglycaemia in the Teneligliptin–Metformin group. **Conclusion:** Both combinations effectively improved glycaemic control; however, Teneligliptin–Metformin achieved a greater HbA1c reduction and showed a better safety profile with fewer hypoglycemic episodes.

INTRODUCTION: Diabetes mellitus (DM) has emerged as one of the most widespread chronic illnesses globally and continues to increase at an alarming pace.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.17(5).1630-34

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.17(5).1630-34

As of 2024, an estimated 89.8 million adults in India were living with diabetes, with a prevalence of approximately 10.5% among adults aged 20–79 years, and this number is projected to rise to 156.7 million by 2050 [1, 2].

Achieving sustained glycaemic control remains the central goal in the management of type 2 diabetes mellitus (T2DM), as prolonged hyperglycaemia is strongly associated with microvascular and macrovascular complications [3]. Conventional management of T2DM follows a step-wise

approach, progressing from lifestyle modification to pharmacological monotherapy and subsequent combination therapy when glycaemic targets are not achieved, as recommended by international and national guidelines [4]. However, delayed treatment intensification may result in prolonged periods of suboptimal glycaemic control, thereby increasing the risk of diabetes-related complications. Increasing evidence supports early combination therapy using agents with complementary mechanisms to improve metabolic control, reduce long-term glycaemic burden, and enhance cost-effectiveness [4]. By the time T2DM is diagnosed, β-cell function is often reduced by 50–80%, and many patients already have microvascular or macrovascular complications, highlighting the need for proactive therapeutic strategies [5, 6].

Metformin remains the first-line oral antihyperglycaemic agent due to its proven efficacy and safety. Teneligliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, enhances endogenous incretin activity, thereby improving insulin secretion and suppressing glucagon release in a glucose-dependent manner with a low risk of hypoglycaemia, and is considered cost-effective in the Indian setting [7, 8]. In contrast, glimepiride, though effective, is associated with a higher risk of hypoglycaemia and weight gain [9].

Objectives:

Primary Objective: To compare the efficacy of Glimepiride Metformin and Teneligliptin Metformin combination therapies in patients with type 2 diabetes mellitus.

Secondary Objective: To compare the safety profile of Glimepiride–Metformin and Teneligliptin–Metformin combinations in patients with type 2 diabetes mellitus

MATERIALS AND METHODS: This prospective, interventional, randomized, open-label, comparative, parallel-group study in patients with uncontrolled T2DMattending the outpatient department of Medicine at Mc Gann Teaching District Hospital, Shivamogga. Patients included in the study as per the inclusion and exclusion criteria were randomized into two groups using block randomization with allocation ratio 1:1. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) with reference number SIMS/IEC/427/2018-19. Written informed consent was obtained from all participants in their regional language, and the study was conducted in accordance with the Declaration of Helsinki. Participants aged between 30 and 60 years with poorly controlled T2DMwere considered for inclusion, particularly those who failed to achieve adequate glycaemic control on metformin alone and who provided written informed consent. Individuals were excluded if they had type 1 diabetes mellitus, acute metabolic complications such as diabetic ketoacidosis or hyperosmolar hyperglycaemic state, clinically significant renal or hepatic impairment, congestive cardiac failure, a recent episode of acute coronary syndrome, or if they were pregnant or breastfeeding. Patients outside the specified age range or those receiving drugs known to interfere with glucose metabolism including corticosteroids, octreotide, beta-blockers, thiazide diuretics, haloperidol, quinidine, or pentamidine were also not enrolled.

All data were entered in Microsoft Excel. Categorical variables were expressed as frequencies and analyzed using the Chi-square test, while continuous variables were presented as mean ± SD and compared between groups using the unpaired t-test. A p value < 0.05 was considered statistically significant at a 95% confidence interval. Based on a previous study by Kim *et al.*[10] reporting a mean HbA1c of 6.6 ± 0.7 % with Glimepiride–Metformin, the expected HbA1c for the Teneligliptin–Metformin group was assumed to be 6.3%. With equal variance, a power of 80%, and a two-sided alpha of 5%, the sample size was calculated using the standard formula for comparing two means. Based on the sample size calculation, 85 participants were required per group; allowing for a 20% dropout rate, this was increased to 102 subjects in each group (Glimepiride–Metformin, n = 102; Teneligliptin–Metformin, n = 102).

RESULTS: A total of 204 individuals with inadequately controlled T2DM were screened and deemed eligible for analysis. Most participants (61.7 %) were between 50–60 years of age. The mean age in Group A was 50.98 ± 6.34 years, compared with 51.33 ± 5.73 years in Group B.

