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RESEARCH ARTICLE

COMPARITIVE STUDY ON EFFECT OF COMBINATION OF METFORMIN-VILDAGLIPTIN VS METFORMIN-GLIMEPRIDE ON LIPID PROFILE IN PATIENTS OF TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: The global burden of Type 2 diabetes mellitus (T2DM) is on a rise.It is an endrocrine disorder characterised by hyperglycaemia. Cardiac morbidity in patients of long standing type 2 diabetes mellitus is said to occur due to dyslipidaemia seconadary to hyperglycaemia. Good glycaemic control may prevent such a mobidity to occur by intake of efficacious antidiabetic drugs either alone or in combination. Thus, our aim was to analyse the effect of metformin-vildagliptin vs metformin-glimepride on lipid profile of patients of type 2 diabetes mellitus. ***Methods:*** Our study was an observational comparative study where 200 patients of type 2 diabetes mellitus attending medicine department OPD at Shri Shankaracharya Institute of Medical Sciences (SSIMS), Bhillai were included. They were divided in two equal groups of 100 each, where group A were using Metformin-vildagliptin combination, whereas Group B were using Metformin- glimepride combination. All blood investigations were done to decipher glycaemic control and lipid profile status. The results of the two groups were compared and statiscally analysed. ***Results:*** Better glycaemic control was seen in patients of group A as compared to those in Group B after treatment, which was statistically significant. A reduction in triglyceride (TGL), low density lipoprotein (LDL) levels and improvement in high density lipoprotein (HDL) levels was seen in patients of Group Aas compared to those in Group B, which was statistically significant. ***Conclusions:*** Patients on combination of met formin-vildagliptin (Group A) had greater reduction in lipid profile parameters as compared to metformin- glimepride (Group B).

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INTRODUCTION

According to the International Diabetes Federation, India has the second-highest number of patients with diabetes aged between 20 and 79 years as of 2019 (1). Diabetes contributes to diverse complications and mortality and burdens the socioeconomic expense and health-care systems (2,3). Long term complications involve almost all vital organs like heart, eyes, kidney, blood vessels and nervous system. There is a close association between complications of diabetes and diabetic dyslipidaemia (4). Atherosclerosis is a primary cause of death in patients with diabetes (5). The pathophysiology of the development of atherosclerosis is complex and multifactorial. Diabetic dyslipidaemia accounts for around 80% of diabetic death due to cardiovascular complications. A growing body of evidence shows that hyperglycemia and dyslipidaemia are connected with excess cardiovascular risk (6). Metformin monotherapy is considered a first-line treatment in patients prone to weight gain and/ or dyslipidaemia and who have failed to achieve adequate glycaemic control on dietary management alone.

Metformin is also combined with other hypoglycemic agents and insulin to provide satisfactory long-term glycaemic control (7). Glimepiride is a second-generation sulfonylurea, an oral hypoglycaemic agent, commonly used as a monotherapy or in combination with other hypoglycaemic agents. Glimepiride lowers blood glucose levels primarily by stimulating the release of insulin from pancreatic β-cells, and the action of insulin stimulation is independent of glucose levels. Glimepiride is pharmacologically distinct from other sulphonylureas because of the differences in receptor binding properties and potential selective effects on AT Psensitive K+ channels (8). Vildagliptin, a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor, increases the availability of endogenous incretin hormones, glucagon-like peptide (GLP-1), and glucose-dependent insulinotropic polypeptide. Incretin hormones further stimulate insulin synthesis and secretion and inhibit glucagon release from pancreatic islets (9). Both vildagliptin and Metformin stimulate insulin secretion from pancreatic Beta-cells; however, the mode of action of these agents on insulin secretion are different. Owing to the differences in the mechanisms of action on hyperglycaemia between vildagliptin and glimepiride, vildagliptin is expected to be associated with fewer glucose fluctuations based on

the glucose-dependent effects for both hyperglycaemia and hypoglycaemia (10) . As add-on therapy to Metformin, Vildagliptin was previously reported to show similar efficacy to the combination of glimepiride and Metformin in a 2-year clinical study in patients with T2DM (11). In Western populations, sulfonylurea and DPP4 inhibitors also exhibited comparable glucose-lowering efficacy (12). The effects on lipid and renal profiles for these combined anti-diabetic drugs are poorly described in the Indian clinical practice. Therefore, the present study aimed to compare the efficacy of glimepiride and vildagliptin as add-on therapy to Metformin in patients with T2DM in achieving glycaemic control and also to compare their lipid profiles before and after therapy.

