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Research Article

Comparative evaluation of voglibose versus pioglitazone on glycaemic control and lipid profile in patients of type 2 diabetes mellitus on glimepiride and metformin in punjabi population

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ABSTRACT

Background: Type 2 Diabetes mellitus (DM) is a heterogeneous group of disorders associated with both microvascular and macrovascular complications. Due to progressive nature of type 2 DM, dual / triple drug therapy produce additive effects, less side effects and allows the use of submaximal doses of individual agents. Therefore, the present study was designed to study the effect of voglibose in comparison to pioglitazone on glycaemic and lipid profile as an add-on drug in patients with DM whose glycaemic status was uncontrolled with glimepiride and metformin.
Methods: The present study was open, randomized parallel group comparison of two active treatment groups over a six months period. Sixty patients of either sex in the age group of 30-75 years, suffering from type 2 DM, with FBG> 126 mg/dl and HbA1c between 7- 10 % were selected at random. The effect of voglibose and pioglitazone were observed on various parameters i.e. FBG, PPBG, HbA1c and lipid profile (Total cholesterol, TG, LDL, VLDL).
Results: At the end of 6 months it was observed that though both pioglitazone and voglibose reduced FBG, PPBG and HbA_{1C} significantly but pioglitazone caused a significantly greater percentage change in FBG as well as in PPBG whereas the difference in mean percentage change in HbA_{1C} was not significant. Also, fall in total cholesterol, TG, LDL and VLDL was significantly greater with pioglitazone than voglibose. Few side effects were observed with voglibose and not with pioglitazone.
Conclusions: Though pioglitazone and voglibose were equally effective in lowering HbA_{1C} levels yet pioglitazone showed better results in improving FBG, PPBG and lipid profile as compared to voglibose. Pioglitazone had minimal side effects as compared to voglibose.

Keywords: Diabetes mellitus, Voglibose, Pioglitazone

INTRODUCTION

Diabetes mellitus (DM) is one of the most common non - communicable diseases globally. The prevalence of diabetes is steadily increasing worldwide, particularly in the developing countries like India.[1] India had 40.9 million diabetics in 2006 and it is expected to increase to 69.9 million by 2025.[2] The incidence of diabetes in urban punjab is on the rise and the number of diabetics is increasing year by year.[3] The predominant clinical form of DM is Type 2 DM which accounts for more than 90 % of all cases.[4] Its association with developing complications severely alters the quality of life and imposes an enormous burden on health care system.

The key management goals in Type 2 DM are the relief of acute symptoms and prevention of long term complications, whilst avoiding hypoglycaemia. The relationship between the degree of glycaemic control and microvascular complications in Type 2 DM is well established. Aggressive, tight control of serum glucose reduces risk of microvascular disease. However, for prevention of macrovascular disease improving glycaemic control is necessary but not sufficient.[5]

According to UKPDS 38[6], treating other risk factors like dyslipidemia and hypertension have been shown to be effective in reducing macrovascular disease.[7]

Dietary and lifestyle modifications form the mainstay of therapy for Type 2 DM.[8] Pharmacological therapy is advocated when treatment goals are not achieved with lifestyle modifications. Several oral antihyperglycaemic agents are available to optimize the management of Type 2 DM. Based on their mechanism of action, they are subdivided into agents that increase insulin secretion like sulfonylureas, meglitinides, GLP-1 agonists, DPP-4 inhibitors, reduce glucose production like biguanides, increase insulin sensitivity like thiazolidinediones and reduce carbohydrate absorption like α-glucosidase inhibitors.

Sulfonylureas have been in use since 1950s. They increase insulin levels acutely and thus should be taken shortly before a meal**.**[9] They require the presence of functioning ß cells for their action. Meglitinides are non sulfonylurea insulin secretagogues. They are relatively rapidly acting agents helps in reducing postprandial hyperglycaemia.[10]

Metformin acts by decreasing hepatic glucose production and increasing sensitivity of peripheral tissues to insulin. It improves glycaemic control and has been shown to lower both total and LDL cholesterol and serum TG in Type 2 DM.[11]

Pioglitazone is an insulin sensitizer which acts by improving insulin sensitivity at the cellular level. It reduces insulin resistance by binding to PPAR γ which results in change of expression of genes involved in regulating glucose and lipid metabolism, insulin signal transduction and other tissue differentiation.

