A COMPARATIVE STUDY TO ASSESS SAFETY AND EFFICACY OF VILDAGLIPTIN AND METFORMIN WITH GLIMEPIRIDE AND METFORMIN AMONG TYPE 2 DIABETES PATIENTS

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Date Received:
January 22, 2021
Date Revised:
December 27, 2021
Date Accepted:
December 29, 2021

This article may be cited as
Ahmed I, Ali Z, Afridi MAR, Ali S, Nawaz M, Ghaffar T. A comparative study to assess safety and efficacy of vildagliptin and metformin with glimepiride and metformin among type 2 diabetes patients. J Postgrad Med Inst 2021;35(3):136-42. https://doi.org/10.54079/jpmi.35.3.2832.

ABSTRACT

Objective: To assess the safety and efficacy of Vildagliptin with metformin and Glimepiride with metformin among Type 2 Diabetes Mellitus (T2DM) patients with inadequate glycemic control using Metformin mono-therapy.

Methodology: This comparative, interventional study was conducted at the Medicine and Endocrinology Department, Lady Reading Hospital, Peshawar. A total of 180 T2DM patients were divided into two groups (Glimepiride-Metformin group and Vildagliptin-Metformin group), with 90 patients in each group. Glycosylated hemoglobin (HbA1c), Fasting Plasma Glucose (FPG), Postprandial Glucose (PPG) were assessed with hypoglycemic incidences, weight gain, other adverse drug reactions were also monitored. The 1st follow-up visit was planned after 12-weeks of receiving the treatment and the 2nd after 24-weeks. Recorded data was analyzed through SPSS v.22.0.

Results: The mean decrease in the FPG level after 24-weeks of treatment was -42.93±13.46 mg/dl in Vildagliptin-Metformin group, while it was. -46.76±11.04 mg/dl in the Glimepiride-Metformin group. Similarly, both drugs, Vildagliptin-Metformin vs Glimepiride-Metformin decreased mean PPG and HbA1c level i.e., -42.93 mg/dl vs. -46.76 mg/dl and -3.12% vs. -2.39% respectively ($p<0.05$). Mild adverse effects, like hypoglycemic incidences (10%) and weight gain (73.31±13.94 kg at 2nd visit) was more prominent among the Glimepiride-Metformin group.

Conclusion: In terms of safety and efficacy, the Vildagliptin-Metformin combination showed a considerably healthier response in achieving the HbA1c level among T2DM patients, with no weight gain and decreased risk of hypoglycemia as compared to Glimepiride.

Key Words: Type 2 Diabetes Mellitus; Vildagliptin; Glimepiride; Metformin; Combination therapy.

INTRODUCTION

Diabetes mellitus (DM) is the most chronic endemic among non-communicable diseases worldwide, with slow and minimal eradication and lifetime complications. The International Diabetes Federation (IDF) Diabetes Atlas Ninth Edition 2019 confirms that around 463 million people are living with diabetes, which is expected to excel up to 578 million by 2030.[1] Pakistan ranks 4thamong the countries with the highest number of diabetic adults.[1] A large national study of T2DM from Pakistan, including 18, 856 subjects showed that the overall prevalence of pre-diabetes was 10.9%, and type 2 diabetes was 16.9%.[2] The key targets of management include good glycemic control, along with the prevention of micro and macrovascular complications. However, there are numerous other factors for a better and safest therapeutic approach, including efficacy profile, treatment duration, adversities, and associated complications to be taken into account before treatment initiation.[3]

Based on the guidelines provided by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), initial hypoglycemic monotherapy is recommended for achieving glycemic control among the newly diagnosed T2DM patients, but due to the subpar efficacy profile of the monotherapy, as it is unlikely to maintain the glycemic profile among the patients with high HbA1c level (≥ 9%)[4], combination therapy has become an alternative approach for such settings.[5,6]

Combination therapies aid in the rapid lowering of HbA1c levels, reduce the chances of treatment inactivity and improve the functioning of ß-cell.[7,8] Due to delayed diagnosis, the treatment complications associated with T2DM elevation and endorses DM related morbidity and mortality rate.[9,10] Among more than half of the cases, 50% of the β-cell function has already

been lost at the time of diagnosis, and many patients are presented with secondary complications along with diabetes.[9] Therefore, the diagnosis and treatment of DM in the early stage is very crucial.

