



A Comparative Study of Vildagliptin-Metformin Versus Glimepiride-Metformin Therapy in Type 2 Diabetes Mellitus At A Tertiary Hospital of North India

KEYWORDS

Type 2 diabetes mellitus, dipeptidyl-peptidase-4(DPP4) inhibitors, metformin, glimepiride.

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ABSTRACT Diabetes mellitus (DM) is one of the most common chronic disorders attaining epidemic proportions worldwide. There are different classes of drugs available to treat it. The present study was undertaken to study comparison between vildagliptin-metformin combination versus glimepiride-metformin combination.

Aims and objectives: To compare the efficacy of vildagliptin with glimepiride as an add-on therapy to metformin in patients of type-2 diabetes mellitus in terms of glycemic control parameters like fasting blood glucose, 2 hour postprandial glucose and reduction in HbA1C levels from baseline and to compare the tolerability and development of side effects in patients on vildagliptin-metformin therapy versus those on glimepiride-metformin therapy.

Materials and methods: This comparative study was conducted on 100 type 2 diabetes mellitus patients at Government Medical College, Amritsar. Half of them were put on vildagliptin-metformin and the other half was given glimepiride-metformin. Blood sugar levels, HbA1c were measured serially and the data tabulated and analysed statistically.

Conclusion: It was seen that vildagliptin and glimepiride were equally efficacious in reducing fasting plasma glucose when given as add-on to metformin. However HbA1c control was better in vildagliptin-metformin group. Incidence of hypoglycaemia was much less in same group. As far as weight change was concerned, vildagliptin-metformin combination led to weight loss while weight gain was seen with glimepiride-metformin combination.

INTRODUCTION

Type 2 diabetes (T2DM) is a chronic and complex disease which involves multiple pathophysiological defects, including impaired islet function and insulin resistance, resulting in impaired glucose tolerance and inappropriately high fasting hepatic glucose production. While insulin resistance remains essentially unchanged over time, the deficit in islet function is a progressive process with quantitative and qualitative abnormalities in insulin and glucagon secretion kinetics. A role of excess glucagon cannot be underestimated; indeed, type 2 diabetes is an islet paracrinopathy in which the reciprocal relationship between the glucagon-secreting alpha cell and the insulin-secreting beta cell is lost, leading to hypoinsulinemia and hyperglucagonemia and hence the consequent hyperglycemia.¹ These defects in islet function are present early on and worsen with the natural history of the disease.^{2,3,4}

The increasing prevalence of diabetes mellitus is increasing the economic burden of controlling blood glucose levels and treating complications.^{5,6} Diabetes mellitus patients also exhibit a more than 3-fold greater risk of cardiovascular disease (CVD) and mortality than non-diabetic subjects.⁷ Established management of T2DM starts with lifestyle changes, i.e introducing a healthier diet and increasing physical activity in order to improve glucose utilization and promote weight loss. This is accompanied by rapid or even concomitant introduction of an oral anti-diabetic agent. Metformin is widely used as the first-line anti-diabetic drug of choice.^{8,9} Metformin was reported to be equally effective in lowering glucose in non-obese and obese patients

and can thus be used independent of an individual's BMI.¹⁰ More importantly, it is the only drug which has demonstrated beneficial effects on cardiovascular events, as reported in the UKPDS substudy of overweight patients.¹¹

Metformin is therefore recommended by all guidelines as first-line therapy for T2DM. The International Diabetes Federation (IDF) suggests to use Metformin in all cases inadequately controlled by non-pharmacological treatments (IDF, on line) while a recent consensus document of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends to prescribe metformin at diagnosis, together with lifestyle interventions.^{12,13}

Upon progression of the disease, progressive loss of β -cell function and mass makes it difficult for patients to maintain glycemic control with monotherapy. As a result, combination therapy involving agents with complementary mechanism of action is the next logical step in the management of T2DM. Since metformin lowers plasma glucose without affecting insulin secretion, it is often combined with an agent stimulating insulin secretion, like a sulfonylurea. Adding a sulfonylurea to metformin has thus been the conventional and the gold standard combination therapy for decades. However, while previous therapeutic goals made this combination quite attractive, the lower glycemic targets for intensification of therapy substantially increase the risk of hypoglycaemia. Therefore, the need for more glucose-sensitive agents as alternative combination therapies was warranted.