Voglibose is a competitive inhibitor of α- glucosidase enzyme present in brush border of small intestine. It inhibits the cleavage of complex carbohydrates into simple sugars and inhibits their absorption from small intestine.

Although all the oral antidiabetic agents are reasonably effective as monotherapy in improving glycaemic control but due to progressive nature of type 2 DM, monotherapy is often associated with inadequate control of glycaemia and loss of efficacy over time**.**[12] Combining agents with different modes of action produce additive effects on glycaemic control, allows the use of submaximal doses of the agents, thereby decreasing the unwanted side effects and have complementary benefits on cardiovascular risk factors.[13,14]

Therefore, the present study was designed to study the effect of voglibose on glycaemic and lipid profile as an add-on drug (agent) in patients with DM whose glycaemic status was uncontrolled with glimepiride 2 mg BD and metformin 500 mg BD and also to compare the efficacy and tolerability of voglibose with pioglitazone which was also used as a third agent in patients with DM whose glycaemic status was uncontrolled with above two antihyperglycaemic drugs.

METHODS

Study design and settings:

The present study was open, randomized parallel study evaluating the comparative effect of voglibose and pioglitazone in combination with sulfonylurea (glimepiride 2 mg BD) and biguanide (metformin 500 mg BD) on glycaemic and lipid profile in diabetic patients over a period of six months in medicine outpatient department of tertiary care hospital of Amritsar. The study was conducted after obtaining approval from institutional ethical committee and was conducted from January 2010 to December 2010. Written informed consent was obtained from all the patients prior to their enrollment.

Flow of the participants through the study including randomization, medications and drop outs are shown in figure 1.

Inclusion criteria:

Previously diagnosed type 2 diabetes mellitus (DM) patients in the age group of 30-75 years of either sex, on sulfonylurea (glimepiride 2 mg BD) and biguanide (metformin 500 mg BD) for at least one year and whose FBG >126 mg/dl, PPBG >200 mg/dl and HbA_{1C} between 7-10%.

Exclusion criteria:

Patients with history of Type 1 DM, with acute medical emergencies like diabetic ketoacidosis, renal failure, liver failure, cardiac failure, any microvascular complication, who are likely to undergo surgery during the study period, with history of laparotomy and ileus, with chronic intestinal disease, with history of hypersensitivity to the test drug, pregnant and lactating women were excluded from the study.

Intervention drugs:

After meeting the inclusion criteria, patients were randomized into two groups of 30 each on the basis of additional anti hyperglycaemic drugs to be given. To group 1, Tab. Voglibose 0.2 mg TDS orally was given for 6 months and to group 2, Tab. Pioglitazone 15 mg BD orally for 6 months was given and the patients were directly started at this dose. To check compliance and ensure regular medication by the patient, a log book was checked regularly which was given to each patient.

On the start of the study, (Day 0), after taking the history of the patients and doing the clinical examination, routine investigations were sent. The baseline FBG, PPBG, HbA_{1C} and lipid profile were obtained after 12 hour overnight fasting. Patients were given a 15 day supply of either drug with proper directions and asked to report back after 15 days. Initially patients were followed after 15 days and subsequently every month up to 6 months. FBG and PPBG were recorded monthly while HbA_{1C}, lipid profile, SGOT/SGPT and serum creatinine levels were recorded at 3 months intervals.

