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Original Research Article

Comparison of combination metformin-vildagliptin versus metformin-glimepiride in patients of type 2 diabetes mellitus with inadequately controlled metformin monotherapy

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ABSTRACT

Background: Metformin has been recommended as a first-line therapy for T2DM in many guidelines. Adding a sulfonylurea to metformin has been a conventional and gold standard for decades to achieve tight glycaemic control. dipeptidyl peptidase-4 (DPP-4) inhibitors, an incretin-based therapy has emerged as important adjunctive drugs in T2DM. Therefore, the present study was planned to evaluate and compare the efficacy and safety of combination metformin-vildagliptin and metformin-glimepiride in patients of T2DM inadequately controlled with metformin monotherapy.
Methods: A total 45 patients were allocated to each metformin-vildagliptin group and metformin-glimepiride group. Fasting plasma glucose, post prandial plasma glucose, body weight, adverse events were recorded at 0 week, 6 weeks, and 12 weeks. Glycosylated haemoglobin was recorded at 0 week and 12 weeks.
Results: There was no statistically significant difference between the two groups ($p>0.05$) at the end of 12 weeks in the mean percentage reduction in FPG, PPPG and HbA1c.There was statistically highly significant ($p<0.0001$) difference between the two groups in mean percentage change in weight at the end of 12 weeks. Hypoglycemic events were significantly ($p<0.05$) more in metformin-glimepiride group. There was no statistically significant difference in the incidence of other adverse events between the two groups ($p>0.05$).
Conclusions: In patients of T2DM with inadequately controlled metformin monotherapy, combination metformin-vildagliptin provides comparable efficacy in terms of FPG, PPPG and HbA1c to that of combination metformin-glimepiride with no risk of weight gain reduction in risk of hypoglycemic events.

Keywords: Type 2 diabetes mellitus, Metformin-vildagliptin, Metformin-glimeperide, Hypoglycamia

INTRODUCTION

Diabetes mellitus is one of the most common chronic noncommunicable disease resulting in increased blood glucose levels.[1,2] Type 2 diabetes mellitus (T2DM) is a heterogeneous syndrome characterised by abnormalities in carbohydrate and fat metabolism. The causes of T2DM are multi-factorial and include both genetic and environmental elements that affect beta-cell function and tissue insulin sensitivity.[1] Incidence of diabetes mellitus is increasing rapidly all over the world. India is one of the epicenters of the global diabetes mellitus pandemic.[3] T2DM accounts for 90% diabetes mellitus cases and the proportion of people with T2DM is increasing in most countries.[2,4] T2DM is a progressive disease characterised by declining β-cell function and insulin resistance which leads to loss of glycemic control.[1] The importance of glycaemic control in diabetic patients in reducing microvascular and macrovascular complications has been established in the diabetes control and complications trial

(DCCT), United Kingdom prospective diabetes study (UKPDS), Steno-2 and several other clinical trials.[5] Therefore to minimize microvascular and macrovascular risk, many international guidelines like American diabetes association (ADA) and international diabetes federation (IDF) recommend therapy to target glycosylated haemoglobin (HbA1c) < 7%.[6-8]

Metformin, a biguanide, has number of complementary but not yet fully understood mechanism of action. The accepted pharmacological actions are reduction in hepatic glucose output, but it also increases peripheral glucose utilisation, increases peripheral tissue sensitivity to insulin, decreases fatty acid oxidation and reduces intestinal carbohydrate absorption.[9] Metformin has been recommended as a first-line therapy for T2DM in guidelines published by the ADA and IDF for being efficacious, well tolerated, inexpensive but failure rate of 4% with metformin monotherapy has been recorded.[6,7,10] In order to achieve glycaemic targets, patient often require a combination therapy with complimentary mechanism of action.[9] Since metformin lowers plasma glucose levels without affecting insulin secretion, it is often combined with an agent stimulating insulin secretion like glimepiride, a sulfonylurea. Adding a sulfonylurea to metformin has been a conventional and gold standard for decades.[11] Although a sulfonylurea is well known as being effective in lowering plasma glucose levels, it is frequently associated with body weight gain and sever hypoglycaemic events.[12] In overweight and obese patients with T2DM, modest and sustained weight loss has been shown to improve glycemic control. Hypoglycemic events are observed to be associated with cognitive impairment, dementia, morbidity and mortality in patients of T2DM in several studies.[7] Current treatment guidelines for management of T2DM recommend a patient-centred approach considering factors such as effectiveness, tolerability, long-term safety, cost, and patient preferences when choosing antidiabetic agent. So, it is important to consider the addition of a second antidiabetic agent that improves glycemic control without increasing the risk of hypoglycemic events or weight gain.[13]