The utilization of combination therapies initially from the time of diagnosis is a positive approach in therapeutic care. The trending combinations for the treatment of T2DM include Metformin and Sulfonylureas, due to cost-effectiveness and quick management of HbA1c levels.[9] But its use is prevented by the associated side-effects, including weight gain and severe hypoglycemic incidences. Vildagliptin, on the other hand, functions via Dipeptidyl Peptidase-4 (DPP-4) inhibition and prevents Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP) degradation, bearing high safety and efficacy profile with minimal side-effects reported.[11]

In the current study, a comparative efficacy profile of the two combination therapies (Vildagliptin-metformin and Glimepiride-metformin) is presented with assessment of efficacy and side-effects among newly diagnosed T2DM patients over the period of 24 weeks.

METHODOLOGY

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RESULTS

A total of 180 T2DM patients were enrolled in the study, of which 90 patients were placed in the Vildagliptin-Metformin group and the remaining 90 in the Glimepiride-Metformin group (Figure 1). The baseline demographic and clinical characteristics of the patients are summarized in Table 1.

According to the intragroup analysis, the mean HbA1c was decreased from 10.56±1.69 to 7.44±1.286 in the Vildagliptin-Metformin group and from 10.45±1.71 to 8.06±1.46 in the Glimepiride-Metformin group ($p<0.05$) (Figure 2). The mean difference was higher in the Vildagliptin-Metformin group as compared to Glimepiride-Metformin.

The intragroup comparison indicates that the mean FPG reduction is comparable between the two groups. In the Vildagliptin-Metformin group, the mean FPG level decreased from 156.23±25.44 mg/dl (baseline) to 113.3±11.98 mg/dl (24 weeks), while in the Glimepiride-Metformin group, it reduced from 163.36±28.07 mg/dl (baseline) to 116.6±17.03 mg/dl (24 weeks) (Figure 3a). Moreover, there was a significant decline in the mean PPG level from baseline to 2nd follow-up visit (24 weeks) among the patients. However, the deviations were parallel in the two groups (Figure 3b).

