National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Comparison of efficacy and safety of metformin and vildagliptin versus metformin and glimepiride in patients of Type 2 diabetes mellitus

Harinika Gullapalli[1], Savithri Desai[2]

[1]Department of Pharmacology, Siddhartha Medical College, Vijayawada, Andhra Pradesh, India, [2]Department of Pharmacology, Gulbarga Institute of Medical Sciences, Gulbarga, Karnataka, India

Correspondence to: Savthri Desai, E-mail: savithridesai@gmail.com

Received: November 04, 2017; **Accepted:** November 17, 2017

ABSTRACT

Background: Diabetes mellitus is a heterogeneous chronic metabolic disorder principally characterized by persistent hyperglycemia resulting from defects in insulin action and/or insulin secretion. In course of time, prolonged hyperglycemia and associated metabolic aberrations result in tissue toxicity manifested as accelerated atherosclerosis, renoretinal microangiopathy, and neuropathy leading to a variety of vascular, neurological, and focal complications. **Aim and Objective:** The aim of this study is to evaluate the efficacy and safety of metformin and vildagliptin versus metformin and glimepiride in patients with Type 2 diabetes mellitus. **Materials and Methods:** This is a longitudinal interventional study. A total of 60 patients were enrolled in the study. Those patients who were already on metformin 500 mg bid with poor glycemic control were included in the study. These 60 patients were divided into two groups each consisting of 30 patients. Group A patients received glimepiride 1 mg bid and metformin 500 mg bid. Group B patients received vildagliptin 50 mg bid and metformin 500 mg bid. The total period of the study was 3 months. **Results:** After 3 months of treatment, both the groups caused a significant decline in blood glucose levels both fasting blood sugar (FBS) as well as postprandial blood sugar (PPBS) levels. There was a significant difference between the two groups in reducing the FBS levels and PPBS. Hemoglobin A_{1c} (HbA1c) was also reduced significantly in both groups at 12 weeks. After 3 months of therapy, there was a reduction in HbA_{1C} in B group. The reduction of HbA_{1C} was not statistically significant between the two groups. Adverse effects were more with metformin and glimepiride group at the end of 3 months therapy. There was a significant difference in the incidence of adverse effects between both the groups. **Conclusions:** Vildagliptin and metformin combination provided better efficacy comparable to that of glimepiride and metformin combination and resulted in better adverse effect profile with lower risks of hypoglycemia and weight gain.

KEY WORDS: Diabetes Mellitus; Hemoglobin A_{1C}; Fasting Blood Sugar; Postprandial Blood Sugar

INTRODUCTION

Diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk reduction strategies beyond glycemic control. Diabetes mellitus is a chronic disease resulting in increased blood glucose levels due to deficiency of insulin secretion by the pancreas or ineffectiveness of secreted insulin, which can either be inherited or acquired.

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2018.8.1143618112017	

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The global prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014. In 2015, an estimated 1.6 million deaths were directly caused by diabetes. The World Health Organization (WHO) projects that diabetes will be the seventh leading cause of death in 2030.[1,2] Diabetes

is a major cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputations. Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication, and regular screening and treatment for complications.[2]

Current American Diabetes Association Guidelines for the Diagnosis of Diabetes[3]

- A1C ≥6.5%. The test should be performed in a laboratory using a method that is the National Glycohemoglobin Standardization Program-certified and standardized to the diabetes control and complications trial assay;
  OR
- Fasting plasma glucose ≥126 mg/dL (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h;
  OR
- 2-h plasma glucose ≥200 mg/dL (11.1 mmol/l) during an oral glucose tolerance test. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water;
  OR
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/l);
- In the absence of unequivocal hyperglycemia, the result should be confirmed by repeat testing.