In last few years, dipeptidyl peptidase-4 (DPP-4) inhibitors, an incretin based therapy has emerged as important adjunctive drugs in T2DM.[14] Vildagliptin, a potent and selective inhibitor of DPP-4 improves glycaemic control by increasing availability of endogenous incretin hormones, glucagon like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Complementing the pharmacological effect of metformin, vildagliptin enhances glucose dependent insulin secretion and suppresses glucagon release, there-by improving glycaemic control and contributing to weight neutrality and reduced hypoglycaemic events.[15] There is scarcity of research comparing the commonly used combinations of metformin-glimepiride and metformin-vildagliptin in clinical practice for management of T2DM. However, data only from the developed countries is available. Therefore, the present study was planned to evaluate and compare the efficacy and safety of combination metformin-vildagliptin and metformin-glimepiride in patients of T2DM inadequately controlled with metformin monotherapy.

METHODS

The study was conducted in a tertiary care hospital attached to a medical teaching institute. This was prospective, comparative, randomized, open labelled study. Patients with type 2 diabetes mellitus, of either gender, aging 20-70 years, visiting Diabetes Clinic of Medicine OPD were enrolled in study. Inclusion criteria was patients with type 2 diabetes mellitus receiving metformin ≥1000 mg daily (divided doses) at least for 12 weeks (according to ADA guidelines 7) prior to screening, HbA1c ≥ 7%- 9%, FPG ≥ 126 mg/dl, PPPG ≥ 200 mg/dl. Pregnant/ lactating women, patients on insulin 6 months prior to screening, patients with any acute or chronic complication of diabetes mellitus, patients with infection 4 weeks prior to screening, patients on parenteral glucocorticoids, growth hormone, patients suffering from active or chronic hepatic disease, patients with renal disease were excluded from study. Total of 90 patients were recruited for the study, based on calculated sample size of 45 in each treatment arm using formula;[16]

$$\text{Sample size (n)} = (Z\,1-\alpha/2)2(p)\,(1-p)/d2$$

A written informed consent was taken from all participants. The patients were allocated to either group A or group B of the treatment based on simple random sampling (Chit-Pull method). On the first visit (0 week), patients' characteristics such as age, sex, registration no, a brief medical history were noted. Patients were counselled by physician regarding their diet and encouraged to have regular exercise according to standards of medical care in diabetes-2017 given by ADA.[7] Group A received tablet metformin 500 mg and tablet vildagliptin 50 mg twice a day, 30 min before meal, orally for 12 weeks and group B received tablet metformin 500 mg and tablet glimepiride 2 mg twice a day, 30 min before meal, orally for 12 weeks. FPG, PPPG, HbA1c and weight were recorded on the first visit (week 0). Study treatment was started on the day of randomization and continued for 12 weeks. After randomization, follow up visits were scheduled at 6 weeks and 12 weeks. On second visit (6 weeks) FPG, PPPG and weight were recorded, and on third visit (12 weeks) FPG, PPPG, HbA1c and weight were recorded. Patients were interviewed and examined for occurrence of any adverse event at 6 weeks and 12 weeks. The primary efficacy end point was the mean percentage change in HbA1c from baseline to final assessment (12 weeks). The secondary efficacy end points included the mean percentage change in FPG, PPPG and weight from baseline to final assessment (12 weeks).

Statistical analysis

Data was entered in MicroSoft-Excel 2013 and spreadsheets were used for calculation. Categorical data in demographic parameters was analyzed by using 'Z' test for difference between two proportions. Continuous variables between the two treatment groups were analysed by unpaired t test. Efficacy endpoints within the group were analyzed by using paired t-test. Safety parameters were analysed using 'Z' test for difference between two proportions, $p<0.05$ was considered statistically significant.[16]

RESULTS

A total 90 patients were included in the study, of which 45 patients were allocated to metformin-vildagliptin group (group A) and 45 patients to metformin-glimepiride group (group B). During the study period, one patient from metformin-vildagliptin group and two patients from metformin-glimepiride group were lost to follow up. Two patients from metformin-vildagliptin group and three patients from metformin-glimepiride group withdrew consent. Thus, 42 patients from metformin-vildagliptin group and 40 patients from metformin-glimepiride group completed the study and were considered for the analysis of data. Demographic characteristics like age and sex of both the groups are depicted in (Table 1).

Table 1: Demographic characteristics of two treatment groups.

