Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

Medicine

Comparative Evaluation of Pioglitazone versus Voglibose on Lipid Profile in Patients with Type 2 Diabetes Mellitus Add On Metformin

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Original Research Article

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Article History
Received: 06.09.2018
Accepted: 17.09.2018
Published: 30.09.2018

DOI:
10.36347/sjams.2018.v06i09.044

Abstract: Type 2 Diabetes mellitus (Type 2 DM) is a heterogeneous group of disorders associated with both macrovascular and microvascular complications. Due to progressive nature of type 2 DM, dual drug therapy produces additive effects, allows the use of submaximal doses, and less side effects of individual agents. Therefore, the present study was designed to study the effect of pioglitazone in comparison to voglibose on Lipid profile control as an add-on drug in patients with Type 2 DM whose glycemic status was uncontrolled with metformin alone. The present study was open, randomized parallel group comparison of two active treatment groups over a period of six months. Sixty-seven patients of either sex in the age group of 30-60 years, suffering from type 2 DM, with FBG ≥ 126 mg/dl and PPBG ≥ 200 mg/dl as per ADA were selected at randomly. The effect of pioglitazone and voglibose were observed on various parameters of Lipid Profile (Total cholesterol, TG, HDL, LDL, VLDL). At the end of 6 months it was observed that though both pioglitazone and voglibose reduced Lipid levels significantly but pioglitazone caused a significantly greater percentage change in Lipid levels as compared with voglibose. Few side effects were observed with voglibose and not with pioglitazone. Though pioglitazone and voglibose were equally effective in lowering Lipid levels yet pioglitazone showed better results in improving dyslipidemia, as compared to voglibose. Pioglitazone had minimal side effects as compared to voglibose.

Keywords: Diabetes mellitus, Voglibose, Pioglitazone.

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM is associated with abnormalities in carbohydrates, fats and protein metabolism [1]. Symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. The chronic hyperglycemia of diabetes is accompanied with long-term damage, dysfunction, and failure of various organs, especially the kidneys, eyes, nerves, heart, and blood vessels. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome [2].

Worldwide, 3.2 million deaths are attributable to diabetes every year. One in 20 deaths is attributable to diabetes; 8700 deaths every day; six deaths every minute. At least one in ten deaths among adults between 35 and 64 years is attributable to diabetes [3]. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease [4,5]. Estimates of global diabetes prevalence predicts, 6.4% in 2010 affecting 285 million adults and will increase to 7.7% and 439 million adults by 2030[6].

Pioglitazone, insulin-sensitizing Thiazolidinediones, is widely used for the treatment of type 2 diabetes. Thiazolidinediones are known to activate peroxisome proliferator-activated Receptor- γ (PPAR- γ) which are ligand activated transcription factors which belong to the nuclear receptor superfamily [7]. PPAR- γ activation by pioglitazone lead to increases insulin sensitivity in liver, fat and skeletal muscle cells, increases peripheral and splanchnic glucose uptake and decreases hepatic glucose output [8]. Pioglitazone is dependent on the presence of insulin in order to exert its beneficial effects and may help preserve β-cells of the islets of Langerhans, but does not act as an insulin secretagogue [9]. Pioglitazone promotes lipid storage and redistribution from visceral to subcutaneous deposits, resulting in an increase in whole body adiposity, while promoting the differentiation of adipocytes [10].

Voglibose is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with type-2 DM. It reduces intestinal absorption of starch, dextrin, and disaccharides by inhibiting the action of α-glucosidase in the intestinal brush border. Inhibition of this enzyme catalyzes the decomposition of disaccharides into monosaccharides and slows the digestion and absorption of carbohydrates. α - Glucosidase inhibitors do not stimulate insulin release and therefore do not result in hypoglycemia. Voglibose is most effective α - glucosidase inhibitor among its class [11,12].