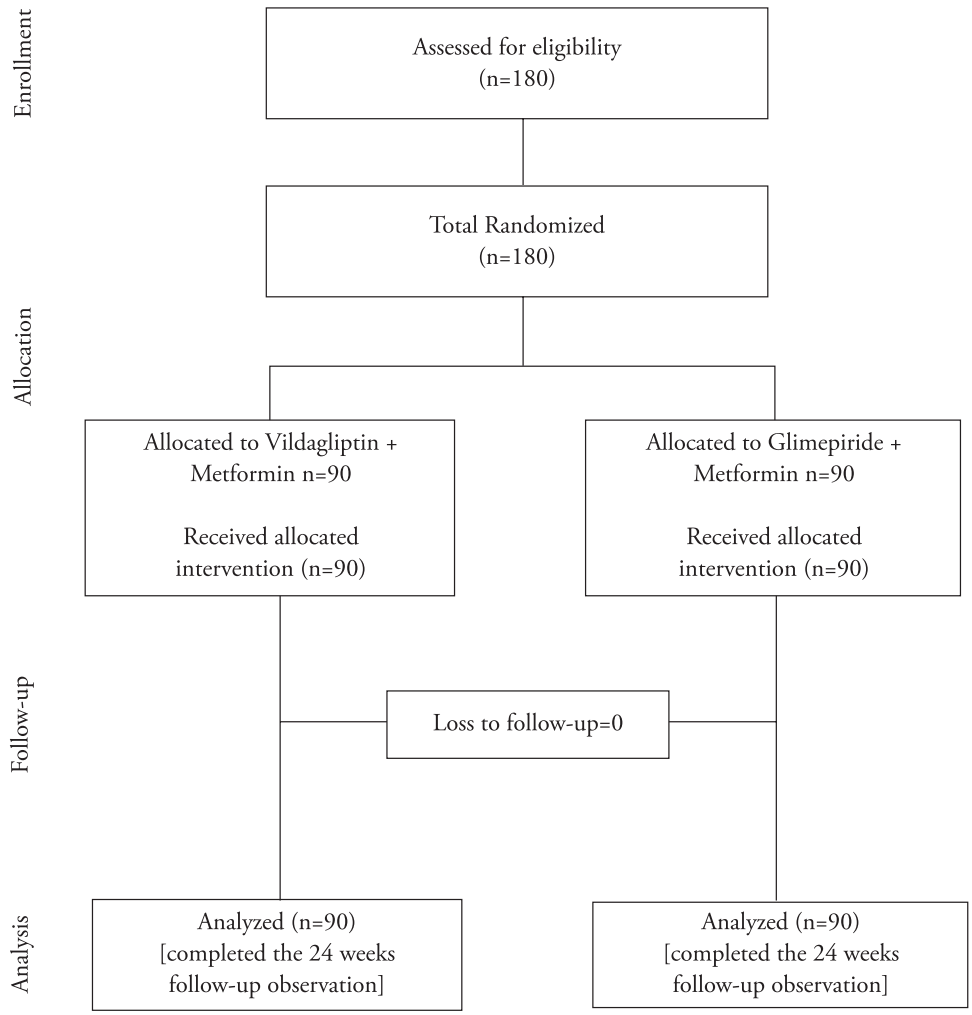

Figure 1: Consort flow diagram for enrollment of the participants

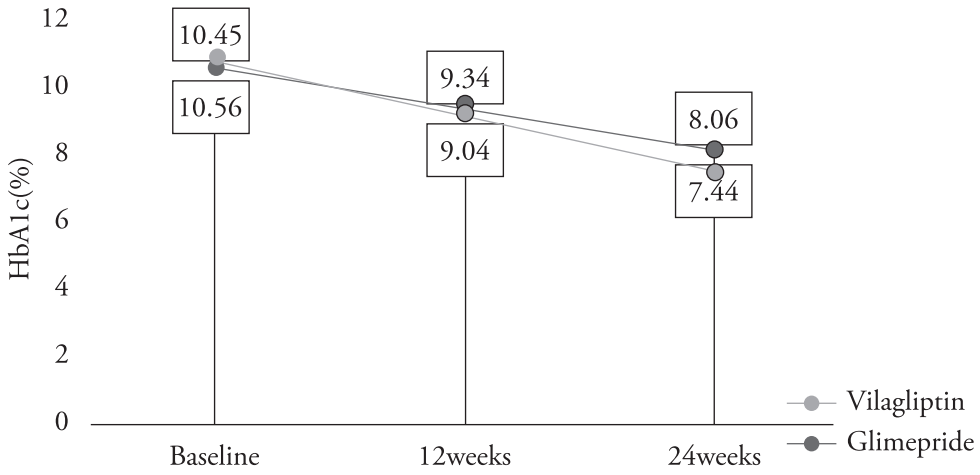

Figure 2: Reduction in the level of hba1c from baseline to week 24 after the treatment with vildagliptin or glimepiride