Variables	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Age (years)[#]			
Mean±SD	51.24±7.02	51.78±8.44	0.756[#]
Gender**			
Male	24	23	0.798**
Female	18	17	0.826**

Unpaired t test, ** Z test, SD=Standard deviation.

The baselines mean values of FPG, PPPG, HbA1c and weight in two groups is shown in (Table 2). The mean values of FPG in the two groups at baseline, 6 weeks and 12 weeks is shown in (Table 3). The mean percentage reduction in FPG in the two groups at 12 weeks is shown in (Figure 1). The mean percentage reduction in FPG in metformin-vildagliptin group was higher than in the metformin-glimepiride group at the end of 12 weeks; but this did not amount to statistically significant difference ($p>0.05$). The mean values of PPPG in the two groups at baseline, 6 weeks and 12 weeks is depicted in (Table 4). The mean percentage reduction in PPPG in the two groups at 12 weeks is depicted in (Figure 2). The mean percentage reduction in PPPG in metformin-vildagliptin group was higher than in the metformin-glimepiride group at the end of 12 weeks; but this did not amount to statistically significant difference ($p>0.05$). The mean values of HbA1c in the two groups at baseline, and 12 weeks as shown in (Table 5). The mean percentage reduction in HbA1c in the two groups at 12 weeks as depicted in (Figure 3). The mean percentage reduction in HbA1c in metformin-vildagliptin group was higher than in the metformin-glimepiride group; but this did not amount to statistically significant difference ($p>0.05$).

Table 2: Baseline profile of parameters in two treatment groups.

Variables	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
FPG (mg/dl)	171.48±8.14	172.05±8.59	0.758
PPPG (mg/dl)	276.12±17.13	272.83±18.69	0.409
HbA1c (%)	8.13±0.40	7.94±0.50	0.069
Weights (kg)	76.07±8.29	73.25±6.52	0.101

#Unpaired t-test, Values are expressed as Mean±SD.

Table 3: Fasting plasma glucose (mg/dl) in two treatment groups.

Groups	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Baseline	171.48±8.14	172.05±8.59	0.758
6 weeks	129.88±7.43	132.13±7.77	0.186
12 weeks	112.33±8.70	114.83±6.18	0.138

#Unpaired t-test, Values are expressed as mean±SD.

Table 4: Postprandial plasma glucose (mg/dl) in two treatment groups.

Groups	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Baseline	276.12±17.13	272.83±18.69	0.409
6 weeks	221.14±17.49	223.80±19.90	0.524
12 weeks	187.12±19.55	188.93±21.35	0.407

#Unpaired t-test, Values are expressed as mean±SD.

The mean values of weight in the two treatment groups at baseline, 6 weeks and 12 weeks as shown in (Table 6). There was no statistically significant (paired t test, $p>0.5$) difference in weight in metformin-vildagliptin group at the end of 6 weeks and 12 weeks. There was a statistically highly significant (paired t test, $p<0.0001$) increase in weight in metformin-glimepiride group at the end of 6 weeks and 12 weeks. There was no statistically significant ($p>0.05$) difference between two groups in mean values of weight at the end of 6 weeks and 12

weeks. The mean percentage change in weight in the two groups at 12 weeks is shown in (Table 7).

Table 5: HbA1c (%) in two treatment groups.

Groups	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Baseline	8.13±0.40	7.94±0.50	0.069
12 weeks	6.99±0.26	6.88±0.31	0.088

#Unpaired t-test, Values are expressed as mean±SD.

Table 6: Weight (kg) in two treatment groups.

Groups	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Baseline	76.07±8.35	73.25±6.52	0.091
6 weeks	75.88± 8.13	74.30±6.54	0.334
12 weeks	75.79±8.59	75.30±6.43	0.772

#Unpaired t-test, Values are expressed as mean±SD.

Table 7: Mean percentage change (%) in weight at 12 weeks.

Groups	Metformin-vildagliptin group (N=42)	Metformin-glimepiride group (N=40)	P value
Mean percentage change	0.41±1.34	2.85±1.49	<0.0001

#Unpaired t-test, Values are expressed as mean±SD.

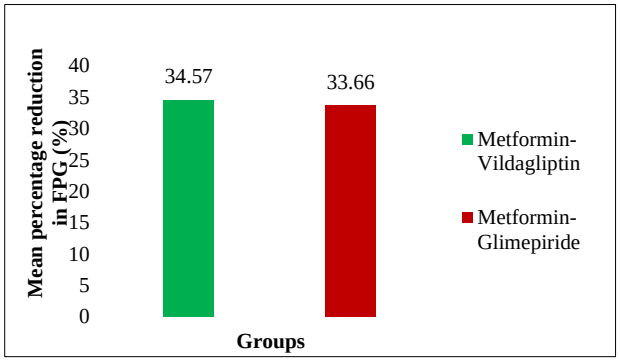

Figure 1: Mean percentage reduction in fasting plasma glucose at 12 weeks.

