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Original Research Article

Hypolipidemic effect of sitagliptin, voglibose and glimepiride in combination with metformin in patients with type 2 diabetes mellitus at a tertiary care teaching hospital: a comparative study

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ABSTRACT

Background: The prevalence of coronary artery disease has been increased in diabetic dyslipidemia; hence the present study would like to compare the dyslipidemic effects of Sitagliptin, Voglibose, and Glimepiride in combination with Metformin in type 2 diabetes mellitus patients.
Methods: This study was a Prospective, Randomized Clinical trial conducted at SRM medical College Hospital and Research centre. Potheri, Kancheepuram District in diabetic outpatient department after obtaining approval from Institutional Ethics Committee. The patients receiving antidiabetic drugs were divided into three groups. Patients received Metformin with Sitagliptin were grouped as I, Metformin with Voglibose were named as Group II and Metformin with Glimepiride were marked as Group III. Based on the inclusion and exclusion criteria, in each group, 40 patients were assigned as per simple randomization method. The level of lipid profile and BMI was evaluated at the end of 6 months.
Results: There was a significant reduction of Total Cholesterol (TC) in Group II and Group III (p value- <0.001, <0.006). Group I showed significant elevation of HDL-C level with the p value of <0.03. Group III showed significant reduction of Triglyceride (TG) level with the p value of <0.04, significant reduction of Low Density Lipoprotein Cholesterol (LDL-C) level with the p value of <0.02 and significant reduction in Very Low Density Lipoprotein Cholesterol (VLDL-C) level with the p value of <0.05. There was no significant reduction in Body Mass Index (BMI) among the groups. On multiple comparisons, Group III showed higher efficacy in reducing TC, TG, LDL-C and VLDL-C levels.
Conclusions: The results of this study were analysed and it could be concluded as Metformin with Glimepiride combination (Group III) showed significant reduction of TC, TG, LDL-C and VLDL-C levels.

Keywords: Diabetic dyslipidemia, Glimepiride, Metformin, Sitagliptin, Voglibose

INTRODUCTION

Diabetes mellitus is a metabolic disorder in which the patient has high blood glucose level either because of inadequate insulin production in the body or irresponsiveness of the cells to insulin or both. In 2010, among Indian population Diabetes had affected 50 million and expected to increase to 87 million by 2030 and global prevalence rate in 2010, was 285 million and expected to be 439 million by 2030.[1] Urbanization, sedentary lifestyle, obesity and unhealthful dietary habits are the etiological factors for increased prevalence of diabetes.[2] In Action in Diabetes and Vascular Disease, Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial proved that hyperglycaemia is strongly associated

with major macro and micro vascular complications.[3] The risk of dyslipidemia is also increasing in a diabetic population due to poor lifestyle habits. Dyslipidemia is one of the major risk factors for cardiovascular disease in diabetes which increases the mortality rate. The characteristic features of diabetic dyslipidemia are a high Triglyceride (TG), increased small dense Low Density Lipoprotein Cholesterol (LDL-C) and low High Density Lipoprotein Cholesterol (HDL-C).[4] Insulin resistance has prominent effects on lipoprotein size and particle concentrations for Very Low Density Lipoprotein Cholesterol (VLDL-C), LDL-C, and HDL-C.[5,6] Many studies have reported an association between small dense LDL-C with coronary artery disease (CAD). LDL-C is a predictive factor for coronary events, independent of other coronary disease risk factors.[7,8] Lowering LDL-C level is important for reducing the morbidity and mortality in cardiovascular disease. Insulin resistance is one of the cause for the development of Diabetic dyslipidemia.[9] The Framingham Heart Study documented that 13% of men and 24% of women with diabetes mellitus shown increased total plasma cholesterol levels when compared with 14% of men and 21% of women without diabetes mellitus.[10] The HDL-C Intervention Trial (HIT) reported that Gemfibrozil treatment was associated with a 22% reduction in the risk of CAD and a 25% reduction in the risk of stroke.[11] The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effects of Fenofibrate on coronary morbidity and mortality in diabetes mellitus but did not show a statistically considerable reduction in CAD related death.[12] The prevalence of coronary artery disease has been increased in diabetic dyslipidemia; hence the present study would like to compare the dyslipidemic effects of Sitagliptin, Voglibose, and Glimepiride in combination with Metformin in type 2 diabetes mellitus patients.

METHODS

Source of data

The present study was conducted at SRM medical College Hospital and Research centre. Potheri, Kancheepuram District in diabetic outpatient department. The study was approved by the Institutional Ethics Committee of SRM MCH and RC.

Period of study was from January 2013 to January 2014.