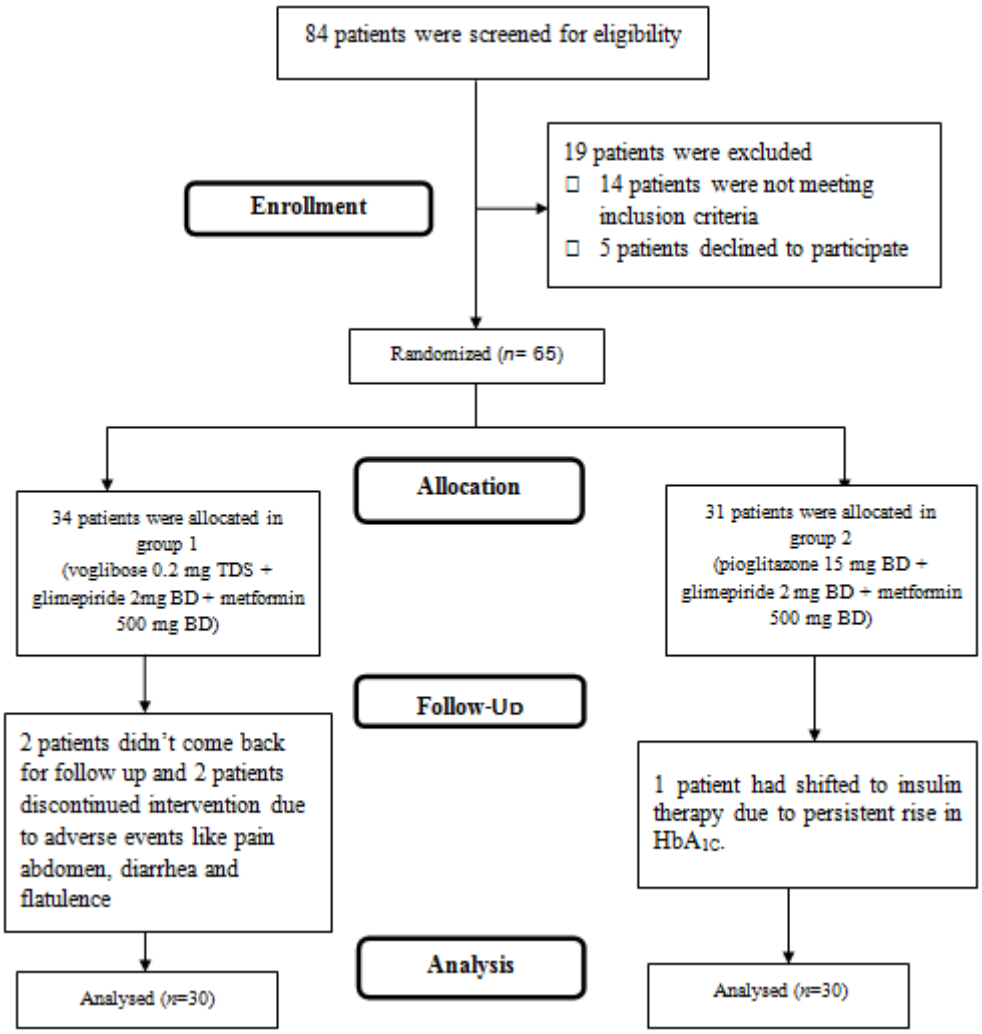

Figure 1: Flow chart of the participants.

Sample size estimation:

Sample size was calculated from the results of initial pilot study (5 in each group) done before starting the trial, formula for comparison of two sample means of PPBG values.

$$n = \frac{2\,(Z\alpha + Z\beta)^2\sigma^2}{\delta^2}$$

$$n = \frac{2\,(1.96 + 1.282)^2(1.8)^2}{(1.6)^2} = 26.60 \sim 27$$

n ~ 27 (in each group)

Where,
Type I error (α) = 0.05, Type II error (β) = 0.20,
Power= (1-β) = 0.80
n = sample size
Zα= 1.96 (at 95% level of confidence)
Zβ= 1.282 (for Power= 0.80)

Statistical analysis:

The results were tabulated as mean ± standard deviation (SD) and analyzed using student's t test. The level of significance was determined as its '*p*' value with $p > 0.05$ taken as not significant, $p < 0.05$ taken as significant at 5% significance level, $p < 0.01$ taken as significant at 1% significance level and $p < 0.001$ taken as highly significant. ITT analysis was not done despite drop outs. Because 4 drops outs happened within 1st month with no readings available and only 1 drop out was there after 1 month. So drop outs were not considered in the analysis.