Metformin, a biguanide class of oral hypoglycemic agents, is the first line drug for the treatment of type 2 diabetes mellitus [13]. Metformin is used clinically for the treatment of obesity and diabetes, and its mechanism of actions include the following: (1) lowers plasma glucose levels by inhibiting gluconeogenesis in liver (2) decreasing the intestinal absorption of glucose, and (3) improving insulin sensitivity by increasing peripheral glucose uptake and utilization [14]. Additionally, metformin has a variety of pleiotropic effects including improved lipid and cholesterol metabolism, decreased inflammation and inhibition of cell growth [15]. (4) Increases plasma levels of glucagon-like peptide 1 (GLP-1) is a member of the incretin family of peptide hormones release incretin from the gut in response to ingested glucose. It induces insulin release from pancreatic β-cells, retards gastric emptying, inhibits glucagon release from α cell, and produces a feeling of satiety [16].

Clinically, it has been proposed that a combination of changes in lifestyle modification with pharmacological approaches could be a more effective strategy for the management of obesity with Type 2 DM. In addition, unlike their relatively lean counterparts, the obese with Type 2 DM patients require specific dosing for a curative response to treatment. On these lines, we hypothesized that weight control with diabetes interventions in conjunction with Metformin and Pioglitazone versus Metformin and Voglibose therapy could have a significant positive impact on the management of obesity with Type 2 DM. By implicating pharmacological and dietary interventions to contain adiposity, we have explored the therapeutic outcome of obese with Type 2 DM Patients.

Therefore, the prevention and improvement of obesity with Type 2 DM, particularly decrease of visceral fat is important in the control of these metabolic diseases. In the present study, we were targeted Type 2 DM subjects and confirmed the antiobesity effects of Metformin, where a reduction in the abdominal body fat area and body fat percent will be the primary outcome.

The primary end point of the study was to evaluate the efficacy and safety of two drugs combination (i.e. Metformin with Pioglitazone, Metformin with Voglibose) which group improves obese with Type 2 DM control compared with each other and its impact on dyslipidemia. We used six markers that are commonly used to evaluate dyslipidemia in obese with Type 2 DM:

MATERIALS AND METHODS

Study design and settings

The present study was Prospective, Randomized, Open-label, Single Center, and Parallel-group, evaluating comparative effect of Metformin and Pioglitazone combination versus Metformin and Voglibose combination on lipid profile in Type 2 diabetic patients over a period of six months in outpatient department of Medicine in MGM Hospitals and College, Aurangabad. The study was conducted after institutional ethical committee approval, informed consent regulations, as per Declaration of Helsinki, ICH good Clinical Practice (GCP) guidelines and the ICMR guidelines for Biomedical Research on Human Subjects, 2006.

Inclusion criteria

Patients with Type 2 DM diagnose according to American Diabetes association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-65 years of either sex, all patients provided written, vernacular, witnessed, informed consent to participate in the trial, Patients willing to take medications as directed & willing to come for the follow-ups.

Exclusion criteria

Patients with history of Type 1 DM, with acute medical emergencies like diabetic ketoacidosis, polycystic ovarian disease, liver disease, kidneys disease, cardiovascular disease, any microvascular complication, with chronic GIT disease, concomitant with steroid therapy and history of hypersensitivity to test drug, pregnant and lactating women also excluded from the study.