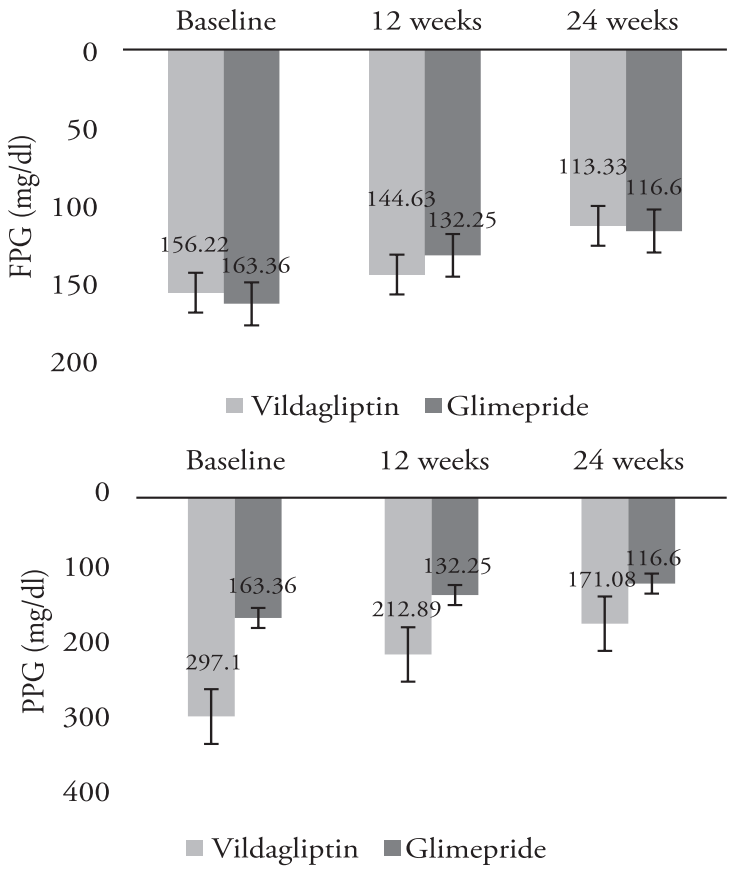

Figure 3a & 3b: Mean fasting plasma glucose (fpg) and post-prandial glucose (ppg) reduction after treatment with vildagliptin or glimepiride.

Table 1: Baseline demographic and clinical characteristics of the study population

Baseline Characteristics		Study Groups (n=180)	
		Vildagliptin + Metformin	Glimepiride + Metformin
Gender	Male	46(51.11)	40(44.4)
	Female	44(48.88)	50(55.6)
Age (years)		48.91±11.11	46.20±10.34
Weight (kg)		78.86±13.82	72.56±14.10
Height (ft)		6.00±5.02	5.31±0.30
BMI (kg/m2)		28.53±5.85	27.69±4.95
HbA1C (%)		10.56±1.69	10.45±1.71
FPG (mg/dl)		156.23±25.44	163.36±28.07
PPG (mg/dl)		297.10±52.92	300.66±60.50
Duration of DM (years)		1.90±3.21	2.29±3.72

Table 2: Adverse drug reactions reported over the period of 24 weeks from baseline in the treatment groups

Adverse Drug Reactions	Vildagliptin + Metformin	Glimepiride + Metformin
Nasopharyngitis	44(48.8)	25(27.7)
Headache	16(17.7)	11(12.2)
Nausea	11(12.2)	2(2.2)
Hypoglycemia	7(7.7)	9(10)
Dizziness	4(4.4)	5(5.5)
Joint Pain	1(1.1)	38(42.2)
Jaundice	7(7.7)	0(0)

The hypoglycemic incidences were more common among patients treated with the Glimepiride-Metformin combination, i.e. out of 9 hypoglycemic incidences, the condition worsened in one case only, which was handled with oral dextrose without treatment cessation, while no serious hypoglycemic incidences observed in patients treated with Vildagliptin. Among other mild adverse drug reactions common in both groups were nasopharyngitis (27.7% vs. 48.8%), headache (12.2% vs. 17.7%) and joint pain (42.2% vs. 1.1%) etc. (Table 2).

Statistically, a significant difference was observed in the patients' patients' body weight, and BMI enrolled in both study groups ($p<0.05$). The mean difference in the body weight among the patients administering Vildagliptin-Metformin was -0.64, indicating weight loss. In contrast, the Glimepiride-Metformin combination resulted in a weight gain of 0.75 kg (Table 3).

DISCUSSION

As already known our study found out that epilepsy patients in Pakistan too, were more likely to have anxiety and depression symptoms as compared to their healthy counterparts. Available data showed prevalence of symptoms of depression in 7.5% to 80% patients.[7,9,12] Similarly, anxiety was found in 10% to over 40% of similar patients,[14,15] which is in agreement with our findings. However, in our study 33% patients scored in the morbid range of both anxiety and depression symptoms.