RESULTS

Sixty patients (35 females and 25 males) who were randomized (by random number tables) and completed the study were included in the analysis.

In both the groups, maximum number of patients was in the age group of >60-70 years and least number of patients were within 30-40 years of age. Mean age in

group 1 was 56.43 ± 8.49 and in group 2 was 55.37 ± 11.40. There was no statistically significant difference in age distribution between the two groups.

Body mass index (BMI) of patients indicates that majority of the patients (14 patients in group 1 and 16 patients in group 2) were in the overweight range (25-29.9 kg/m^2) in both the groups and few (4 patients in group 1 and 4 patients in group 2) were in obese (> 30 kg/m^2) category. No obvious changes in the BMI were observed after 6 months of treatment in both the groups.

FBG and PPBG levels during treatment with voglibose and pioglitazone over a period of six months are shown in figure 2. Fasting blood glucose levels within both the groups showed significant reduction over a period of 6 months. But on comparison between group 1 versus group 2 patients, there was a significant difference in mean percentage change in FBG levels at the end of 1st month ($p< 0.05$) and this difference was highly significant at 2nd, 3rd, 4th, 5th and 6th month of study period (Table 1, $p< 0.001$).

Table 1: Percentage change in fasting blood glucose and postprandial blood glucose (mean ± SD in mg/dl) during treatment with voglibose and pioglitazone over six months period.

Duration	FBG			PPBG		
	Group 1 (*n*=30)	Group 2 (*n*=30)	*p* value	Group 1 (*n*=30)	Group 2 (*n*=30)	*p* value
0-1 Month	5.68 ± 3.41	7.44 ± 3.07	0.041	15.52 ± 5.06	20.70 ± 8.52	0.006
0-2 Month	7.35 ± 3.69	14.78 ± 6.98	0.000	22.31 ± 7.44	28.55 ± 8.15	0.003
0-3 Month	8.68 ± 4.44	19.34 ± 7.66	0.000	26.81 ± 7.49	33.26 ± 9.24	0.004
0-4 Month	9.90 ± 5.08	23.29 ± 8.35	0.000	30.07 ± 7.28	37.48 ± 8.78	0.001
0-5 Month	10.84 ± 5.01	26.36 ± 8.81	0.000	32.33 ± 7.29	39.92 ± 8.21	0.000
0-6 Month	12.55 ± 5.73	29.15 ± 9.59	0.000	35.35 ± 6.89	42.54 ± 8.31	0.001

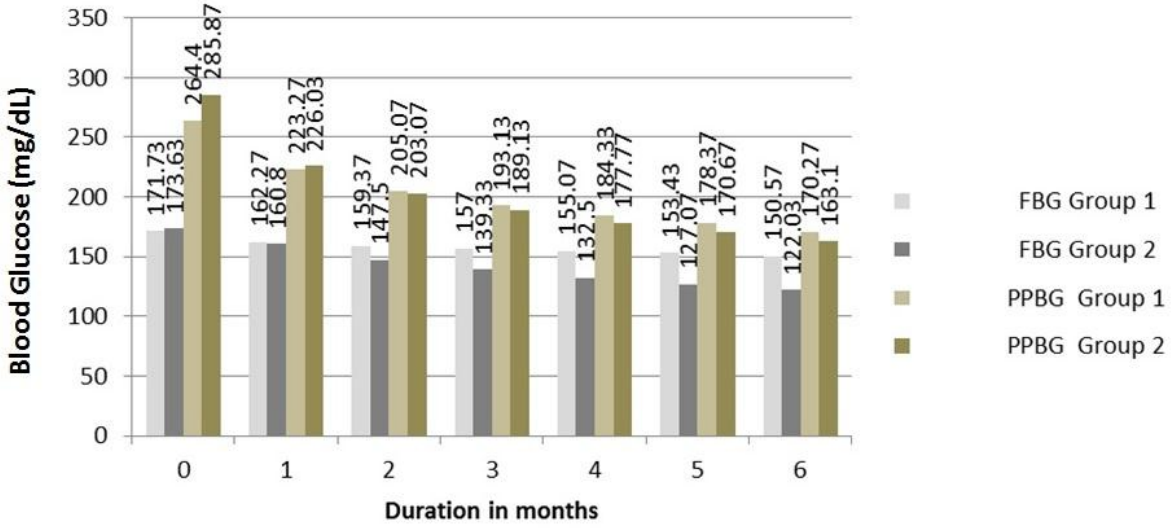

Figure 2: FBG and PPBG levels during treatment with voglibose and pioglitazone over a period of six months.