Intervention drugs

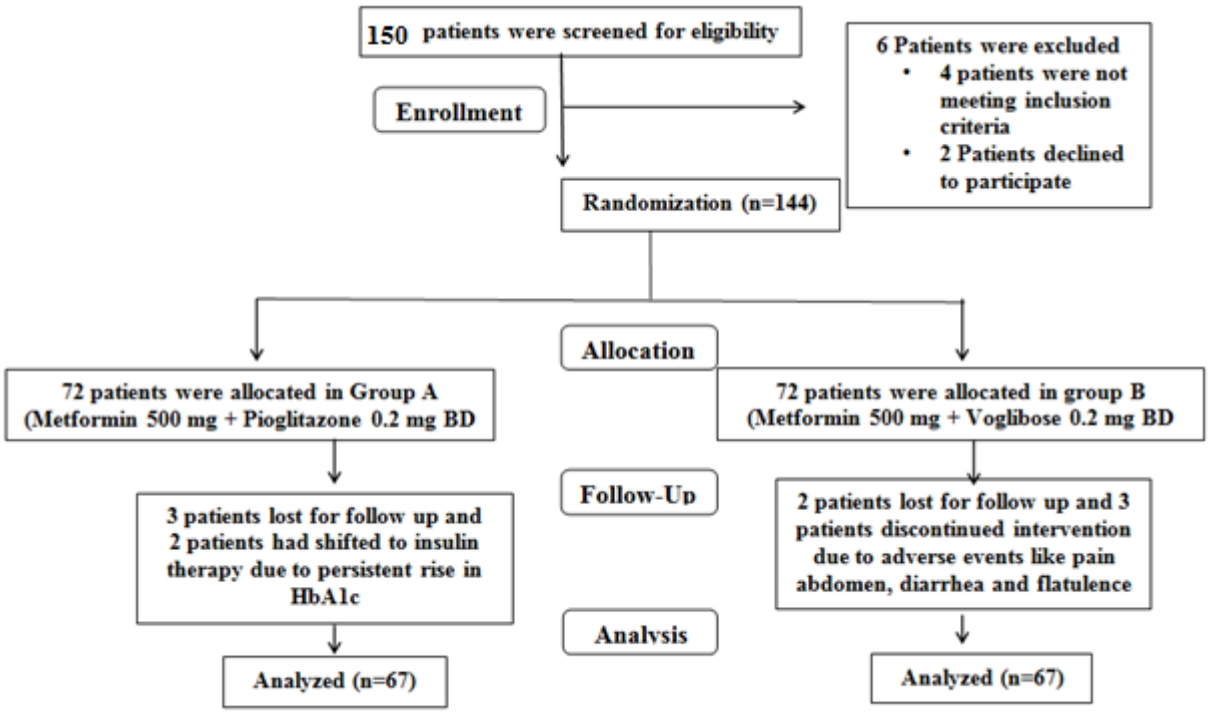
After meeting the inclusion criteria, patients were randomized by a computer generated randomization sequence into two groups, each consist of 67 patients. In group A: Tab. Metformin 500 mg + Tab. Pioglitazon 7.5 mg combination BD orally was given for 6 months and group B: Tab. Metformin 500 mg + Tab. Voglibose 0.2 mg combination 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 medical history, demographic details, physical

measures (waist circumference, body mass index (BMI)), general and systemic examination of the patients, routine laboratory investigations were sent. The baseline fasting Blood glucose (FBG), post-prandial blood glucose (PPBG), factors related to fasting lipid profile (Including Total Cholesterol (TC), Triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), Very low density lipoprotein (VLDL) were measured.

Patients were given a 15 days' 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 lipid profile was recorded at 3 and 6 months' intervals.

STUDY FLOW CHART



The participants through the study including randomization, medications and drop outs are shown in flow chart.

STATISTICAL ANALYSIS

The collected data was compiled in MS Excel sheet for analysis in Statistical Package for the Social Sciences (SPSS) version 20th was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram etc. Quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline and after three months' effect of Metformin and Pioglitazone Combination Versus Metformin and Voglibose combination in Type 2 DM patients. A paired't' test was applied and also quantitative data was represented in the form of bar diagram. The level of significance was determined as its '*p*' value with $p < 0.05$ was taken as significant at 5% significance level, $p < 0.01$ was taken as significant at 1% significance level and $p < 0.001$ was taken as highly significant, $p > 0.05$ was taken as insignificant. Drop outs were not considered in the analysis.