Sulfonylureas are usually the first-line choice in non-obese and metformin in obese diabetics. The combination of metformin and sulfonylureas is most commonly used in India because of its low cost and can attain a greater reduction in hemoglobin A1c (HbA1c) than either drug alone.[4] However, this combination therapy is prone to weight gain and severe hypoglycemia. In spite of well-planned dosage regimens containing oral hypoglycemic agents (OHAs), glycemia control is poor in some Type 2 diabetic patients and many OHAs produce adverse drug reactions (ADRs) such as weight gain and hypoglycemia. In this situation, search is going on for better OHAs.

Recently, the role of "incretins" particularly that of glucagon-like peptide (GLP-I) has been firmly established. The peptide GLP-I increases insulin secretion and decreases glucagon levels in response to rise in plasma glucose. However, this peptide hormone cannot be used orally as such because of very short plasma t1/2 (2 min) and chemical nature. Hence, to prolong the duration of action of endogenous GLP-I, compounds have been synthesized which inhibit dipeptidyl peptidase-4 (DPP-4), the enzyme responsible for metabolic degradation of GLP-1. Vildagliptin is a potent, selective, and reversible inhibitor of DPP-4 that improves glycemic control in patients with Type 2 diabetes mellitus (T2DM).[5-8]

In this scenario, the current study was undertaken to evaluate and compare the efficacy and safety of combinations of metformin and vildagliptin and metformin and glimepiride in T2DM patients.

MATERIALS AND METHODS

Study Design

This is a longitudinal interventional study. The protocol was approved by the Institutional Ethics Committee. A total of 60 patients from medical outpatient department diagnosed with T2DM were screened for this study. Those patients who were already on metformin 500 mg bid with poor glycemic control were included in this study. These 60 patients were divided into two groups with each group consisting of 30 patients. Group A patients received glimepiride 1 mg bid and metformin 500 mg bid. Group B patients received vildagliptin 50 mg bid and metformin 500 mg bid. The total period of the study was 3 months. Periodical blood sugar levels (both fasting and post prandial) were measured at the end of every month. Blood glucose and HbA_1c levels were estimated before and at the end of the study.

Males and females between 40 and 70 years with Type-2 diabetes already on treatment but with uncontrolled blood sugars, i.e., (fasting blood sugar [FBS] >126 mg/dl and postprandial blood sugar (PPBS) >200 mg/dl) with hypertension and on treatment with angiotensin-converting enzyme inhibitors were included in the study.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences version 22. Mean ± standard deviations were calculated for quantitative variables for both the groups. Statistical significance between both groups was assessed using independent *t*-test. Intragroup comparison from baseline to 6 and 12 weeks was done using unpaired *t*-test. $P < 0.05$ was considered as statistically significant.

RESULTS

A total of 60 patients were enrolled in the study. Maximum number of patients belonged to the age group of 50–54 years, i.e., 66% ($n = 20$). There were no patients below the age of 40 years [Figure 1].

Of 60 patients, 47% ($n = 28$) of patients were males and 53% ($n = 32$) of patients were females.

Average of FBS in Groups A and B before initiation of therapy was 204.13 mg/dl and 215 mg/dl. At the end of 3rd month of therapy, an average of FBS in Groups A and B was reduced to 132.5 mg/dl and 120.97 mg/dl. After 90 days

of treatment, both the groups showed a significant decrease in FBS. There was a significant difference between the two groups in decreasing the FBS levels ($P < 0.0001$) [Figure 2].

Average of PPBS in Groups A and B before initiation of therapy was 288.57 mg/dl and 303.33 mg/dl. At the end of 3rd month of therapy, average of PPBS in Groups A and B reduced to 203.47 mg/dl and 199.67 mg/dl. After 3 months of treatment, both the groups showed a significant decrease in the PPBS levels. There was no significant difference between the two groups in decreasing the PPBS levels ($P = 0.472$) [Figure 3].

Baseline mean value of HbA1C in Group A before with glimepiride is 8.49, and mean value of HbA1C in Group B with vildagliptin before initiation of therapy is 8.83. Average of HbA1C at the end of 12 weeks in Groups A and B was 8.53 and 8.79. The reduction of HbA1C was not statistically significant between the two groups ($P = 0.200$) [Figure 4].