Table 2: Percentage change in glycosylated haemoglobin (mean ± SD in %) during treatment with voglibose and pioglitazone over six months period.

Duration	Group 1 (*n*=30)	Group 2 (*n*=30)	*p* value
0-3 Month	12.84 ± 4.72	11.86 ± 4.95	0.432
0-6 month	21.47 ± 4.80	21.57 ± 3.79	0.933

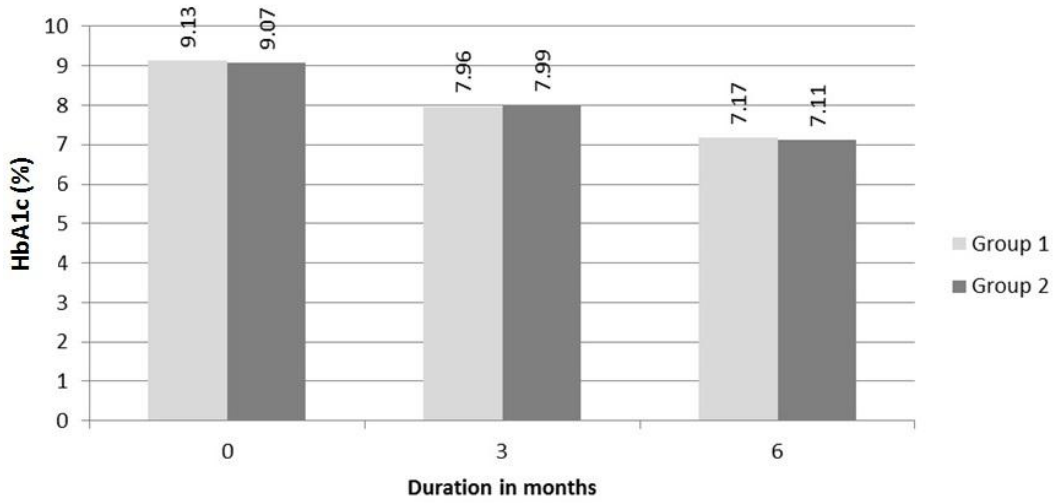

Figure 3: Glycosylated hemoglobin levels (HbA1c) during treatment with voglibose and pioglitazone over a period of six months.

Table 3: Percentage change in serum total cholesterol, triglycerides, LDL, VLDL and HDL during treatment (mean ± SD in mg/dl) with voglibose and pioglitazone over six months period.

Parameters	Duration	Group 1 (*n*=30)	Group 2 (*n*=30)	*p* value
TC	0-3Month	2.33 ± 4.95	5.77 ± 5.80	0.016
	0-6 Month	3.42 ± 6.34	10.52 ± 7.08	0.000
TG	0-3Month	4.39 ± 7.62	9.74 ± 6.00	0.004
	0-6 Month	5.23 ± 8.49	15.83 ± 6.83	0.000
LDL	0-3Month	1.57 ± 1.40	3.19 ± 2.10	0.001
	0-6 Month	2.49 ± 2.19	5.50 ± 2.95	0.000
VLDL	0-3Month	1.95 ± 2.99	5.06 ± 31.00	0.586
	0-6 Month	3.01 ± 4.68	10.35 ± 7.27	0.000
HDL	0-3Month	2.2 ± 3.12	8.03 ± 7.33	0.000
	0-6 Month	2.13 ± 4.32	13.28 ± 11.09	0.000