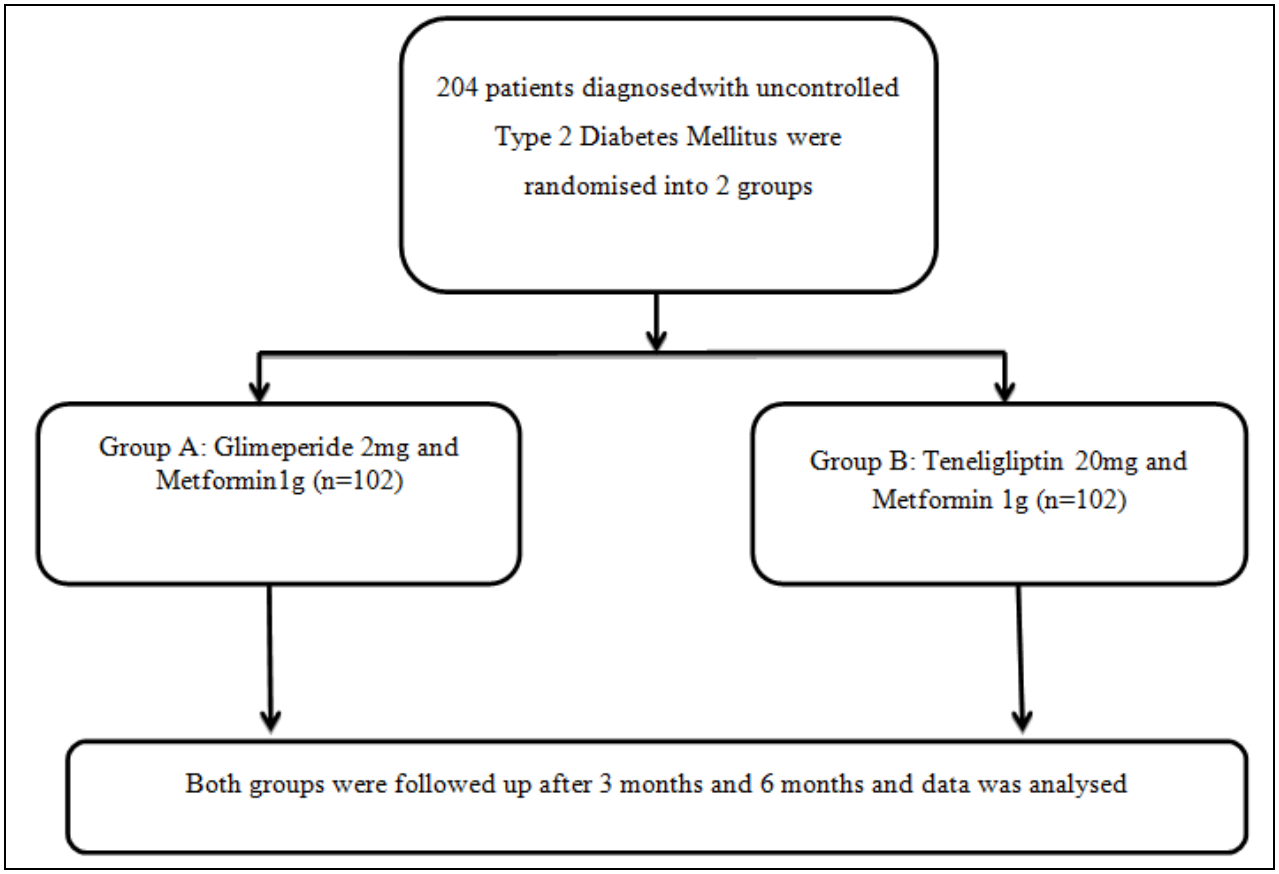

FIG. 1: PATIENT RECRUITMENT FLOW CHART

At baseline, glycaemic parameters were comparable between the two groups. The mean fasting blood glucose (FBS) was 179.52 ± 33.88 mg/dL in Group A and 171.60 ± 22.90 mg/dL in Group B, with no statistically significant difference between them (P = 0.25). Similarly, mean post-prandial blood glucose (PPBS) values were 272.26 ± 41.51 mg/dL in Group A and 269.22 ± 38.29 mg/dL in Group B (P = 0.45). Baseline HbA1c levels were also comparable, measuring 8.80 ± 0.53 % in Group A and 8.99 ± 0.54 % in Group B (P = 0.82).