A variety of potential drugs have been developed to control the glucose levels and reduce severe hypoglycemia. Among these drugs, dipeptidyl peptidase-4 (DPP-4) inhibitors have proven effective for glucose control without inducing hypoglycemia and are widely used as the primary therapeutic option. By stabilizing endogenous incretin hormones at physiological concentrations, DPP-4 inhibitors increase the sensitivity to glucose of both insulin and glucagon secretion (i.e, increase insulin secretion and suppress glucagon secretion in a glucose-dependent manner), thereby lowering glucose levels. DPP-4 inhibitors are thus the first oral agents addressing the dual β - and δ -islet cells dysfunction present in T2DM.

Our main focus in this study is to compare the effect of vildagliptin (a DPP-4 inhibitor) and glimepiride (a sulphonylurea) on fasting blood sugar, post-prandial blood sugar, HbA1c and body weight as an add on therapy to metformin as well as to note and compare the incidence of hypoglycemia with each of these therapies.

MATERIALS AND METHODS

One hundred patients of type-2 diabetes mellitus were selected from the patients admitted to various wards and visiting OPDs of Government Medical College, Amritsar. Patients were labelled as diabetic based on WHO criteria for diagnosis of diabetes mellitus which is :-

1) Symptoms of diabetes mellitus plus a random glucose concentration ≥ 200 mg/dl (11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydipsia and unexplained weight loss

OR

2) Fasting blood glucose ≥ 126 mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8 hours

OR

3) 2 hour post prandial glucose ≥ 200 mg/dl (11.1 mmol/l). Among diabetics, the above criteria will be considered to include the patients for the study.

Inclusion criteria for case selection:

- 1) Type-2 diabetes mellitus, either naïve or on monotherapy with metformin or glimepiride and having HbA1c $> 7.0\%$
- 2) Age group 18-70 years
- 3) Body mass index (BMI) in the range 22-45

Exclusion criteria:

Patients < 18 years or > 70 years of age, type-1 diabetes mellitus, diabetic ketoacidosis, renal failure, heart failure, pregnancy and breast feeding were excluded from the study.

These 100 patients were divided into two groups of 50 patients each. Group I was given glimepiride 1mg and metformin 500mg combination, Group II was given vildagliptin 50mg plus metformin 500mg combination. Patients in both groups were age matched and as far as possible duration matched. The efficacy variables were fasting blood glucose, 2-hour postprandial glucose and HbA1c. These were measured at 4 weekly intervals for the total period of study of 24 weeks. The data was tabulated and analysed statistically using Student's t-test and the Chi-square (χ^2) test, respectively. All p values less than 0.05 were regarded as statistically significant.

OBSERVATIONS

The study included 100 patients of type 2 diabetes mellitus who were divided into two groups of 50 each. Group I was given glimepiride-metformin, Group II was given vildagliptin-metformin combination. Mean age of pa-

tient was 52.8 years. 48% (n=48) patients were males and 52% (n=52) were females. The mean fasting blood glucose, 2 hour postprandial glucose and HbA1c levels were 162.56mg/dl, 268.68mg/dl and 8.49% respectively. Out of 100 patients enrolled in the study, 52 were females and 48 were males. Out of 52 females, 28 were included in Group I (glimepiride-metformin) group and 24 were included in Group II (vildagliptin-metformin) group. Out of 48 males, 22 were included in Group I and 26 were included in Group II.

Fasting blood sugar levels for glimepiride-metformin combination (GROUP I) decreased from a baseline mean value of 164.12 ± 13.68 mg/dl to 115.24 ± 12.88 mg/dl at the end of 24 weeks, a mean reduction of 48.88 mg/dl. This decrease was statistically significant. Two hour post prandial blood glucose levels for glimepiride-metformin group (GROUP I) decreased from 271.70 ± 21.08 mg/dl to 156.18 ± 11.88 mg/dl after 24 weeks of therapy, a mean reduction of 115.52 mg/dl. This change was statistically significant.

HbA1c levels for glimepiride-metformin group (GROUP I) showed a mean reduction of 1.36% from $8.59 \pm 1.23\%$ to $7.24 \pm 0.62\%$. The decline in HbA1c levels after 24 weeks of treatment was statistically significant.