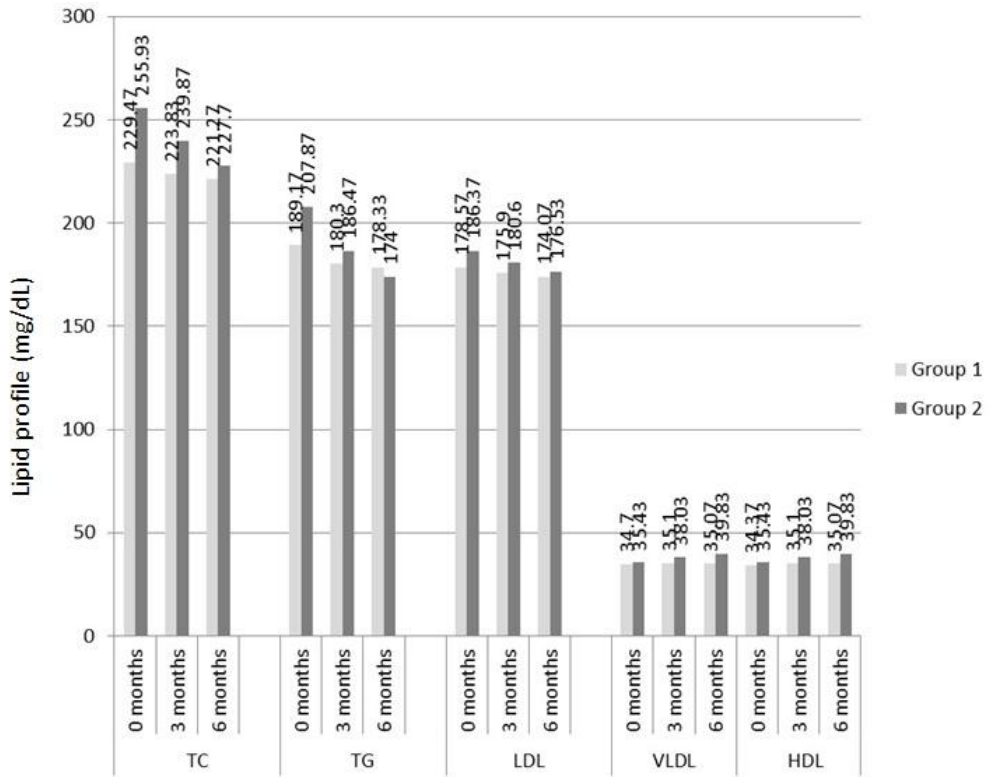

Figure 4: Serum total cholesterol (TC), TG, LDL, VLDL and HDL levels during treatment with voglibose and pioglitazone over a period of six months.

Postprandial blood glucose levels within both the groups showed significant reduction over a period of 6 months. On comparison between group 1 versus group 2 patients, a significant difference in mean percentage change in PPBG levels was observed at the end of 1st, 2nd and 3rd month ($p< 0.05$) and a highly significant difference was observed at the end of 4th, 5th and 6th month (Table 1, $p< 0.001$).

HbA1c levels during treatment with voglibose and pioglitazone over a period of six months are shown in figure 3. HbA1c levels within both the groups showed significant reduction over a period of 6 months. But on comparison between group 1 versus group 2 patients, there was no significant difference in mean percentage change in HbA_{1C} at the end of 3rd and 6th month of study period (Table 2, $p> 0.05$).

Serum total cholesterol (TC), TG, LDL, VLDL and HDL levels during treatment with voglibose and pioglitazone over a period of six months are shown in figure 4. Serum total cholesterol within both the groups showed a significant reduction over a period of 6 months. On comparison between group 1 versus group 2 patients, there was a significant difference in mean percentage change in serum total cholesterol at the end of 3rd month ($p< 0.05$) whereas at the end of 6th month this difference was highly significant (Table 3, $p< 0.001$).

Serum triglycerides within both the groups showed significant reduction over a period of 6 months. On comparison between group 1 versus group 2 patients, there was a significant difference in mean percentage change in serum triglycerides at the end of 3rd month ($p< 0.05$) and a highly significant difference at the end of 6th month of study period (Table 3, $p< 0.001$).