Inclusion criteria

- Patients with Type 2 Diabetes Mellitus
- Both male and female of age group 20-65 years
- HbA1c level 6.5% to 8.5%
- Patients with elevated lipid profile but not on hypolipidemic drugs

Exclusion criteria

- Type 1 Diabetes Mellitus
- Pregnant and lactating females

Sample size calculation

The sample size was estimated by using hypothesis testing for two means of FPG and PPG (equal variances) based on the previous studies with the accuracy considered was 1% as α error, and power of 90% with sample size 40 was calculated in each group.

Body Mass Index (BMI)

BMI was calculated based on the formula for patients in all the three groups.

$$BMI = \frac{\text{Weight (kg)}}{\text{Height (m2)}}$$

Study design

The present study was a Prospective, Randomized Clinical trial and initiated after the approval of Institutional Ethics Committee. Written informed consent was obtained from the patients in English and local language. The patients receiving antidiabetic drugs were divided into three groups. Patients received Metformin with Sitagliptin were grouped as I, Metformin with Voglibose were named as Group II and Metformin with Glimepiride were marked as Group III (Table 1). Based on the inclusion and exclusion criteria, in each group, 40 patients were assigned as per simple randomization method. The level of lipid profile and BMI was evaluated at the end of 6 months.

Table 1: Study groups.

Group	Drug	Frequency
Group I	Sitagliptin 50 mg and Metformin 500 mg	Morning once daily- after food
Group II	Voglibose 0.2 mg and Metformin 500 mg	Morning once daily- along with food
Group III	Glimepride 1 mg and Metformin 500 mg	Morning once daily- half an hour before food

Statistical methods

Statistical analysis was done using the Statistical Package for the Social Sciences (SPSS) version 17. Results were presented as Mean±Standard Error Mean.

p value <0.05, indicates - significant (95%), p value <0.01, indicates- moderately significant (99%), p value <0.001, means- highly significant (99.9%). Paired Student T test was used to find the significance of study parameters in the three groups (Intra group analysis). Multiple comparisons were done in between groups at the end of the 6th month using Analysis of variance (ANOVA).

RESULTS

The present study compared the hypolipidemic effects of Sitagliptin, Voglibose, and Glimepiride in combination with Metformin in type 2 diabetes mellitus patients. With reference to the impact of TC value with the three Groups, significant reduction was seen in Group II and III with p value of 0.001 and 0.006 respectively. There was increased level of HDL in Group I which had a p value of 0.039 and subsequently Group II and III did not show any remarkable changes. The level of TG were not reduced significantly in Group I and II, but in Group III, a considerable reduction was seen with p value 0.043. LDL was significantly reduced in Group III with the p value 0.020, but no major change was observed in Group I and II. The level of VLDL was significantly reduced in Group III with the p value 0.052, but no changes was seen in Group I and II (Table 2). On multiple comparisons, Group III showed higher efficacy in reducing TC, TG, LDL-C and VLDL-C levels (Table 3). The effect on BMI in all groups were insignificant (Table 4).

Table: 2. Comparison of lipid profile parameters in the three groups.

Groups	Total cholesterol (mg/dl)			HDL (mg/dl)			Triglyceride (mg/dl)			LDL (mg/dl)			VLDL (mg/dl)		
	Pre treatment	Post treatment	P value	Pre treatment	Post treatment	P value	Pre treatment	Post treatment	P value	Pre treatment	Post treatment	P value	Pre treatment	Post treatment	P value
Group- I Metformin with Sitagliptin n=40	172.1 ±7.32	156.00±12.75	0.088 NS	35.36 ±3.59	51.55±6.33	0.039*	169.1±28.62	152.64±13.62	0.530 NS	96.91±9.11	93.00±12.90	0.746 NS	33.83±2.02	31.54±1.49	0.306 NS
Group- II Metformin with Voglibose n=40	183.07 ±6.47	158.64±7.84	0.001#	37.93±1.12	39.07±1.69	0.431NS	213.79±33.02	181.07±41.96	0.172 NS	109.43±6.35	93.50±8.04	0.076 NS	42.76±1.89	38.98±1.15	0.087 NS
Group- III Metformin with Glimepiride n=40	170.82±10.31	120.36±9.163	0.006#	38.80±1.33	41.73±2.89	0.339NS	175.73±29.85	104.18±10.29	0.043*	95.55±8.41	60.55±7.67	0.020*	35.15±2.03	26.46±0.92	0.052*

Data are expressed as Mean±Standard Error Mean. * P value < 0.05, # P value <0.001, NS- Non Significant

Table: 3. Multiple comparison of BMI and lipid profile parameters in the post treatment groups.