We found the age of the patient associated significantly with both anxiety and depression symptoms. The highest incidence of anxiety was found in the age group of over 55 years. The little sample that we had from Considerably enormous data exists in support of diabetes progression, genetic and physiological complexities that clearly define the importance of early diagnosis and maintenance of glycemic target as necessitates for prevention of diabetes associated complications. In place of monotherapy, the initial combination therapies are now being used for the treatment of diabetes pathophysiology, including increased insulin secretion and sensitivity and inhibition of glucose production from the liver.[14] A multicentre, randomized, double-blind trial showed high tolerability and greater long term benefits with Vildagliptin-Metformin combination therapy among the newly diagnosed T2DM patients compared to the standard Metformin monotherapy.[15]

The current study showed that Vildagliptin-Metformin combination therapy provided better efficacy outcomes with minimal side-effects in comparison to glimepiride-metformin (Table 2). However, the reduction in HbA1c level was comparable in both groups over a period of 24 weeks, i.e. the decrements of -3.12% for Vildagliptin and -2.39% for Glimepiride ($p<0.001$) (Figure 2). Parallel with this, a study reported a mean reduction in HbA1c from 8.01 to 7.07 among the patients administering Vildagliptin and from 8.13 to 7.13 among those administering Glimepiride.[13] Another study also displayed supporting outcomes, a mean HbA1c reduction of -0.44% (Vildagliptin group) and -0.53% (Glimepiride group).[16] Moreover, a study from India also reported the mean decline in the HbA1c levels from baseline to follow-up (end of 12 weeks), i.e. the HbA1c level among patients given Glimepiride was 8.49 at baseline, which increased to 8.53 while among the Vildagliptin group, it reduced from 8.83 to 8.79.[17]

In terms of safety, patients in the Vildagliptin-metformin group exhibited better hypoglycemic profile, i.e. the hypoglycemic incidences were more than twice among the patients treated with Glimepiride-Metformin as compared to those in the Vildagliptin-Metformin group. Moreover, no severe hypoglycemia was observed among patients of either group (Table 2). It is evident that Glimepiride administration is linked to hypoglycemia and weight gain, which in turn leads to adverse clinical outcomes.[18-20] A similar study also supported our findings, and Vildagliptin-metformin represents a more effective combination as it is associated with a significantly reduced risk of hypoglycemia.[21] Another study indicated a significant association of hypoglycemia with cardiovascular risk leading to major microvascular events due to heart rate variations.[22]

Weight alterations varied between the treatment groups. Patients in the Glimepiride-Metformin group reported weight gain after 24 weeks of treatment compared to their baseline weight, an average increase of 0.75 kg. In contrast, a mean decrease of 0.64 kg was observed among the patients treated with Vildagliptin-Metformin (Table 3). Our results are consistent with the results of another study reporting increase in mean body weight among the patients treated with Glimepiride-Metformin, i.e. 2.35 ± 1.21 kg gain of weight from baseline to week 24. In comparison, the weight gain was less prominent among those treated with Vildagliptin-Metformin (0.23 ± 0.69 kg).[13]

Based on our findings, it is evident that DPP-4 inhibitors, namely Vildagliptin, have greater tolerability and are efficacious in providing favorable glycemic target as add-on therapy with Metformin, which is also supported by existing literature.[23] Although, other combination therapies have taken over the pharmaceutical market and disease management system. But to date, the associated adherence rate is yet to be discovered.[24] The study had several limitations, including the lesser sample size, single study site and open labelling that might have caused treatment bias, and the outcomes cannot be generalized. However, considering the safety and efficacy profile of the Vildagliptin-Metformin combination, it proved to be a better therapeutic option in comparison to the Glimepiri-

de-Metformin combination.

CONCLUSION

Both the combination therapies used in the current study effectively controlled glycemic profile among T2DM patients with Metformin monotherapy failure. However, the presented efficacy profile of the patients provided with a combination therapy of Vildagliptin and Metformin displayed better outcomes in terms of HbA1c reduction, reduced risk of hypoglycemia and lower weight gain risk. Furthermore, in both groups, the observed adverse drug reactions were mild and non-serious.

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Author's Contribution

IA drafted the manuscript, conception, and collected the data, ZA interpreted the data, collected the data, and drafted the manuscript, MARA collected the data, and drafted the manuscript SS collected the data, and drafted the manuscript, MN interpreted the data, and drafted the manuscript, TG collected the data, and drafted the manuscript. Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest

Authors declared no conflict of interest

Grant Support and Financial Disclosure

None

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.