ADRs

1. Hypoglycemia: Mild-to-moderate hypoglycemic symptoms were observed in 53% ($n = 16$) of Group A patients and 3% of Group B patients.
2. Weight gain: Weight gain was observed only in 13% ($n = 4$) of patients on metformin and glimepiride combination.
3. Headache: Headache was reported by 6% ($n = 2$) of patients on metformin and vildagliptin group [Figure 5].

DISCUSSION

The new approach of treatment for diabetes mellitus achieved by DPP-4 inhibition has the potential to reduce and may even normalize both fasting and postprandial glucose concentrations without adverse effects such as weight gain and hypoglycemia. This approach also raises the hope that such a therapy may be able to delay or even halt the progression of the disease or possible even prevent its development by providing a means of safety in treating subjects with impaired glucose tolerance. Finally, this approach may turn out to be inherently safer than existent insulin secretagogue because of its glucose dependency. Thus, DPP-4 inhibitors have not been associated with any incidence of severe hypoglycemia even when given in combination with existing oral antidiabetic agents.

In the present study, the patients on metformin and vildagliptin combination showed a significant decline in

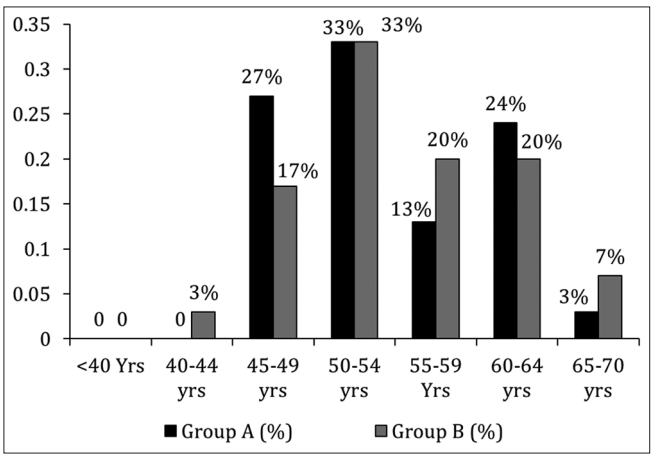

Figure 1: Age wise distribution of cases

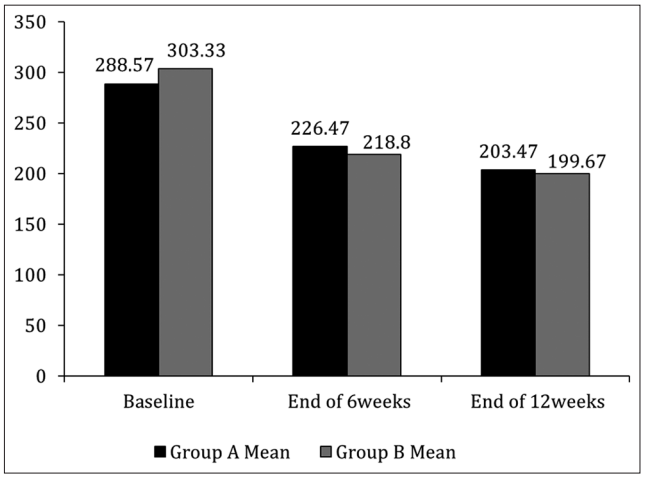

Figure 3: Comparison of postprandial blood sugar in Groups A and B

