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ORIGINAL ARTICLE

Comparative Study on Safety & Efficacy of Glimepiride-Metformin with Vildagliptin-Metformin Combination in Patients with Type-2 Diabetes Mellitus

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ABSTRACT

Background & objective: Metformin is a cornerstone in the management of Type 2 Diabetes Mellitus (T2DM); however, monotherapy with metformin often fails to achieve optimal glycemic control in many patients, especially in elderly or inadequately managed cases. Consequently, combination therapies involving agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., vildagliptin) or sulfonylureas (e.g., glimepiride) are frequently employed. Nonetheless, limited studies have directly compared the efficacy and safety profiles of commonly used combinations of metformin with vildagliptin (MF-VG) versus metformin with glimepiride (MF-GP). This study aimed to evaluate and compare the efficacy and safety of these two combination therapies in patients with uncontrolled T2DM.

Methods: This randomized, comparative clinical trial was conducted over a one-year period (July 2019 to June 2020) at the Department of Pharmacology and Therapeutics, in collaboration with the Rajshahi Diabetic Association, General Hospital, Rajshahi. A total of 70 patients with uncomplicated T2DM, with or without stable co-morbidities, who had been on metformin therapy (1000-2500 mg/day) for at least four weeks but remained inadequately controlled (HbA1c ≥ 6.5%, FBG ≥ 126 mg/dL, or PPG ≥ 200 mg/dL), were enrolled. Participants were randomly assigned to two groups: MF-VG (n = 35) and MF-GP (n = 35). Outcomes—measured at 6 and 12 weeks—included changes in FBG, PPG, HbA1c, and the incidence of adverse events.

Results: The two groups were comparable in terms of age, sex, and BMI ($p = 0.490$, $p = 0.811$, and $p = 0.392$, respectively). Baseline glycemic parameters (FBS, PPG, HbA1c) were elevated above the normal range, with no significant differences between groups ($p = 0.104$, $p = 0.108$, and $p = 0.130$, respectively). Both groups demonstrated significant reductions in FBG, PPG, and HbA1c levels from baseline to 12 weeks ($p < 0.05$). The mean FBS decreased by 2.7 mmol/L in the MF-VG group and 2.6 mmol/L in the MF-GP group. PPG reductions were 4.3 mmol/L and 4.4 mmol/L, respectively. HbA1c levels declined by approximately 1.5% in the MF-VG group and 1.1% in the MF-GP group. Notably, the incidence of weight gain and hypoglycemia was higher in the MF-GP group.

Conclusion: Both metformin-vildagliptin and metformin-glimepiride combinations effectively improve glycemic control in patients with uncontrolled T2DM on metformin monotherapy. However, considering safety profiles—particularly the lower incidence of weight gain and hypoglycemia—the MF-VG combination appears to be a more favorable therapeutic option. These findings support the use of vildagliptin in combination with metformin as an effective and safer alternative to glimepiride-metformin therapy in managing uncontrolled T2DM.

Keywords: Type 2 diabetes mellitus, efficacy, safety, Glimepiride-Metformin, Vildagliptin-Metformin etc.

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INTRODUCTION:

Diabetes mellitus (DM) remains one of the most prevalent non-communicable diseases globally, necessitating ongoing research to optimize management strategies. It is a chronic metabolic disorder of multifactorial etiology characterized primarily by persistent hyperglycemia resulting from disturbances in carbohydrate metabolism due to insulin resistance.[1] Currently, diabetes imposes a significant health burden worldwide, with its prevalence steadily rising. In Bangladesh, the figures are particularly alarming, affecting approximately 8.4 million individuals-around 10% of the total population.[2]

Although diabetes mellitus is not curable, it can often be managed effectively through lifestyle modifications such as dietary changes and regular physical activity, often in conjunction with pharmacotherapy.[3] Uncontrolled diabetes heightens the risk of numerous complications, including coronary artery disease, stroke, nephropathy, retinopathy, erectile dysfunction, neuropathy, gangrene, and gastroparesis.[4] Data indicate that over half of patients with type 2 DM despite taking antidiabetic medications fail to achieve target glycemic levels, with a glycosylated hemoglobin (HbA1c) level below 7% being elusive for many.[5]