Groups	BMI	TC	HDL	TG	LDL	VLDL
Group- I Metformin with Sitagliptin n = 40	26.433±0.721	156.00±12.75	51.55±6.33	152.64±13.62	93.00±12.90	31.54±1.49
Group- II Metformin with Voglibose n = 40	26.109±0.660	158.64±7.84	39.07±1.69	181.07±41.96	93.50±8.04	38.98±1.15
Group- III Metformin with Glimepiride n = 40	26.447±0.750	120.36*±9.163	41.73±2.89	104.18*±10.29	60.55*±7.67	26.46*±0.92

Data are expressed as Mean ± Standard Error Mean. *p value <0.05

Table 4: Comparison body mass index in the three groups.

Groups	Body Mass Index		
	Pre treatment	Post treatment	P Value
Group- I Metformin with Sitagliptin n = 40	26.724±0.681	26.433±0.721	0.119 NS
Group- II Metformin with Voglibose n = 40	26.334±0.657	26.109±0.660	0.089 NS
Group- III Metformin with Glimepiride n = 40	26.601±0.763	26.447±0.750	0.229 NS

Data are expressed as Mean ± Standard Error Mean. *p value <0.05

DISCUSSION

Dyslipidemia is an important risk factor for the development of coronary artery disease in Type 2 Diabetes. Relationship between LDL-C and the incidence of cardiovascular events are similar in individuals with and without diabetes mellitus. Adequate control of diabetes will improve the dyslipidemia. In the present study, the subjects were not on hypolipidemic drugs but there was a reduction in the lipid levels after the anti-diabetic drugs. Takami K et al, observed that, there was a significant reduction of TC and TG by Voglibose.[13] Ingle PV et al, reported that, the combination treatment of Metformin with Glimepiride was more effective in improving lipid profile in Type 2 Diabetes than Metformin with Glibenclamide.[14] Najim HD et al, proved that, Metformin as monotherapy and combination with Glimepiride reduced TC, LDL-C with increase HDL-C level and non-significant reduction in TG levels.[15] Monami M et al, did a meta-analysis study and reported that DPP-4 inhibitors, Acarbose and Pioglitazone seem to have a more favourable effect on the lipid profile than sulfonylureas.[16] In the present study, there was a significant reduction in the TC of Group II and Group III (p value- <0.001, <0.006), but Group I did not show any significant reduction (Table 2). Shigematsu et al, described that, Sitagliptin increases HDL-C level.[17] Najim HD et al, reported that, Glimepiride with Metformin increases the HDL-C level.[15] In the present study, the Group I showed significant elevation of HDL-C level with the p value of <0.03 but the effect on HDL-C of other two groups were insignificant (Table 2). Hadeel Delman Najim et al. reported that, Glimepiride with Metformin showed reduction of TG level which was statistically insignificant.[15] Kazuya Shinozaki et al, stated that, Voglibose showed a significant reduction of TG even in non-diabetic individuals.[18] The reduction in TC and TG by Voglibose and reduced glycemic excursions were noted by Kazunari Matsumoto, MD et al.[19] In the present study, Group III showed significant reduction of TG level with the p value of <0.04 but in Group I and II reduction of TG were insignificant (Table2). Najim HD et al, found that, Glimepiride with Metformin reduced the LDL-C level.[15] In the present study, Group III showed significant reduction of LDL-C level with the p value of <0.02. Najim HD et al, reported that Glimepiride with Metformin showed insignificant changes in VLDL-C levels.[15] In the present study, Group III showed significant reduction of VLDL-C level with the p value of <0.05. The remaining two groups did not show any significant reduction . There was higher efficacy seen in Group III in the reduction of TC, TG, LDL-C and VLDL levels on multiple comparisons (Table 3). In a Korean study by Jung SH et al, Voglibose showed effective weight reduction when compared with Glimepiride.[20] Negishi M et al, described in their study that Voglibose prevented increase in body weight, which was induced by Pioglitazone in Type 2 Diabetes patients.[21] Similarly, in this study, there was a minimal BMI reduction seen in Metformin with Voglibose (Group II) among the three groups with the p value <0.08. But it was not statistically significant (Table 4).

CONCLUSION

The relationship between diabetes and dyslipidemia is still not clearly understood. The prevalence of cardiovascular disease has been increasing in diabetes. Adequate control of diabetes mellitus will improve the dyslipidemia and its complications. So, the role of the treating physician should have the knowledge to choose the oral hypoglycemic agent having the dyslipidemic effects too. The results of the present study were analysed and it could be concluded as Metformin with Glimepiride combination (Group III) showed significant reduction of TC, TG, LDL-C and VLDL-C levels.

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