MATERIALS AND METHODS

Our study was a hospital based comparative observational study over a duration of 2yrs.200 prediagnosed Type 2 diabetes mellitus patients attending OPD of Medicine Department, at SSIMS were included in the study having age between ≥18yr to ≤70yr, BMI range from 22-45 kg/m2, HbA1C >6 % and inadequately controlled T2DM with metformin monotherapy up to the dose of 1 gm/day for at least six months. Those having history of diabetic ketoacidosis, diabetic nephropathy, drug or alcohol abuse, acute myocardial infarction ,acute hepatitis, pregnancy and breast feeding ,disseminated tuberculosis and other infectious diseases, adverse reactions to any of the study drug medication, lipid lowering drug intake ,were excluded from the study. Patients were distributed into groups A and B, with 100 participants in each group. Group-A received Metformin (500 mg BID) and glimepiride (2 mg BID) and Group-B received Metformin (500 mg BID) and vildagliptin (50 mg BID) for 26weeks. Demographic data and vitals of the study population were recorded .Blood sample was collected for investigations such as Glycosylated haemoglobin (HBA1c; %), Fasting plasma glucose (FPG; mg/dl), Postprandial plasma glucose (PPG; mg/dl), total cholesterol (TCh; mg/dl), triglycerides (TG; mg/dl), Low density lipoprotein (LDL; mg/dl) cholesterol, High density lipoprotein (HDL; mg/dl) cholesterol, urea (mg/dl), creatinine (mg/dl) at initiation of treatment and at the end of 26 weeks, after treatment. Statistical analysis was performed using the Statistical Package for Social Sciences, version-25 (IBM, SPSS, Chicago, USA). Data were tabulated in Microsoft Excel version 2019. Continuous variables were presented in mean ± standard deviation and compared among the two groups using paired and unpaired T-tests. The Chi-square test was used to analyze the significance of difference between frequency distribution of the data. Kolmogorov-Smirnov analysis was performed to check the linearity of the data. p-value < 0.05 was considered statistically significant.

RESULTS

Table 1. Comparison of Age (years)

Age (years)	Group	Mean ± SD	Significance (p-value)
	Group-A (Metformin and glimepiride)	51.4 ± 8.44	0.21
	Group-B (Metformin and vildagliptin)	49.9 ± 8.69	

The mean (± SD) age of participants in Group-A and Group-B were 51.4 ± 8.44 and 49.9. ± 8.69 years, respectively. There was no statistically significant difference among the groups with respect to age (p = 0.21).

Table 2. Comparison of Gender

Gender	Groups	Male	Female
	Group-A (Metformin andglimepiride)	61 (61%)	39 (39%)
	Group-B (Metformin andvildagliptin)	56 (56%)	44 (44%)

In Group-A, 61% (n = 61) of the participants were male and 39% (n = 39) of them were female. In Group-B, 56% (n = 56) of the participants were male and 44% (n = 44) of them were female. There was no statistically significant difference among the group with respect to gender. Before treatment, the mean (± SD) BMI of participants in Group-A and Group-B were 28.4 ± 3.03 and 27.9 ± 2.26 kg/m^2, respectively.

Table 3. Comparison of BMI (kg/m^2) among the groups

BMI (kg/m^2)		Group-A (Metformin and glimepiride)	Group-B (Metformin and vildagliptin)	Significance (p-value)
	Before treatment (at first visit)	28.4 ± 3.03	27.9 ± 2.26	0.18
	After treatment (at 26th week)	29.7 ± 2.47	27.1 ± 2.63	<0.0001
	Significance (p-value)	0.001	0.02	

Similarly, the mean (± SD) BMI of participants in Group-A and Group-B after treatment were 29.7 ± 2.47 and 27.1 ± 2.63 kg/m^2, respectively. There was no statistically significant difference among the groups before treatment withrespect to BMI (p = 0.18). However, the BMI after treatment among the groups showed statistically significant results (p <0.0001). After treatment, there was a statistically significant increase in BMI within group-A (p =0.001), and BMI decreased within Group-B (p = 0.02). The mean (± SD) HbA1c of participants in Group-A and Group-B before treatment were 7.9 ± 0.5 and 8.0 ± 0.6 %, respectively. After treatment, the mean (± SD) HbA1c of participants in Group-A and Group-B were 6.9 ± 0.4 and 6.6 ± 0.3 %, respectively.