There was statistically highly significant (p<0.0001) difference between the two groups in mean percentage change in weight at the end of 12 weeks. The comparative data regarding the percentage of patients who reported adverse events in the two groups is shown in (Table 8). Hypoglycemic events were significantly (p<0.05) more in metformin-glimepiride group compared to metformin-vildagliptin group. There was no statistically significant difference in the incidence of other adverse events between the two groups (p>0.05).

Table 8: Incidence of adverse events in the two treatment groups.

Adverse events	Metformin-vildagliptin group (N=42)		Metformin-glimepiride group (N=40)		P value
	N	%	N	%	
Headache	2	4.76	2	5	0.960
Hypoglycemic event	1	2.38	6	15	0.040
Diarrhoea	1	2.38	2	5	0.528
Nausea	1	2.38	3	7.5	0.282
Dizziness	1	2.38	1	2.5	0.972
Arthralgia	2	4.76	1	2.5	0.586
Dyspepsia	1	2.38	1	2.5	0.972

**Z test for difference between two proportion.

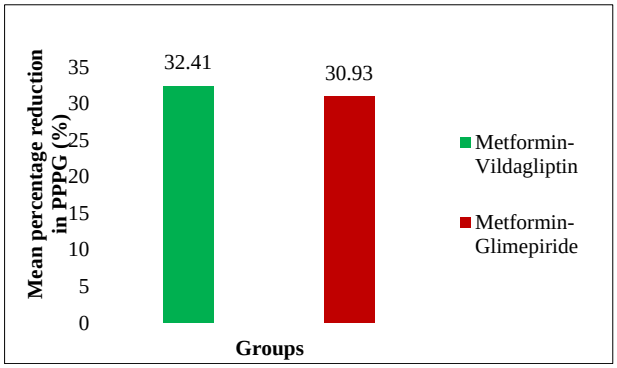

Figure 2: Mean percentage reduction in postprandial plasma glucose at 12 weeks.

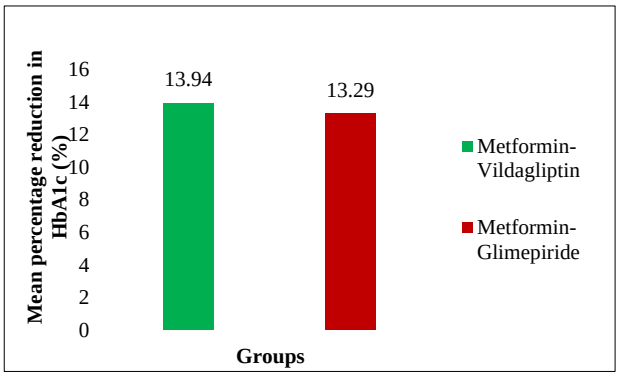

Figure 3: Mean percentage reduction in HbA1c at 12 weeks.

DISCUSSION

Metformin is recommended as first line therapy for T2DM by guidelines published by ADA and IDF.[6,7,10] However, due to the progressive nature of T2DM, combination therapies with complimentary mechanism of action are often required to achieve glycaemic targets and prevent long term complications.[9]

Adding a sulfonylurea to metformin has been a conventional and gold standard for decades.[11] However its use is frequently associated with body weight gain and sever hypoglycemic events.[12] In overweight and obese patients with T2DM, modest and sustained weight loss has been shown to improve glycemic control. Hypoglycemic events in T2DM patients are observed to be associated with cognitive impairment; dementia, morbidity and mortality in several studies.[7] Current treatment guidelines for management of T2DM recommend a patient-centred approach considering factors such as effectiveness, tolerability, long-term safety, cost, and patient preferences when choosing antidiabetic agents. So, it is important to consider the addition of a second antidiabetic agent in patients of T2DM uncontrolled with metformin monotherapy, that improves glycemic control without increasing the risk of hypoglycemic events or weight gain.[13] Vildagliptin, a potent selective inhibitor of DPP-4, improves glycaemic control by increasing the availability of endogenous incretin hormones, GLP-1 and GIP. It enhances glucose-dependent insulin secretion along with suppression of glucagon release and compliment pharmacological effect of metformin with reduced risk of weight gain and hypoglycemic events.[15]