The treatment of type2 or non-insulin dependent diabetes mellitus (NIDDM) primarily involves multiple pathophysiological defects, including islets dysfunction, impaired insulin secretion, resistance to insulin and impairment in incretin system.[6] Insulin secretagogues, insulin sensitizers and newer drug like DPP-4 inhibitors are mainly prescribed in Type 2 diabetic patients. Metformin, a member of the biguanide class, is the frontline pharmacotherapy in Type 2 DM owing to its favorable safety profile and multiple beneficial effects at the molecular and physiological levels. It primarily reduces hyperglycemia by decreasing intestinal glucose absorption, enhancing peripheral glucose uptake, and improving insulin sensitivity.[7] Nonetheless, monotherapy with metformin is insufficient in approximately 4% of patients, especially among older or poorly managed diabetics, necessitating combination therapy.[8] Glimepiride, a widely used sulfonylurea, enhances insulin secretion by stimulating pancreatic β-cells. While effective, prolonged use is associated with β-cell exhaustion, leading to diminished efficacy over time, and carries risks of hypoglycemia and weight gain.[7] Hence, the patients on MF monotherapy with inadequate response require a combination therapy.

The combination of metformin and glimepiride is well-established and widely prescribed, particularly in regions like India, owing to its cost-effectiveness and superior glycemic control compared to either agent alone.[9] However, this combination poses concerns related to hypoglycemia and weight gain, prompting dose adjustments to mitigate adverse effects. Alternatively, studies have demonstrated that vildagliptin, a DPP-4 inhibitor, in combination with metformin, offers comparable glycemic control to glimepiride–metformin therapy, with a superior safety profile characterized by lower risks of hypoglycemia and weight gain.[10,11] Vildagliptin functions by inhibiting DPP-4, thereby increasing levels of incretin hormones such as GLP-1 and GIP, which enhance glucose-dependent insulin secretion and suppress glucagon release, ultimately improving postprandial glucose regulation.

Given their distinct mechanisms, the combined use of metformin with vildagliptin potentially offers advantages in improving β-cell function, increasing endogenous incretin levels, and reducing HbA1c without significant weight gain or hypoglycemia.[12] Nonetheless, there is a paucity of studies directly comparing the efficacy and safety profiles of metformin-glimepiride versus metformin-vildagliptin combinations in clinical settings, particularly in developing countries. Consequently, this study aims to compare these two combination therapies in terms of their efficacy and safety in patients with Type 2 DM.

METHODS

This randomized clinical trial aimed to compare the efficacy and safety profiles of two combination therapies-Metformin with Glimepiride (MF-GP) and

Metformin with Vildagliptin (MF-VG)-in patients with Type 2 Diabetes Mellitus was conducted at the Department of Pharmacology and Therapeutics in collaboration with the Rajshahi Diabetic Association, General Hospital, Rajshahi. The study spanned a period of one year, from July 2019 to June 2020, following approval from the Institutional Review Board (IRB) of Rajshahi Medical College, Rajshahi. A total of 70 patients diagnosed with Type 2 Diabetes Mellitus (T2DM) were enrolled as participants. Eligible patients included those with uncomplicated T2DM, with or without stable co-morbid conditions, who had been on treatment with metformin (MF) for at least four months with its maximum tolerated dose (ranging from 1000 to 2500 mg/day) but still exhibited inadequate glycemic control, defined as HbA1c ≥ 6.5%, fasting blood glucose (FBG) ≥ 126 mg/dL (≥ 7 mmol/L), or postprandial glucose (PPG) ≥ 200 mg/dL (11.1 mmol/L) (American Diabetes Association, 2012). Exclusion criteria encompassed pregnant or lactating women, individuals with known allergies or intolerances to study medications, and patients with various complications of diabetes-such as acute or chronic diabetic complications, recent ischemic events like myocardial infarction, unstable angina, previous bypass surgery, liver disease, renal impairment, or conditions that could interfere with study outcomes. Patients currently on medications known to significantly affect blood glucose levels, such as corticosteroids or other long-term glucose-altering drugs, were also excluded. The outcomes evaluated included changes in glycemic parameters and adverse events.