There was no statistically significant difference among the groups with respect to HbA1c before treatment (p = 0.20). However, the HbA1c among the groups after treatment showed statistically significant results (p <0.0001). After treatment, there was a statistically significant reduction in HbA1c within group-A (p <0.0001) and Group-B (p <0.0001) both. The mean (± SD) TCh of participants in Group-A and Group-B before treatment was 170.5 ± 20.5 and 168.1 ± 18.7 mg/dl, respectively. After treatment, the mean (± SD) TCh of participants in Group-A and Group-B were 158.7 ± 19.3 and 149.6 ± 17.1 mg/dl, respectively. There was no statistically significant difference among the groups with respect to TCh before treatment (p = 0.388). However, the TCh among the groups after treatment showed statistically significant results (p = 0.0005). After treatment, there was a statistically significant reduction in TCh within group-A (p <0.0001) and Group-B (p <0.0001) both. The mean (± SD) TG of participants in Group-A and Group-B before treatment was 128.1 ± 40.6 and 122 ± 33.7 mg/dl, respectively. After treatment, the mean (± SD) TG of participants in Group-A and Group-B were 117.3 ± 31.1 and 106.6 ± 24.8 mg/dl, respectively. There was no statistically significant difference among the groups with respect to TG before treatment (p = 0.24). However, the TG among the groups after treatment showed statistically significant results (p = 0.007). After treatment, there was a statistically significant reduction in TG within group-A (p =0.0035) and Group-B (p <0.0003). The mean (± SD) HDL of participants in Group-A and Group-B before treatment were 33.6 ± 6.8 and 34.8 ± 6.2 mg/dl, respectively. After treatment, the mean (± SD) HDL of participants in Group-A and Group-B were 39.4 ± 6.1 and 47.2 ± 5.5 mg/dl, respectively. There was no statistically significant difference among the groups with respect to HDL before treatment (p = 0.19). However, the HDL among the groups after treatment showed statistically significant results (p <0.0001). After treatment, there was a statistically significant increase in HDL within group-A (p <0.0001) as well as in Group-B (p <0.0001). The mean (± SD) LDL of participants in Group-A and Group-B before treatment were 116.3 ± 13.7 and 119.3 ± 13.9 mg/dl, respectively.

Table 4. Comparison of HbA1c (%) among the groups before and after treatment

		Group-A (Metformin and glimepiride)	Group-B (Metformin and vildagliptin)	Significance (p-value)
HbA1c(%)	Before treatment (atfirst visit)	7.9 ± 0.5	8.0 ± 0.6	0.20
	After treatment(at 26th week)	6.9 ± 0.4	6.6 ± 0.3	<0.0001
	Significance(p-value)	<0.0001	<0.0001	

Table 5. Comparison of FBS, PPG (mg/dl) among the groups before and after treatment

		Group-A (Metformin and glimepiride)	Group-B (Metformin and vildagliptin)	Significance (p-value)
	Before			
FPG (mg/dl)	treatment (at first visit)	138.4 ± 10.4	135.7 ± 13.2	0.109
	After treatment(at 26th week)	117.3 ± 8.6	114.4 ± 11.9	0.049
	Significance(p-value)	<0.0001	<0.0001	
PPG (mg/dl)		Group-A (Metformin and glimepiride)	Group-B (Metformin and vildagliptin)	Significance (p-value)
	Before treatment (at first visit)	178.3 ± 16.6	182.6 ± 18.2	0.08
	After treatment (at 26th week)	149.1 ± 14.5	144.5 ± 15.7	0.032
	Significance (p-value)	<0.0001	<0.0001	

Table 6. Comparison of TCh (mg/dl) among the groups before and after treatment

		Group-A (Metformin and glimepiride	Group-B (Metformin and vildagliptin	Significance (p-value
TCh (mg/dl)	Before treatment(at first visit)	170.5 ± 20.5	168.1 ± 18.7	0.388
	After treatment(at 26th week)	158.7 ± 19.3	149.6 ± 17.1	0.0005
	Significance(p-value)	<0.0001	<0.0001	

Table 7. Comparison of TG (mg/dl) among the groups before and after treatment

		Group-A (Metformin and glimepiride	Group-B (Metformin and vildagliptin	Significance (p-value
TG (mg/dl)	Before treatment(at first visit)	128.1 ± 40.6	122 ± 33.7	0.24
	After treatment(at 26th week)	117.3 ± 31.1	106.6 ± 24.8	0.007
	Significance(p-value)	0.035	0.0003	