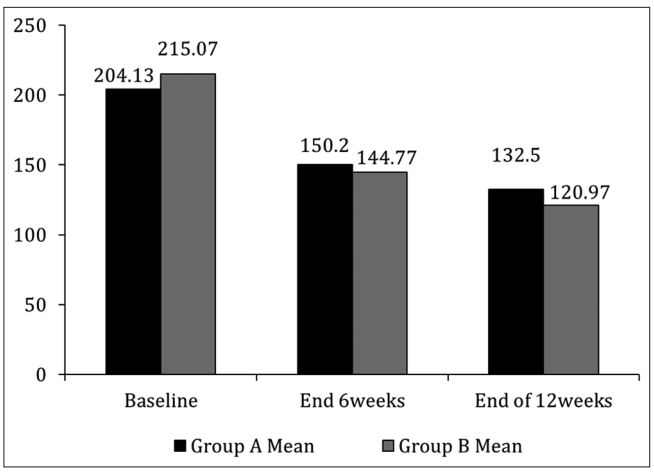

Figure 2: Comparison of fasting blood sugar in Groups A and B

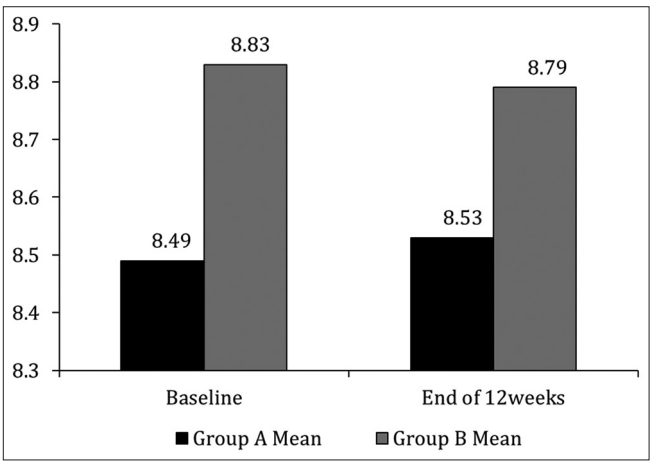

Figure 4: Comparison of hemoglobin A1c in Groups A and B

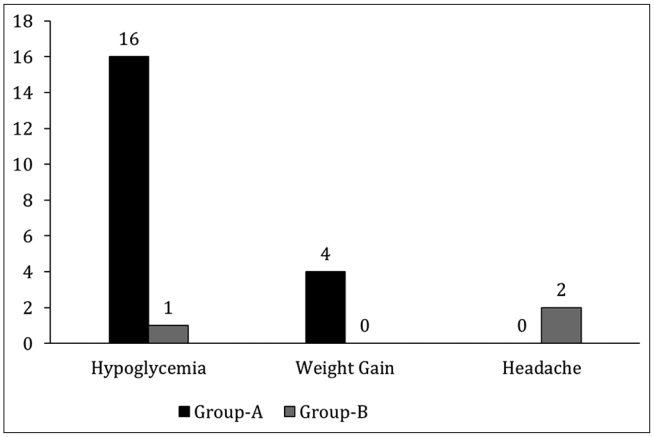

Figure 5: Adverse effects in Groups A and B

mean FBS and PPBS to a maximum of 120 mg/dl and 199 mg/dl at 12 weeks, respectively ($P < 0.01$). The results are comparable with studies done by Bosi *et al.*,[9] who demonstrated significant decrease in FBS and PPBS levels, and Pan *et al.*[10] who showed metformin and vildagliptin combination to significantly reduce fasting blood glucose (FBG) levels ($P < 0.001$) at 24 weeks when compared with metformin placebo.

Chatterjee and Chatterjee,[11] in accordance with the results of present study, showed a significant reduction in FBS in both once daily and twice daily regimen of metformin and vildagliptin from baseline ($P < 0.0001$). The reduction in PPBS level was also highly significant in both groups ($P < 0.0001$).

Matthewes *et al*.[12] showed that vildagliptin added to metformin is not inferior to glimepiride in reducing mean HbA1C levels. Change in HbA1C was comparable between vildagliptin and glimepiride treatment. Fewer patients experienced hypoglycemia with vildagliptin (2.3% vs. 18.2% with glimepiride) with a 14-fold difference in the number of hypoglycemic events (59 vs. 838). Vildagliptin had a beneficial effect on body weight.