RESULTS

Total 150 patients with Type 2 DM were screened out of 144 eligible patients were randomized equally into two treatment groups who were randomized in the study. In group A: 5 patients and in group B: 5 patients were lost from trial. Both the groups were similar in demographic profile at baseline as shown in Figure 1.

In both the groups, maximum number of patients was in the age group of 51-60 years and least number of patients was within ≤40 years of age. Mean age in group A was 51.10 ± 6.62 and in group B was 52.29 ± 6.55. There was no statistically significant difference in age distribution between the two groups.

Table-1: Comparison of Mean Age in Groups

Age-Group	Group A[Met + Pio]		Group B[Met + Vog]	
	No	Percentage	No	Percentage
≤40 year	04	5.9%	02	2.9%
41--50	26	38.8%	26	38.8%
51--60	37	55.2%	39	58.2%
Total	67	100	67	100
Mean±SD	51.10±6.62 years		52.29±6.55 years	

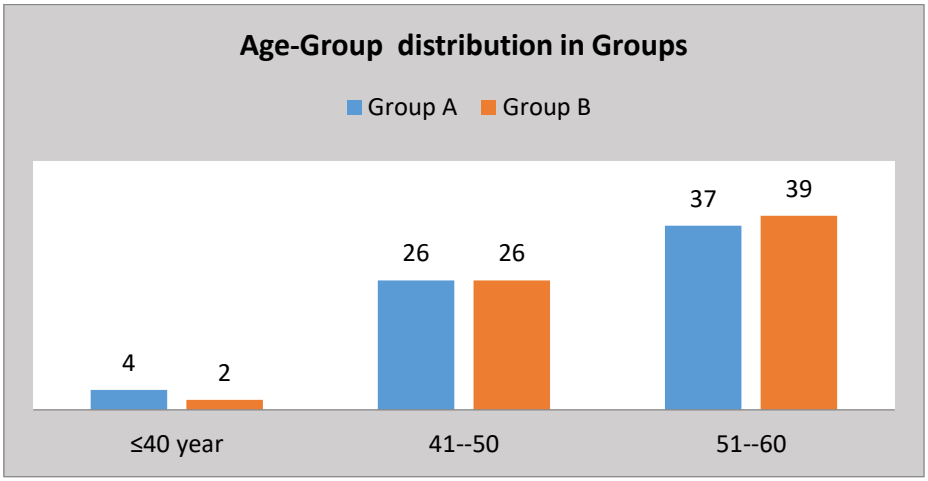


Fig-1: Distribution of Age-group in Group A and B

Table-2: Comparison of Mean Total Cholesterol level (mean ± SD in mg/dl) during treatment with Group A and Group B over six months' period

		Group A Mean±SD	Group B Mean±SD	t-value	p-value
Total Cholesterol	Baseline	237.58±19.37	236.31±18.58	0.387	P=0.700 NS
	After 3 Months	209.85±28.13	212.26±25.43	0.522	P=0.603 NS
	After 6 Months	164.88±14.53	204.79±23.71	11.74	P<0.0001 HS

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, S: Significant, HS: Highly Significant, Unpaired t-test.