Fasting blood sugar levels for vildagliptin-metformin combination (GROUP II) decreased from a baseline mean value of 161 ± 16.57 mg/dl to 110.96 ± 14.22 mg/dl at the end of 24 weeks, a mean reduction of 50.04 mg/dl. This decrease in levels was statistically significant.

Two hour post prandial blood glucose levels for vildagliptin-metformin group (GROUP II) decreased from 265.66 ± 22.12 mg/dl to 154.80 ± 13.50 mg/dl after 24 weeks of therapy, a mean reduction of 110.86 mg/dl. This change was statistically significant.

HbA1c levels for vildagliptin-metformin group (GROUP II) showed a mean reduction of 1.22% from $8.40 \pm 0.70\%$ to $7.18 \pm 0.60\%$. The decline in HbA1c levels after 24 weeks of treatment was statistically significant.

TABLE 1
COMPARISON BETWEEN FBS LEVELS OF GROUP I (GLIMEPRIDE-METFORMIN COMBINATION) AND GROUP II (VILDAGLIPTIN-METFORMIN COMBINATION)

	GROUP I	GROUP II	'p' value	Level of significance
Before start of treatment	164.12 ± 13.68	161 ± 16.57	0.307	Not significant
After 24 weeks of treatment	115.24 ± 12.88	110.96 ± 14.22	0.118	Not significant
FBS reduction	48.88 ± 9.51	50.04 ± 10.03	0.554	Not significant
% decline during period of study	30.33	31.08		

The comparative blood sugar levels are depicted in **Table 1**. In the glimepiride-metformin group (GROUP I) the mean reduction in fasting blood glucose was 48.88 mg/dl, a 30.33% decline during the period of treatment of 24 weeks. The mean reduction in fasting blood glucose levels in vildagliptin-metformin group (GROUP II) was 50.04 mg/

dl, a reduction of 31.08%. The difference in reduction was statistically not significant.

In the glimepiride-metformin group (GROUP I) the mean reduction in 2 hour post prandial blood glucose was 115 mg/dl, a 42.51% decline during the period of treatment of 24 weeks. The mean reduction in 2 hour post prandial blood glucose levels in vildagliptin-metformin group (GROUP II) was 110.86 mg/dl, a reduction of 41.73%. The difference in reduction was statistically not significant.

**TABLE 2
COMPARISON BETWEEN HbA1c LEVELS OF GROUP I (GLIMEPRIDE-METFORMIN COMBINATION) AND GROUP II (VILDAGLIPTIN-METFORMIN COMBINATION)**

	GROUP I	GROUP II	'p' value	Level of significance
Before start of treatment	8.59 ± 1.23	8.404 ± 0.708	0.986	Not significant
After 24 weeks of treatment	7.24 ± 0.62	7.18 ± 0.606	0.626	Not significant
Reduction HbA1c levels	1.36 ± 0.135	1.22 ± 0.227	0.000	Significant

As seen in **Table 2** in the Glimepiride-Metformin group (GROUP I), the mean reduction in HbA1c levels was 1.36% during the period of treatment of 24 weeks. The mean reduction in HbA1c levels in Vildagliptin-Metformin group (GROUP II) was 1.22%. The difference in reduction was statistically significant.

During the entire study period of 24 weeks, 11 episodes of hypoglycemia occurred in Group I (glimepiride-metformin), whereas single episode of hypoglycemia was reported in Group II (vildagliptin-metformin group). The difference was statistically significant. By the end of study period of 24 weeks, the mean change in weight was +1.68±0.75 kg for Group I (glimepiride-metformin group), whereas a change of -0.50±0.46 was observed in Group II (vildagliptin-metformin group). This difference was statistically significant.

DISCUSSION

In our study glimepiride-metformin combination therapy reduced fasting blood sugar levels from a baseline mean value of 164.12±13.68 mg/dl at the start of the study to 115.24±12.88 mg/dl at the end of 24 weeks. Mean decline in fasting blood glucose after 24 weeks of treatment was 48.88 mg/dl. The improvement in fasting blood glucose was highly significant.

Two hour post prandial blood glucose levels for glimepiride-metformin group also decreased significantly from a baseline value of 271.70±21.08 mg/dl to 156.18±11.88 mg/dl after 24 weeks of therapy with a mean reduction of 115.52 mg/dl. This change was statistically highly significant.

effects on fasting blood glucose and 2 hour post prandial glucose levels were observed by use of glimepiride-metformin combination in diabetic patients by Charpentier et al¹⁴, Umpierrez et al¹⁵, Ferrannini et al¹⁶, Hyun Jeong Jeon and Tae Keun Oh¹⁷.