Patients on metformin and glimepiride combination also showed a significant reduction in FBS and PPBS to a maximum of 204 mg/dl and 132 mg/dl at 12 weeks, respectively ($P < 0.01$). This coincides with a study conducted by Charpentier *et al.*, Wang *et al.*, and Pareek *et al.*,[13-15] who showed a significant reduction in FBS and PPBS ($P < 0.001$) from baseline than either glimepiride or metformin alone. The results of the present study coincide with these studies where FBS and PPBS decreased significantly ($P < 0.01$) from baseline to 12 weeks ($P < 0.001$).

Ferrannini *et al*.[16] compared the efficacy and safety of vildagliptin versus glimepiride as add-on therapy to metformin and demonstrated a mean change in baseline HbA1C (7.3%) in both the groups at the end of 52 weeks as −0.44% with vildagliptin and −0.53 with glimiperide. FBG reductions were comparable between groups (mean and standard error) −1.01 mmol/lt and −1.14 mmol/lt, respectively. Our results are in concurrence with Jeon and Oh[17] who conducted a comparative trial of metformin-vildagliptin and metformin-glimepiride combination. A similar reduction in 2 h-PPBS and FBS was demonstrated in both the groups.

In the present study, both the groups showed a significant decrease in mean HbA1c from baseline to the end of the study at 12 weeks ($P < 0.01$). Our results are in concurrence with Bosi *et al.*, Pan *et al.,* and Ved and Shah.[9,10,18]

Bosi *et al*.[9] evaluated the efficacy and safety of vildagliptin when added to metformin is well tolerated and produces clinically meaningful, dose-related decreases in A1C and FBS. Adverse events were reported by 65%. Patients receive vildagliptin 100 mg daily. In our study, only 10% of people receive vildagliptin 50 mg bid reported adverse events.

Vildagliptin significantly reduced body weight relative to glimepiride and resulted in a 10-fold lower incidence of hypoglycemia than glimepiride (1.7 vs. 16.2% presenting at least one hypoglycemic event, and 39 vs. 554 hypoglycemic events $P < 0.01$). No severe hypoglycemia occurred with vildagliptin compared with 10 episodes with glimepiride ($P < 0.01$) and no patient in the vildagliptin group discontinued because of hypoglycemia compared with 11 patients in the glimepiride group.[16]

Limitations of the Study

1. As the sample size is small, the inference of the study has limited value.
2. Cost of vildagliptin is the main limiting factor to enrol more number of patients in a government setup.
3. Although dose ranges are high for studied drugs, i.e., 50–100 mg for vildagliptin and 1–4 mg for glimepiride, we studied the effects with fixed dose, i.e., 50 mg bid for vildagliptin, 1 mg bid for glimepiride.
4. Blood glucose measurements done at the end of every month may not necessarily represent blood sugar levels throughout the month.

CONCLUSION

In this study, both metformin + glimepiride and metformin + vildagliptin achieved optimal glycemic control almost equally at the end of 3 months of therapy. However, in terms of adverse effect profile, hypoglycemia was observed in 53% of glimepiride group and 3% in vildagliptin-treated group. Weight gain was reported only in glimepiride group. Headache was reported 6% in vildagliptin group. Hence, vildagliptin + metformin offers advantage and represents an important new treatment option for optimal glycemic control

without weight gain and risk of hypoglycemia. Vildagliptin is effective, better tolerated than glimepiride for the treatment of diabetes mellitus. When combined with metformin, it showed improved efficacy over time (may be due to GLP-1 induced increase in beta cell numbers and mass) without weight gain and hypoglycemia which are the common side effects with other antidiabetic drugs. Due to glucose-dependent insulinotropic action of GLP-1, hypoglycemia is less with vildagliptin. Inhibition of gastric emptying might account for the satiety after GLP-1 administration.