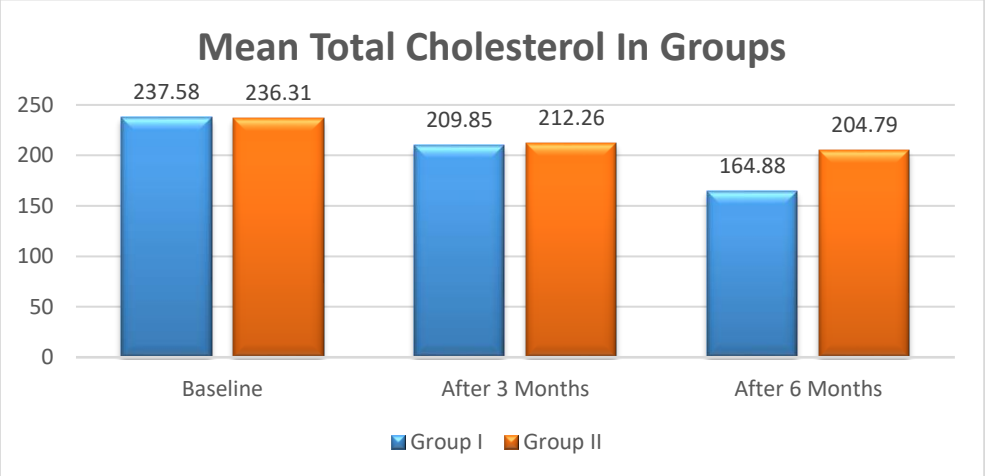


Fig-2: Comparison of Mean Total Cholesterol (mg/dl) during treatment with Group A and Group B over a period of six months

Serum total cholesterol (TC) levels during treatment with pioglitazone and voglibose over a period of six months are shown in Table 2 and Figure 2. Serum total cholesterol within both the groups showed a

significant reduction over a period of 6 months. On comparison between groups A versus group B 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 ($p< 0.001$).

Table-3: Comparison of Mean Difference Total Cholesterol level (mg/dl) in Group A and Group B

Total Cholesterol	Group A			Group B		
	Mean Difference	t-value	p-value	Mean Difference	t-value	p-value
Baseline vs After 3 Months	27.73	6.81	P<0.0001 S	24.05	5.41	P<0.0001 S
Baseline vs After 6 Months	72.70	23.96	P<0.0001 S	31.56	8.67	P<0.0001 S
After 3 Months vs After 6 Months	44.97	13.16	P<0.0001 S	7.65	3.45	P<0.0001 S

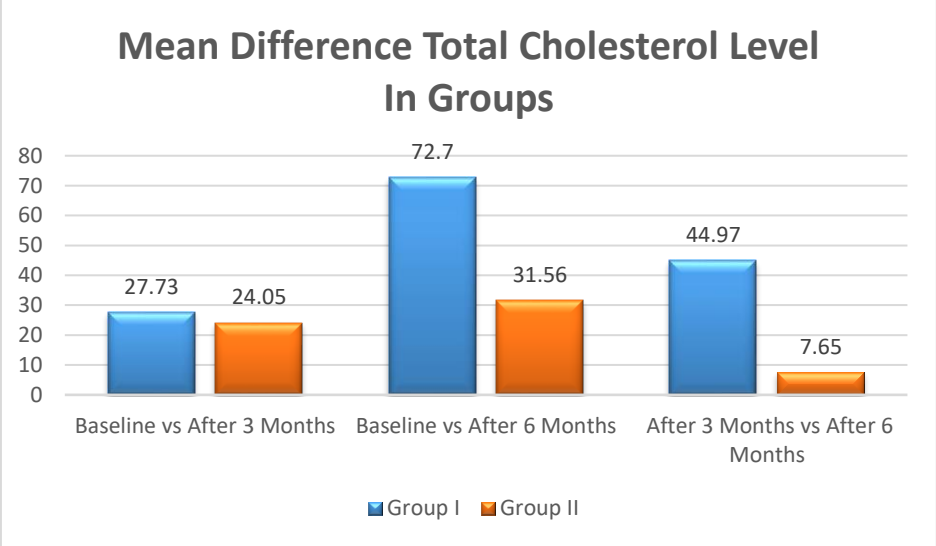


Fig-3: Comparison of Mean Difference Total Cholesterol (mg/dl) level during treatment with Group A and Group B

Table-4: Comparison of Mean Triglycerides levels (mean ± SD in mg/dl) during treatment with Group A and Group B over six months' period

		Group I Mean±SD	Group II Mean±SD	t-value	p-value
TG	Baseline	151.48±17.36	145.80±14.98	1.67	P=0.114 NS
	After 3 Months	137.25±13.37	139.67±12.92	1.06	P=0.289 NS
	After 6 Months	117.25±8.19	136.22±12.05	10.66	P<0.0001 HS

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, S: Significant, HS: Highly Significant, Unpaired t-test.