Serum LDL within both the groups showed significant reduction over a period of 6 months. On comparison between the patients of group 1 versus group 2, there was a highly significant difference in mean percentage change in serum LDL levels at the end of 3rd and 6th month of study period (Table 3, $p< 0.001$).

Serum VLDL within both the groups showed significant reduction over a period of 6 months. On comparison between the patients of group 1 versus group 2, there was no significant difference in mean percentage change in serum VLDL levels at the end of 3rd month ($p> 0.05$) but the difference was highly significant at the end of 6th month of study period (Table 3, $p< 0.001$).

There was no significant difference in mean percentage change in serum SGOT/ SGPT and serum creatinine levels between the patients of group 1 versus group 2, at the end of 3rd and 6th month of study period ($p< 0.001$).

DISCUSSION

Diabetes mellitus is a group of a metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both. The management of DM includes diet control, exercise and pharmacological therapy. The drug therapy is generally initiated either with sulfonylurea or metformin as monotherapy. In the present study 60 patients of DM whose glycaemic status was not controlled with two oral hypoglycaemic agents (metformin and glimepiride) were given third drug voglibose or pioglitazone in group 1 and group 2 respectively. The effect of add on therapy with voglibose or pioglitazone as a third agent was observed on various parameters.

Among the clinical parameters, the BMI of majority of the patients included for the study has been found to be 25- 29.9 kg/m^2 designated as overweight. There was no significant change observed in BMI at the end of study period in different groups. This is in accordance with the previous studies.[15,16] There was no significant change in body weight in both groups throughout the study period.

A significant reduction in FBG and PPBG was found with both voglibose and pioglitazone. The reduction in FBG and PPBG was observed in chronological sequence commiserating with duration of study i.e. at 1st, 2nd, 3rd, 4th, 5th and 6th months. But on comparison, combination of pioglitazone with glimepiride and metformin resulted in greater reduction in FBG as well as PPBG as compared to combination of voglibose with glimepiride and metformin.

With both pioglitazone and voglibose, a significant reduction occurred in HbA1c commiserating with period of observation i.e. at the end of 3rd and 6th month. But on comparison, no statistical significant difference was observed.

Similarly Roberts *et al*[17] reported a significant reduction in FBG and HbA1c with triple drug combination of metformin, glimepiride and pioglitazone. Derosa *et al*[18] also observed significant reduction in FBG, PPBG and HbA1c with combination of sulfonylurea, metformin and acarbose.

Addition of voglibose or pioglitazone has been reported to have an influence on serum lipids. i.e. TC, TG, LDL and VLDL and these were reduced significantly with both voglibose and pioglitazone. The reduction in these parameters was commensurating with period of observation i.e. 3rd and 6th month with both drugs. On comparison, addition of pioglitazone resulted in greater reduction in TC, TG and LDL than addition of voglibose at the end of 3rd and 6th month of study. However, reduction in VLDL was equal with drugs at 3rd month of observation but at 6th month, the reduction in VLDL was greater with pioglitazone than with voglibose.

Various studies reported significant reduction in TC, TG and LDL with pioglitazone[19-21] and increase in HDL.[19] Reports regarding voglibose on lipids are contrary. In the study conducted by Mughal *et al*[22], there was significant reduction in TG and VLDL but there was no significant effect on TC and LDL with voglibose. Voglibose has been reported to cause increase in TC and LDL and decrease in HDL in type 2 diabetic patients by Iwamoto *et al.*[23]

Among the side effects, weakness was observed with both the drugs whereas pain abdomen, headache, diarrhea, flatulence, sweating and hot flushes were observed only with voglibose and not with pioglitazone, thereby showing that pioglitazone is a safer drug.

CONCLUSION

Though pioglitazone and voglibose were equally effective in lowering HbA_{1C} levels yet pioglitazone showed better results in controlling glycaemic profile (FBG, PPBG) and lipid profile as compared to voglibose. Moreover, pioglitazone had minimal side effects as compared to voglibose.

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