In the present study, there was no statistically significant difference between the two groups ($p>0.05$) at the end of 12 weeks in the mean percentage reduction in FPG, PPPG and HbA1c. Similar findings were observed by studies conducted by Gupta et al, Jeon et al and Mokta et al while Kalaiselvi et al, in newly diagnosed patients of T2DM, reported no statistically significant difference in the percentage reduction in FPG between two group at the end of 12 weeks.[17-20] There was statistically significant difference between the two groups in percentage change in weight at the end of 12 weeks ($p<0.0001$). Similar findings were observed by studies conducted by Ferrannini et al, Matthew et al, Mokta et al and Jeon et al, Gupta et al reported no statistically significant ($p>0.05$) difference in weight between two groups at the end of 12 weeks.[17-22] Kalaiselvi et al observed no statistically significant difference in BMI in two groups at the end of 12 weeks in newly diagnosed patients of T2DM.[20]

In overweight or obese patients with T2DM, successful weight loss can improve glycaemic control and reduce risk of microvascular and macrovascular complications.[23] Vildagliptin prevents weight gain by inhibiting intestinal fat absorption, thereby decreasing chylomicron lipid and apolipoprotein levels. Vildagliptin can increase norepinephrine levels and promote lipolysis through sympathetic stimulation, in conjunction with the postprandial fatty acid mobilization and oxidation. These new potential roles of vildagliptin may contribute to its weight-neutral effect.[24,25] In present study, adverse events reportedmost commonly in the metformin-vildagliptin group and metformin-glimepiride group were hypoglycemic event, headache, nausea, diarrhoea and arthralgia. Hypoglycemic events were significantly ($p<0.05$) more in metformin-glimepiride group compared to metformin-vildagliptin group at the end of 12 weeks. Ferrannini et al, Jeon et al, Mokta et al, Matthew et al and Gupta et al in accordance to our study reported more incidences of hypoglycemic eventsin metformin-glimepiride group.[17-19,22] Vildagliptin binds covalently to the catalytic site of DPP-4, eliciting prolonged enzyme inhibition. This raises intact GLP-1 levels, both after meal ingestion and in the fasting state. Vildagliptin has been shown to stimulate insulin secretion and inhibit glucagon secretion in a glucose dependent manner. At hypoglycemic levels, the counter regulatory glucagon response is enhanced relative to baseline by vildagliptin. Vildagliptin also inhibits hepatic glucose production, mainly through changes in islet hormone secretion, and improves insulin sensitivity, as determined with a variety of methods. These effects cause the improved glycaemic control with low risk for hypoglycemic event.[24] Kalaiselvi et al reported significantly ($p<0.05$) more incidence of diarrhoea with metformin-vildagliptin therapy at the end of 12 weeks.[20] In present study, there was no statistically significant difference in the incidence of other adverse events between the two groups ($p>0.05$). This finding was consistent with the studies conducted by Gupta et al, Matthew et al, Ferrannini et al and Mokta et al which reported no statistically significant difference in incidence of other adverse events between two treatment groups.[17,19,21,22] In the present study, adverse events were mild and none of the patients from either group required discontinuation of the study drugs due to adverse event. The results of present study suggest that, in patients of T2DM with inadequately controlled metformin monotherapy, combination metformin-vildagliptin provides comparable efficacy in terms of FPG, PPPG and HbA1c to that of combination metformin-glimepiride. There is no risk of weight gain with combination metformin-vildagliptin which is desirable in patients of T2DM. Combination metformin-vildagliptin provides a favourable safety profile with a significant reduction in risk of hypoglycemic events. Vildagliptin possesses the unique properties of having a very low risk of hypoglycaemic event and beneficial effects on body weight. These characteristics make vildagliptin as better add-on treatment option in patients of T2DM who have inadequate glycaemic control with metformin monotherapy. The present study was open labelled, at a single centre, with small sample size for the duration of 12 weeks where patients with HbA1c >9% were excluded. Large scale multi-centric trials of longer duration with inclusion of higher levels of HbA1c can go a long way in generalizing the findings of the present study. It is desirable to record and compare the long term efficacy and safety of metformin-vildagliptin verses metformin-glimepiride in T2DM patients uncontrolled with metformin monotherapy.

CONCLUSION

In the present study, we conclude that in patients of T2DM with inadequately controlled metformin monotherapy, combination metformin-vildagliptin provides comparable efficacy in terms of FPG, PPPG and

HbA1c to that of combination metformin-glimepiride with no risk of weight gain and provides a favourable safety profile with a significant reduction in risk of hypoglycemic events.

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