Glimepiride-metformin therapy given for 24 weeks in the same group resulted in fall in HbA1c from 8.59±1.23% to 7.24±0.62% and with a mean reduction of 1.36% which was statistically highly significant. This was similar to that observed by Charpentier et al¹⁴, Umpierrez et al¹⁵, Ferran-

nini et al¹⁶, Hyun Jeong Jeon and Tae Keun Oh¹⁷, Matthews et al¹⁸, Derosa et al¹⁹, Goke et al²⁰ in their studies.

Vildagliptin-metformin combination when administered to Type 2 diabetes mellitus patients, it reduced fasting blood glucose levels from a baseline mean value of 161±16.57 mg/dl to 110.96±14.22 mg/dl at the end of 24 weeks with a mean reduction of 50.04 mg/dl. This decrease in levels was statistically highly significant.

With vildagliptin-metformin therapy, 2 hour post prandial blood glucose levels were reduced from 265.66±22.12 mg/dl to 154.80±13.50 mg/dl after 24 weeks with a mean reduction of 110.86 mg/dl. This change was statistically highly significant.

Vildagliptin-metformin when given for 24 weeks in same group resulted in fall of HbA1c from 8.40±0.70% to 7.18±0.60% with a mean reduction of 1.22%. The decline in HbA1c levels after 24 weeks of treatment was statistically highly significant.

Similar effects on fasting blood glucose, 2 hour post prandial blood glucose and HbA1c by use of vildagliptin-metformin were observed by L. Cai et al²¹, Ferrannini et al¹⁶, Hyun Jeong Jeon and Tae Keun Oh¹⁷, Ahren et al²², Matthews et al¹⁸, Derosa et al¹⁹ and Goke et al²⁰.

On comparison of fall in fasting blood glucose levels between group I (glimepiride-metformin) and group II (vildagliptin-metformin). It was seen that in Group I (glimepiride-metformin group), the mean reduction in fasting blood glucose was 48.88 mg/dl, a 30.33% decline during the period of treatment of 24 weeks. The mean reduction in fasting blood glucose levels in group II (vildagliptin-metformin group) was 50.04 mg/dl, a reduction of 31.08%. The difference in reduction between two groups was statistically not significant (p > 0.05).

In the Group I (glimepiride-metformin group) the mean reduction in 2 hour post prandial blood glucose was 115 mg/dl, a 42.51% decline during the period of treatment of 24 weeks. The mean reduction in 2 hour post prandial blood glucose levels in group II (vildagliptin-metformin) group was 110.86 mg/dl, a reduction of 41.73%. The difference in reduction between two groups was statistically not significant (p > 0.05).

In the glimepiride-metformin group (Group I), the mean reduction in HbA1c levels was 1.36% by the end of 24 weeks as compared to 1.22% in vildagliptin-metformin group (Group II) and the difference between them was statistically significant (p < 0.05).

During the entire study period of 24 weeks in 100 patients, 11 episodes of hypoglycaemia (random blood glucose < 55 mg/dl) occurred in Group I (glimepiride-metformin), whereas single episode of hypoglycemia was reported in Group II (vildagliptin-metformin group). The difference was statistically significant (p < 0.05).

When the effect of two therapies on bodyweight was compared by the end of study period of 24 weeks, it was seen that the mean change in weight was +1.68±0.75 kg for Group I (glimepiride-metformin group), whereas a change of -0.50±0.46 was observed in Group II (vildagliptin-metformin group). This difference was statistically significant (p < 0.05).

These comparative effects in terms of fasting and 2 hour post prandial blood glucose reduction, HbA1c control, incidence of hypoglycemia and weight gain were similar to those observed by Ferrannini et al,¹⁶ Jeon and Keun Oh¹⁷, Matthews et al¹⁸, Derosa et al¹⁹, Goke et al,²⁰ Cai et al,²¹ and Ahren et al.²²

CONCLUSION

Vildagliptin and glimepiride were equally efficacious in reducing fasting plasma glucose levels when given as an add-on therapy to metformin in type 2 diabetes mellitus patients. Mean reduction in 2 hour post prandial glucose levels during the study was similar with both the therapies. HbA1c control was marginally better with glimepiride-metformin therapy as compared to vildagliptin-metformin therapy.