Data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 23.0. The test statistics used to analyze the data were descriptive statistics, Unpaired

t-Test, Repeated Measure ANOVA & Chi-square (χ^2) Tests. While data presented on continuous scale were compared between the two treatment groups using Unpaired t-Test, Repeated Measure ANOVA, data on categorical scale were compared between the groups using Chi-square (χ^2) or Fisher's Exact Test. The level of significance was set at 5% and $p < 0.05$ was considered significant.

RESULTS

The two study groups were comparable in terms of demographic characteristics. The mean age was 48.9 ± 9.6 years in the MF-VG group and 50.5 ± 9.9 years in the MF-GP group. Gender distribution was nearly equal across groups ($p = 0.811$). Similarly, the Body Mass Index (BMI) was comparable between the two groups ($p = 0.392$) (Table I). At baseline, both groups exhibited poor glycemic control, with mean fasting blood glucose (FBS), postprandial glucose (PPG), and HbA1c levels above the normal range. There were no significant differences between groups in terms of FBS, PPG and HBA1c ($p= 0.104$, $p = 0.108$ and $p = 0.130$ respectively) (Table II).

In the MF-VG group, mean FBS decreased from 10.1 mmol/L at baseline to 8.9 mmol/L after 6 weeks, and further declined to 7.4 mmol/L by the end of 12 weeks. The MF-GP group demonstrated a similar trend, with baseline FBS of 9.7 mmol/L decreasing to 8.6 mmol/L at 6 weeks and 7.1 mmol/L at 12 weeks. The within-group reduction in FBS was statistically significant ($p < 0.001$). However, between-group comparisons showed no significant difference at 6 and 12 weeks ($p = 0.110$ and $p=0.228$, respectively) (Table III). For PPG, baseline levels were 14.5 mmol/L in the MF-VG group, decreasing significantly to 12.7 mmol/L at 6 weeks, and further to 10.2 mmol/L at 12 weeks ($p < 0.001$). The MF-GP group exhibited a significant decrease from 14.2 mmol/L at baseline to 9.8 mmol/L at the final assessment ($p < 0.001$). However, no significant intergroup differences were noted at 6 and 12 weeks ($p = 0.218$ and $p = 0.171$ respectively) (Table IV). The mean HBA1c in MF-VG group and MF-GP group at baseline was 8.7% and 8.4% respectively. Both groups demonstrated significant reduction of HBA1c after 12 weeks of intervention ($p = 0.007$ and $p = 0.013$ respectively). Although the reduction was more pronounced in MF-VG group than that in MF-GP group, the difference between the groups after 12 weeks of intervention was not significant ($p = 0.633$) (Table V). Regarding weight changes, the mean weight in the MF-VG group remained essentially stable after 12 weeks ($p = 0.417$). Conversely, the MF-GP group experienced a weight increase from

62.6 kg at baseline to 64.5 kg at 12 weeks, although the change did not turn to statistical significance (p=0.102) (Table VI).

Adverse effects reported are summarized in Table VII. Hypoglycemia episodes were significantly more frequent in the MF-GP group (17.1%) compared to the MF-VG group (2.9%) (p = 0.046). Weight gain during the study period was observed in 11.4% of the MF-GP group and 2.9% in the MF-VG group; however, this difference did not reach statistical significance (p = 0.178).