REFERENCES

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
2. World Health Organization. Diabetes. Factsheet. Geneva: WHO; 2012 Available from: http://www.who.int/mediacentre/factsheets/fs312/en/index.html. [Last cited on 2013 Jun 08]; [Last updated on 2017 Oct12].
3. American Diabetes Association. Standards of medical care in diabetes-2017. Diabetes Care 2017;40 Suppl 1:S6-S10.
4. Charbonnel B, Schernthaner G, Brunetti P, Matthews DR, Urquhart R, Tan MH, *et al.* Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with Type 2 diabetes. Diabetologia 2005;48:1093-104.
5. Winker G. Incretin enhancers, incretinmimetics from therapeutic control to clinical application. Ory Hetil 2007;148:579-87.
6. Holst JJ. Treatment of Type 2 diabetes mellitus with agonists of the GLP-1 receptor or DPP-IV inhibitors. Expert Opin Emerg Drugs 2004;9:155-66.
7. Arulmozhi DK, Portha B. GLP-1 based therapy for Type 2 diabetes. Eur J Pharm Sci 2006;28:96-108.
8. Patel SK, Goyal RK, Anand IS, Shah JS, Patel HU, Patel CN. Glucagon like peptide-1: A new therapeutic target for diabetes mellitus. Indian J Pharmacol 2006;38:231-7.
9. Bosi E, Camisasca RP, Collober C, Rochotte E, Garber AJ. Effects of vildagliptin on glucose control over 24 weeks in patients with Type 2 diabetes inadequately controlled with metformin. Diabetes Care 2007;30:890-5.
10. Pan C, Xing X, Han P, Zheng S, Ma J, Liu J, *et al*. Efficacy and tolerability of vildagliptin as add-on therapy to metformin in Chinese patients with Type 2 diabetes mellitus. Diabetes Obes Metab. 2012;14:737-44.
11. Chatterjee S, Chatterjee S. Glycemic effects of vildagliptin and metformin combination therapy in Indian patients with Type 2 diabetes: An observational study. J Diabetes 2014;6:237-42.
12. Matthewes DR, Dejager S, Ahren B, GFonseca V, Ferrannini E, Cuturier A, *et al*. Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimeperide, with no weight gain: Results from a 2-year study. Horm Metab Res 2009;41:368-73.
13. Charpentier G, Fleury F, Kabir M, Vaur L, Halimi S. Improved glycaemic control by addition of glimepiride to metformin monotherapy in Type 2 diabetic patients. Diabet Med 2001;18:828-34.
14. Wang M, Gao F, Xue YM, Han YJ, Fu XJ, He FY, *et al.* Effect of short-term intensive therapy with glimepiride and metformin in newly diagnosed Type 2 diabetic patients. Nan Fang Yi Ke Da Xue Xue Bao 2011;31:564-6.
15. Pareek A, Chandurkar NB, Salkar HR, Borkar MS, Tiwari D. Evaluation of efficacy and tolerability of glimepiride and metformin combination: A multicentric study in patients with Type-2 diabetes mellitus, uncontrolled on monotherapy with sulfonylurea or metformin. Am J Ther 2013;20:41-7.
16. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahrén B, Byiers S, *et al.* Fifty-two-week efficacy and safety of vildagliptin vs. Glimepiride in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy. Diabetes Obes Metab 2009;11:157-66.
17. Jeon HJ, Oh TK. Comparison of vildagliptin-metformin and glimepiride-metformin treatments in Type 2 diabetic patients. Diabetes Metab J 2011;35:529-35.
18. Ved P, Shah S. Evaluation of vildagliptin and fixed dose combination of vildagliptin and metformin on glycemic control and insulin dose over 3 months in patients with Type 2 diabetes mellitus. Indian J Endocrinol Metab 2012;16 Suppl 1:S110-3.

How to cite this article: Gullapalli H, Desai S. Comparison of efficacy and safety of metformin and vildagliptin versus metformin and glimepiride in patients of Type 2 diabetes mellitus. Natl J Physiol Pharm Pharmacol 2018;8(4):521-525.

Source of Support: Nil, **Conflict of Interest:** None declared.