Hypoglycemia episodes were ten times more with glimepiride-metformin therapy as compared to vildagliptin-metformin therapy. Hence, vildagliptin gives an advantage over glimepiride in this regard. Vildagliptin-metformin was associated with weight loss in study patients whereas weight gain was seen with glimepiride-metformin therapy. Vildagliptin-metformin therapy proved to be beneficial in this regard. Therefore vildagliptin may be a better therapy in an obese type 2 diabetic patient with a lesser tendency for hypoglycaemia.

REFERENCES:

1. Unger RH, Orci L. Paracrinology of islets and the paracrinopathy of diabetes. *Proc Natl Acad Sci U S A*. 2010;107(37): 16009-12.
2. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA and Butler PC. Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes*. 2003;52: 102-10.
3. Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R and Zinman B. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*. 2007;30: 753-9.
4. Virally M, Blicke JF, Girard J, et al. Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives. *Diabetes Metab*. 2007;33: 231-44.
5. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus: present and future perspectives. *Nat Rev Endocrinol*. 2012;8: 228-36.
6. Ginter E, Simko V. Diabetes type 2 pandemic in 21st century. *Bratisl Lek Listy*. 2010;111: 134-7.
7. Fox CS, Coady S, Sorlie PD, D'Agostino RB Sr, Pencina MJ, Vasan RS, et al. Increasing cardiovascular disease burden due to diabetes mellitus: the Framingham Heart Study. *Circulation* 2007;115: 1544-50.
8. Consoli A, Gomis R, Halimi S, et al. Initiating oral glucose-lowering therapy with metformin in type 2 diabetic patients: an evidence-based strategy to reduce the burden of late-developing diabetes complications. *Diabetes Metab*. 2004;30: 509-16.
9. Halimi S. Metformin: 50 years old, fit as a fiddle, and indispensable for its pivotal role in type 2 diabetes management. *Diabetes Metab*. 2006;32: 555-6.
10. Donnelly LA, Doney AS, Hattersley AT, et al. The effect of obesity on glycaemic response to metformin or sulphonylureas in Type 2 diabetes. *Diabet Med*. 2006;23: 128-33.
11. UKPDS 34. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*.1998; 352: 854-65.
12. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*.2006;29: 1963-72.
13. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy: Update regarding the thiazolidinediones. *Diabetologia*. 2008;51: 8-11.
14. 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 Oct;18(10): 828-34.
15. Umpierrez G, Issa M, Vlainic A. Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. *Curr Med Res Opin*. 2006;22(4): 751-759.
16. Ferrannini E, Fonseca V, Zinman B, Matthews D, Ahren B, Byiers S, Shao Q, Dejager S.;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 & Metabolism Journal*. 2011;35(5):529-535. doi:10.4093/dmj.2011.35.5.529.
18. Matthews DR, Dejager S, Ahren B, Fonseca V, Ferrannini E, et al.;Vildagliptin add-on to metformin produces similar efficacy and reduced hypoglycaemic risk compared with glimepiride, with no weight gain: results from a 2-year study. *Diabetes Obes Metab* 2010;12: 780-9.
19. Derosa G, Bonaventura A, Bianchi L, Romano D, Fogari E, D'Angelo A, et al. Vildagliptin compared to glimepiride on post-prandial lipemia and on insulin resistance in type 2 diabetic patients. *Metabolism*. 2014 Jul;63(7): 957-67.
20. Göke R, Gruenberger JB, Bader G, Dworak M. Real-life efficacy and safety of vildagliptin compared with sulphonylureas as add-on to metformin in patients with type 2 diabetes mellitus in Germany. *Curr Med Res Opin*. 2014 May;30(5): 785-9.
21. Cai ML, Cai Y, Lu ZJ, Zhang Y and Liu P. The efficacy and safety of vildagliptin in patients with type 2 diabetes: a meta-analysis of randomized clinical trials. *Journal of Clinical Pharmacy and Therapeutics*, 2012; 37: 386-398.
22. Ahren B, Foley JE, Ferrannini E, Matthews DR, Zinman B, Dejager S, Fonseca VA.;Changes in prandial glucagon levels after a 2-year treatment with vildagliptin or glimepiride in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetes Care* 2010;33: 730-2.