Table I: Demographic characteristics between groups

Demographic characteristics	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
Age# (years)	48.9 ± 9.6	50.5 ± 9.9	0.490
Sex*			
Male	17(48.6)	18(51.4)	0.811
Female	18(51.4)	17(48.6)	
BMI# kg/m²	24.31 ± 1.14	24.09 ± 0.99	0.392

*Data were analyzed using **(χ^2) Test**; figures in the parentheses denote corresponding %. #Data were analyzed using **Unpaired t-Test** and were presented as **mean ± SD.**

Table II: Glycemic status of the patients at baseline

FBS (mmol/L)	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
FBS (mmol/L)	10.1± 0.5	9.7 ± 0.6	0.104
PPG (mmol/L)	14.5 ± 0.9	14.2 ± 0.6	0.108
HbAlc (%)	8.7 ± 0.5	8.4 ± 0.5	0.130

#Data was analyzed using **Student's t-Test** and was presented as **mean ± SD.**

Table III: Changes in FBS from baseline to the end of 12 week

FBS (mmol/L)	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
At baseline	10.1 ± 0.5	9.7 ± 0.6	0.104
Follow-up 6 weeks	8.9 ± 0.5	8.6 ± 0.6	0.110
At 12 weeks	7.4 ± 0.4	7.1 ± 0.6	0.288
P-value*	< 0.001	< 0.001	

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; **p-value** indicates difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA; p-value** indicates difference within group (in each group) from baseline to end-point.

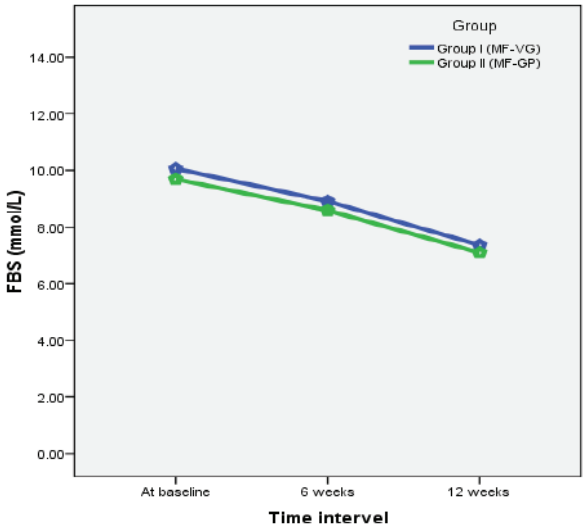

Fig. 1 Showing changes in FBS from baseline to the end of 12 week

Table IV: Changes in PPG at different time intervals between groups

PPG (mmol/L)	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
At baseline	14.5 ± 0.9	14.2 ± 0.6	0.108
At 6 weeks	12.7 ± 0.5	12.3 ± 0.6	0.218
At 12 weeks	10.2 ± 0.5	9.8 ± 0.6	0.171
P-value*	< 0.001	< 0.001	

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; **p-value** indicates difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA; p-value** indicates difference within group (in each group) from baseline to end-point.

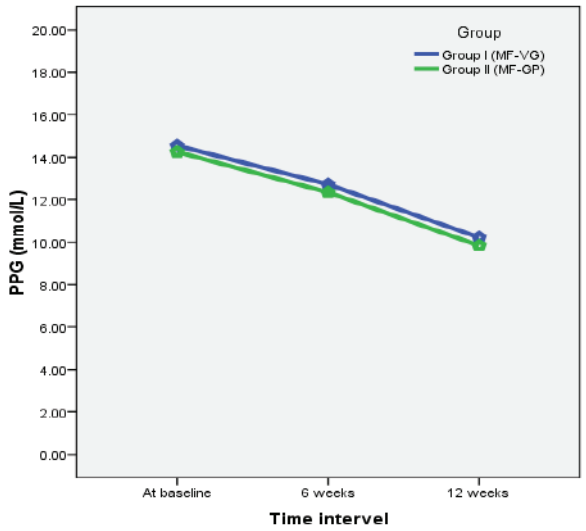

Fig. 2 Showing changes in FPG from baseline to the end of 12 week

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Table V: Changes in HbA1c from baseline to end-point

HbAlc (%)	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
At baseline	8.7 ± 0.5	8.4 ± 0.5	0.210
At 12 weeks	7.2 ± 0.5	7.3 ± 0.5	0.633
P-value*	0.007	0.013	

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; **p-value** indicates difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA; p-value** indicates difference within group (in each group) from baseline to end-point.