TABLE 1: BASELINE DEMOGRAPHIC DATA

Parameter	**Group A**	**Group B**	**P value**
Age (Years)	50.98±6.34	51.33±5.73	0.67
Male (%)	52.94	54.9	0.78
FBS (mg/dL)	179.52±33.88	171.60±22.90	0.25
PPBS (mg/dL)	272.26±41.51	269.22±38.29	0.45
HbA1c (%)	8.80 ±0.53	8.78± 0.54	0.82

At the 3-month follow-up, both groups demonstrated statistically significant reductions in glycaemic indices relative to their baseline values. The mean FBS decreased to 110.45 ± 13.17 mg/dL in Group A and 109.53 ± 12.34 mg/dL in Group B, with no meaningful difference between the two (P = 0.50). Correspondingly, mean PPBS values declined to 158.04 ± 16.60 mg/dL in Group A and 159.20 ± 16.02 mg/dL in Group B (P = 0.61), again showing comparable improvements. Further reductions were seen at 6 months. The mean FBS reached 105.03 ± 12.54 mg/dL in Group A and 104.98 ± 11.70 mg/dL in Group B (P = 0.90), while PPBS values decreased to 154.44 ± 13.25 mg/dL and 153.65 ± 14.71 mg/dL in Groups A and B, respectively (P = 0.45). HbA1c levels also declined substantially over the 6-month period, falling from 8.80 % to 6.75 % in Group A and from 8.99 % to 6.61 % in Group B. Although both groups experienced significant reductions from baseline, the decrease in HbA1c was modestly but statistically significantly greater in Group B (P = 0.018).

TABLE 2: MEAN REDUCTION IN GLYCAEMIC MARKERS BETWEEN THE GROUPS AT BASELINE AND AFTER 3 MONTHS AND 6 MONTHS

Glycaemic parameter	Group A	Group B	P value
FBS			
Baseline	179.52±33.88	171.60±22.90	0.25
3 months	110.45 ±13.17	109.53±12.34	0.50
6 months	105.03 ±12.54	104.98±11.70	0.90
PPBS			
Baseline	272.26±41.51	269.22±38.29	0.45
3 months	158.04±16.60	159.20 ±16.02	0.61
6 months	154.44 ±13.25	153.65 ±14.71	0.45
HbA1c			
Baseline	8.80 ±0.53	8.78± 0.54	0.82
6 months	6.75±0.44	6.61±0.34	0.018

Hypoglycaemia occurred more frequently in the Glimepiride–Metformin group (5 cases, 4.9 %) than in the Teneligliptin–Metformin group (2 cases, 1.96 %). Other adverse events such as headache, abdominal discomfort, diarrhoea, chest discomfort, and dyspnoea were mild and self-limiting.

DISCUSSION: This study demonstrates that both treatment combinations produced significant reductions in FPG, PPG, and HbA1c over the 6-month follow-up, consistent with findings from previous real-world and clinical studies evaluating teneligliptin-based regimens in Indian populations [11]. However, despite these improvements, glycaemic values did not normalize fully, suggesting partial metabolic correction rather than complete disease control.

The metformin–teneligliptin combination showed superior glycaemic improvement, supporting the concept that early combination therapy with agents having complementary mechanisms provides additive benefit over step-wise escalation. Randomized trials and meta-analyses have consistently demonstrated greater HbA1c reduction with teneligliptin added to metformin compared with monotherapy, reinforcing its role as an effective combination partner [12]. Rather than reiterating mechanistic pathways, the present findings align clinically with prior evidence that DPP-4 inhibitor–based combinations preferentially improve both fasting and postprandial glycaemic parameters with a favourable safety profile [13]. With respect to safety, the low incidence of hypoglycaemia observed with teneligliptin–metformin is consistent with earlier controlled trials and pooled analyses, which have shown glucose-dependent efficacy without excess hypoglycaemic risk [14, 15, 16]. In contrast, the higher frequency of hypoglycaemic episodes in the glimepiride group reflects the well-recognized limitations of sulfonylureas. Several important limitations should be emphasized. The open-label design may have introduced performance and reporting bias. The single-centre setting limits external validity, and the short follow-up duration precludes conclusions regarding long-term glycaemic durability, β-cell preservation, and cardiovascular outcomes. Additionally, the absence of systematic assessment of body weight, lipid parameters, and quality-of-life outcomes restricts comprehensive evaluation of metabolic benefits. While intergroup differences in HbA1c were statistically significant, their clinical magnitude was modest, underscoring the need for larger, multicentric, longer-duration randomized studies to confirm these findings.

CONCLUSION: In agreement with existing literature, the results of this study suggest that Teneligliptin–Metformin provides significantly better reductions in HbA1clevels when compared with Glimepiride–Metformin, but with a lower incidence of hypoglycemia, supporting its role as a reliable and well-tolerated therapeutic option for patients with T2DM.

ACKNOWLEDGEMENTS: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Abhishek CP, Rodrigues AJ, Shastry EH, Vedavathi H, Revankar SP and Acharya A: Comparative efficacy and safety of glimepiride–metformin versus teneligliptin–metformin in type 2 diabetes mellitus: a prospective randomized study. Int J Pharm Sci & Res 2026; 17(5): 1630-34. doi: 10.13040/IJPSR.0975-8232.17(5).1630-34.