Table 8. Comparison of HDL (mg/dl) among the groups before and after treatment

		Group-A (Metforminand glimepiride)	Group-B (Metformin and vildagliptin)	Significance(p-value)
HDL (mg/dl)	Before treatment(at first visit)	33.6 ± 6.8	34.8 ± 6.2	0.19
	After treatment(at 26th week)	39.4 ± 6.1	47.2 ± 5.5	<0.0001
	Significance(p-value)	<0.0001	<0.0001	

Table 9. Comparison of LDL (mg/dl) among the groups before and after treatment

		Group-A (Metformin and glimepiride	Group-B (Metformin and vildagliptin	Significance (p-value)
LDL (mg/dl)	Before treatment(at first visit)	116.3 ± 13.7	119.3 ± 13.9	0.12
	After treatment(at 26th week)	109.6 ± 12.4	97.8 ± 13.2	<0.0001
	Significance(p-value)	0.0003	<0.0001	

After treatment, the mean (± SD) LDL of participants in Group-A and Group-B were 109.6 ± 12.4 and 97.8 ± 13.2 mg/dl, respectively. There was no statistically significant difference among the groups with respect to LDL before treatment (p = 0.12). However, the LDL among the groups after treatment showed statistically significant results (p <0.0001). After treatment, there was a statistically significant decrease in LDL within group-A (p =0.0003) as well as in Group-B (p <0.0001).

DISCUSSION

It is well documented that hyperglycaemia is accompanied by lipid profile disturbances manifested as increased TCh, TG, LDL levels and decreased HDL levels [13,14]. Hyperglycaemia is considered a high-risk factor for several complications, especially for diabetic patients, such as atherosclerosis and myocardial infarction [13,15]. Lipid peroxidation generates endogenous toxicants resulting in excessive tissue damage and functional abnormalities via the interaction of DNA and essential proteins [13,15]. It is an established knowledge that hyperglycaemia augments the production of reactive oxygen species by mitochondria, which plays a pivotal event in the development and progression of diabetes morbidity and even more induces; programmed cell death, glycation of several important proteins, in addition to glucose autoxidation [16,17]. Furthermore, reactive oxygen species production could result from increased mitochondrial uncoupling and β-oxidation due to disturbed high lipid profile [18]. It is also well known that combination therapy for diabetes is superior in hyperglycemic control compared to single-agent therapy [19]. The present study evaluated the effect of adding Vildagliptin versus Glimepiride to ongoing Metformin therapy in patients with T2DM in achieving glycemic control and comparing their lipid and renal profiles beforeand after treatment.

The mean age of participants in Group-A and Group-B was 51.4 ± 8.44 and 49.9 ± 8.69 years, respectively. The proportion of men was higher than women in both the groups (group-A 61% v/s Group-B 56%). There were no significant changes among the groups with respect to age, gender and duration of diabetes. A significant decrease in FPG and PPG levels was observed within vildagliptin-metformin group as well as glimepiride-metformin group. In vildagliptin-metformin group, the baseline FPG decreased from 135.17 mg/dl to 114.4 mg/dl at week-26. Likewise, the baseline PPG levels in vildagliptin-metformin treatmentdecreased from 182.6 mg/dl to 144.5 mg/dL after 26 weeks. Similarly, in glimepiride-metformin group, the baseline FPG decreased from 138.4 mg/dl to 117.3 mg/dl, and the baseline PPG levels decreased from 178.3 mg/dl to 149.1 mg/dL after 26 weeks of treatment. FPG and PPG reduction was most significant in the vildagliptin / metformin group, agreeing with findings from similar studies [20, 21, 22, and 23]. Improved glycemic control results from the synergistic mechanism of action of vildagliptin and metformin and enhanced stimulation of postprandial insulin secretion. Vildagliptin increases GLP-1 levels through inhibition of DPP-IV enzyme, whereas metformin, as recently reported, probably raises simultaneously GLP-1 synthesis or induces PPAR- a/PPAR-g-dependent islet gene expression and incretin receptor responsiveness. Some studies indicate that metformin potentiates the effect of insulin on glucose transport at a site beyond insulin receptor binding and phosphorylation. The effect of metformin on insulin-receptor binding and tyrosine kinase activity appeared to be independent of either of these variables, but this issue needs more investigation [24, 25-29]. Few studies were not in agreement with us, claiming equal efficacy of vildagliptin and glimepiride as an add-on to metformin therapy [10, 30, 31]. Sulfonylureas (SUs) are widely used in the management of T2DM as insulin secretagogues and are named for their common core configuration. Glimepiride is a second-generation SU often used in combination with insulin. Glimepiride acts at ATPase-dependent potassium channels in β cells of the pancreas to stimulate insulin release [32, 33, 34]. Hypoglycaemia and weight gain are two important disadvantages of SU therapy. Glimepiride is generally well-tolerated, and data from clinical trials indicate that the overall incidences of adverse events associated with glimepiride are usually lower compared with other SUs [33, 34]. Compared to the pre-treatment level, patients on Glimepiride/Metformin therapy showedsignificant weight gain and significant elevation in BMI (p=0.001), which was in accordance with previous studies [30, 36, 20, 37]. In contrast, Vildagliptin/ Metformin group showed a significant decrease in body weight and BMI after treatment (p=0.02).