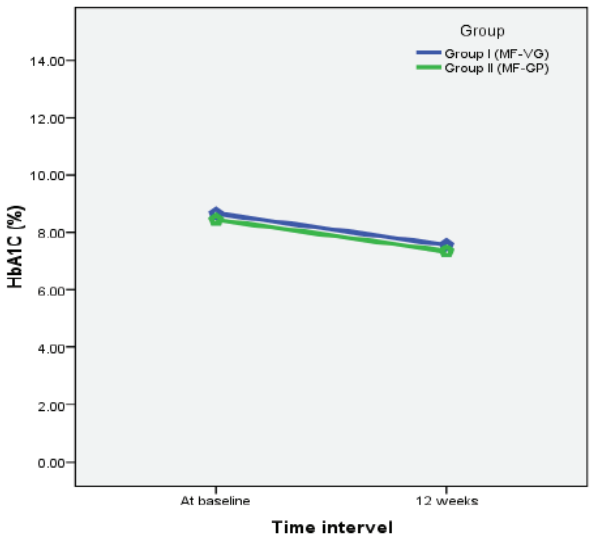

Fig. 3 Showing changes in HbA1c from baseline to the end of 12 week

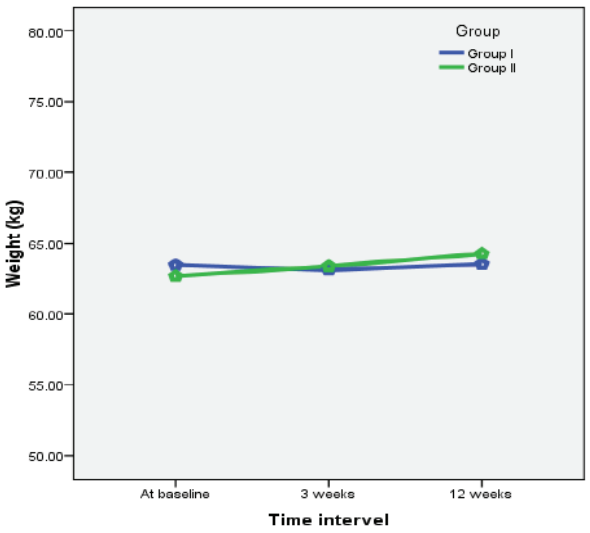

Fig. 4 Showing changes in weight from baseline to the end of 12 week

Table VI: Changes in weight from baseline to end-point

Weight (kg)	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
At baseline	63.4 ± 4.1	62.6 ± 3.8	0.660
At 6 weeks	63.1 ± 3.8	63.4 ± 3.7	0.975
At 12 weeks	63.5 ± 4.1	64.5 ± 3.9	0.975
P-value*	0.417	0.102	

#Data were analyzed using **Student's t-Test** and were presented as **mean ± SD**; **p-value** indicates difference between groups at different time intervals. *Data were analyzed using **Repeated Measure ANOVA; p-value** indicates difference within group (in each group) from baseline to end-point.

Table VII: Comparison of complications/side effects between groups

Complications/ side effects	Group		p-value
	Group-I (MF-VG) (n = 35)	Group II (MF-GP) (n = 35)	
Headache	3(8.6)	2(5.7)	0.500
Dizziness	1(2.9)	2(5.7)	0.500
Hypoglycemia	1(2.9)	6(17.1)	0.046
Weight gain	1(2.9)	4(11.4)	0.178
Nausea	3(8.6)	2(5.7)	0.500
Dyspepsia	1(2.9)	2(5.7)	0.500
Arthralgia	2(5.7)	0(0.0)	0.246

#Data were analyzed using **Fisher's Exact Test** and were presented as **n(%)**.

DISCUSSION

In this study, we evaluated the efficacy and safety of metformin-vildagliptin (MF-VG) compared to metformin-glimepiride (MF-GP) in patients with Type 2 Diabetes Mellitus. The two groups were well-matched in terms of age, sex, & BMI, ensuring comparability of the baseline characteristics. At the outset, all glycemic parameters-fasting blood glucose (FBS), postprandial glucose (PPG), and HbA1c-were elevated above normal limits, with no significant differences between groups.

Following the treatment period, both groups demonstrated significant reductions in glycemic parameters. The mean decreases in FBG were 2.7 mmol/L in the MF-VG group and 2.6 mmol/L in the MF-GP group. Similarly, reductions in PPG were 4.3 mmol/L and 4.2 mmol/L, respectively. HbA1c levels decreased by approximately 1.5% in the MF-VG group and 1.1% in the MF-GP group. These findings are consistent with previous studies by Gupta et al.[13] and Bosi et al.[14] which reported significant

improvements in FBG & PPG with both combinations. Bosi demonstrated significant dose-related decrease in FBG and 2 h post prandial glucose (PPG) levels. Chatterjee and Chatterjee[15] in accordance with the results of the present study showed significant reduction in FBG in both once daily and twice daily regime of MF and VG from baseline ($p < 0.0001$). Wang et al[16] also demonstrated FBG and PPG to decrease significantly ($p < 0.01$) from baseline. Thus, the results underscore that VG when added to MF monotherapy result in significant decrease in FBG and PPG.

Our results align with the findings of Chatterjee and Chatterjee[17], Wang et al.[16] and other studies that confirm the significant glucose-lowering effects of vildagliptin in combination with metformin. The observed improvements underscore the efficacy of adding a DPP-4 inhibitor to metformin in achieving better glycemic control. HbA1c reduction from baseline to week 12 was statistically significant in both groups, with a more pronounced decline in the MF-VG group ($p = 0.010$). This compares well with findings by Bosi et al.[14], Pan et al,[18] Ved and Shah[19], Charpentier et al[20] and Ingle and Talele[21], further fortifying the superior glycemic efficacy of the vildagliptin combination.

In terms of anthropometric changes, weight gain was significantly more common in the MF-GP group, with 11.4% of patients experiencing weight increase, compared to only 2.9% in the MF-VG group. This is consistent with previous studies by Gupta et al.[13] and Bosi et al.[14], which reported minimal or no significant weight changes with vildagliptin. Conversely, Ved and Shah[19] observed a significant weight reduction with MF-VG therapy, highlighting variability across different populations and study designs. Other studies, such as Filozof et al[22], also reported weight loss associated with vildagliptin, although these findings may depend on baseline characteristics and duration of therapy. Like any other scientific studies, the present study was not without limitations. The following limitations deserve mention:

• It was an open-label trial without blinding, which may introduce bias.

• The study was conducted at a single center with a relatively short follow-up period of 12 weeks, limiting the assessment of long-term safety and efficacy.

• Liver and renal functions were not monitored at baseline or endpoint, precluding evaluation of potential hepatic or renal adverse effects.

• No causal assessment of adverse events was performed.

Despite these limitations, the study suggests that MF-VG provides efficacy comparable to MF-GP in glycemic control, with the added advantage of a lower incidence of weight gain and hypoglycemia. These safety benefits are particularly important in clinical settings where minimizing adverse effects is a priority. Therefore, when considering both efficacy and safety, the combination of vildagliptin and metformin may be preferable to the glimepiride–metformin regimen for certain patient populations.

CONCLUSION:

The findings of this study indicate that the combination of metformin and vildagliptin is comparable to metformin and glimepiride in reducing FBG, PPG, and HbA1c levels in patients with Type 2 Diabetes Mellitus. Importantly, the metformin-vildagliptin combination exhibits a superior safety profile, with less weight gain and a lower risk of hypoglycemia. Consequently, when safety considerations are prioritized alongside efficacy, the vildagliptin-metformin regimen may serve as a more favorable therapeutic option for patients inadequately controlled on metformin alone.

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