Additionally, the Vildagliptin/Metformin treated group showed significantly lower BMIthan the Glimepiride/Metformin treated group (p<0.0001). This favourable effect of Vildagliptin/Metformin group on body weight and BMI can be explained because DPP- 4 inhibitors increase endogenous GLP-1 levels via inhibition of the DPP-4 enzyme. Increased GLP-1 levels result in a subsequent reduction in food intake, which accounts for majority of weight loss [37]. In addition, increased thermogenesis and reduced lipid storage in white adipose tissue may play a role in weight reduction [37]. After 26 weeks of treatment and compared with the baseline data, both groups showed a significant decrease in glycated haemoglobin values (HbA1c). These findings were in concordance with other studies showing similar results [38, 39,30]. These beneficial effects could be explained because Glimepiride is a sulfonylurea that targets the ATP-sensitive potassium channel with subsequent stimulation of insulin secretion from pancreatic β- cells [40]. On the other hand, Vildagliptin is a DPP-4 inhibitor which inhibits the enzyme involved in the degradation of GLP-1 and glucose-dependent insulinotropic peptide (GIP) and prolongs the half-life of endogenously released GLP-1 and GIP, resulting in enhanced glucose-dependent insulin secretion and decreased glucose-dependent glucagon secretion [41]. But comparing the HbA1c among the groups revealed that Vildagliptin/Metformin treated group showed significantly lower glycated haemoglobin value (HbA1c) than Glimepiride/Metformin treated group (p<0.0001). Regarding lipid profile, the present study revealed significant improvement in all the lipid parameters in both the groups, but statistical significance was more in Vildagliptin/Metformin than Glimepiride/Metformin. This favourable effect of Vildagliptin/Metformin treatment on lipid parameters may be attributed to the notion that DPP-4 inhibitors increase GLP-1 and GIP concentrations in the body, which have pleiotropic effects including control of blood sugar and improving dyslipidaemia (42). Secondary, activation of GLP-1R signalling inhibits lipoprotein production in the intestine (43). Furthermore, the increased adiponectin level by Vildagliptin treatment may improve the lipid panel since adiponectin enhances triglyceride clearance and increases synthesis of HDL (44). The effect of Glimepiride in improving the majority of lipid parameters may be attributed to glycaemic control (45). These findings reflect the better cardioprotective role of Vildagliptin compared to Glimepiride since HDL was reported to have a cardioprotective effect beyond its anti-atherogenic action, and triglyceride was reported to be strongly associated with CVD risk and insulin resistance (46). The beneficial effect of Vildagliptin on lipid profile has been previously reported (10,47,48). However, our data concerning lipid profile seem in contradiction with Park et al., who reported that neither Glimepiride nor Vildagliptin provoked any change in LDL and HDL levels (49).

CONCLUSION

It could be concluded from the present study that although, as add-on therapy to metformin, both glimepiride and vildagliptin could significantly achieve the target glycaemic control and lipid profile restoration, the vildagliptin/metformin combination is a better alternative to glimepiride/metformin. With vildagliptin/metformin therapy, a modest but significant decrease in body weight can be achieved. The study also reflects significant restoration of HDL levels with Vildagliptin compared to Glimepiride that indicates its cardioprotective effect. Thus, vildagliptin represents an efficacious and well- tolerated pharmacotherapy in the management of diabetes in patients with T2DM.

Glossary of abbreviations

T2DM- type 2 diabetes mellitus
TGL-triglyceride

LDL-low density lipoprotein

HDL- high density lipoprotein

SU- sulphonylureas

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