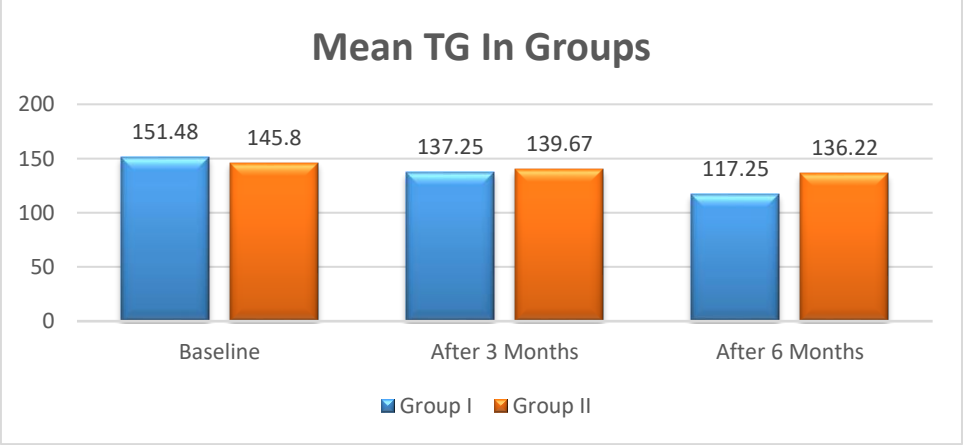


Fig-4: Comparison of Mean Triglycerides levels (mean ± SD in mg/dl) during treatment with Group A and Group B over a period of six months

Serum triglycerides levels during treatment with pioglitazone and voglibose over a period of six months are shown in Table 4 and Figure 4. Serum triglycerides within both the groups showed significant reduction over a period of 6 months. On comparison between group A versus group B 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 ($p< 0.001$).

Table-5: Comparison of Mean Difference Triglycerides levels (mg/dl) in Group A and Group B

TG	Group I			Group II		
	Mean Difference	t-value	p-value	Mean Difference	t-value	p-value
Baseline vs After 3 Months	14.22	5.57	P<0.0001 S	6.12	3.45	P<0.0001 S
Baseline vs After 6 Months	34.22	13.73	P<0.0001 S	9.58	4.56	P<0.0001 S
After 3 Months vs After 6 Months	20.00	10.62	P<0.0001 S	3.44	2.98	P=0.003 S

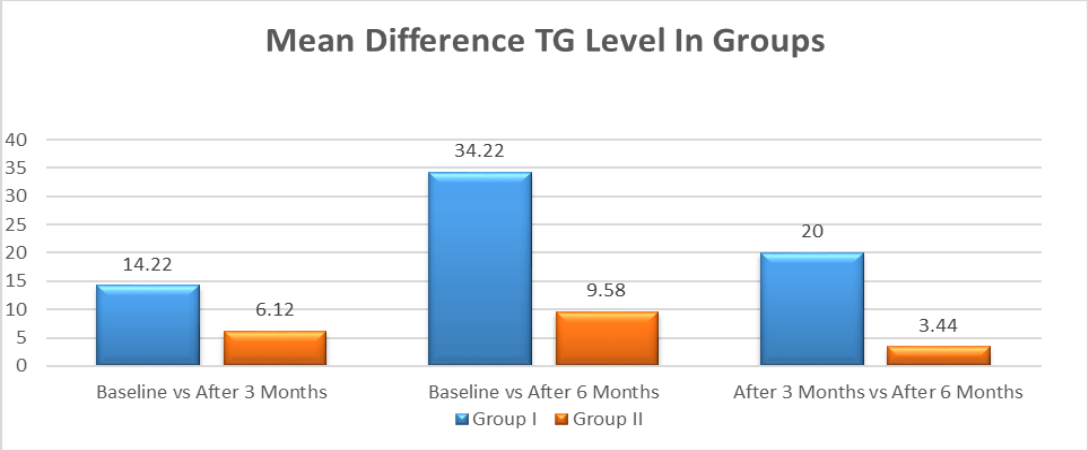


Fig-5: Comparison of Mean Difference Triglycerides (mg/dl) level during treatment with Group A and Group B:

Table-6: Comparison of Mean HDL (mean ± SD in mg/dl) level during treatment with Group A and Group B over six months' period

		Group A Mean±SD	Group B Mean±SD	t-value	p-value
HDL	Baseline	29.41±2.64	28.97±2.22	1.06	P=0.290 NS
	After 3 Months	37.46±3.85	35.29±3.45	3.42	P=0.001 S
	After 6 Months	43.54±3.53	37.49±2.60	3.49	P<0.0001 HS

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, S: Significant, HS: Highly Significant, Unpaired t-test.

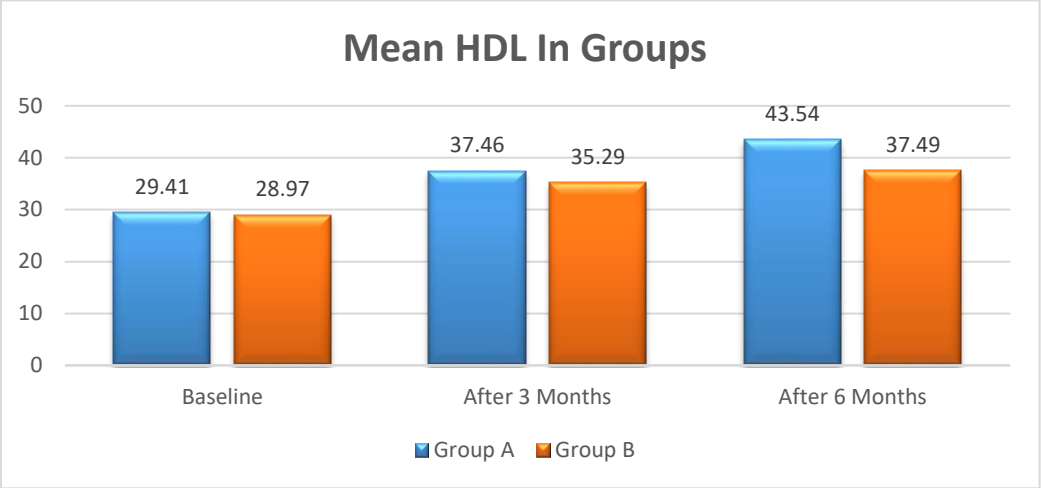


Fig-6: Comparison of Mean HDL (mg/dl) levels during treatment with Group A and Group B over a period of six months

HDL levels during treatment with pioglitazone and voglibose over a period of six months are shown in Table 6 and Figure 6. HDL within both the groups showed significant reduction over a period of 6 months. On comparison between groups A versus group B patients, there was a significant difference in mean percentage change in HDL at the end of 3rd month and a highly significant difference at the end of 6th month of study period ($p< 0.001$).

Table-7: Comparison of Mean Difference HDL levels (mg/dl) in Group A and Group B:

HDL	Group A			Group B		
	Mean Difference	t-value	p-value	Mean Difference	t-value	p-value
Baseline vs After 3 Months	8.04	15.07	P<0.0001 S	5.32	8.32	P<0.0001 S
Baseline vs After 6 Months	14.11	25.93	P<0.0001 S	8.53	12.31	P<0.0001 S
After 3 Months vs After 6 Months	6.07	9.27	P<0.0001 S	2.20	2.27	P=0.004 S

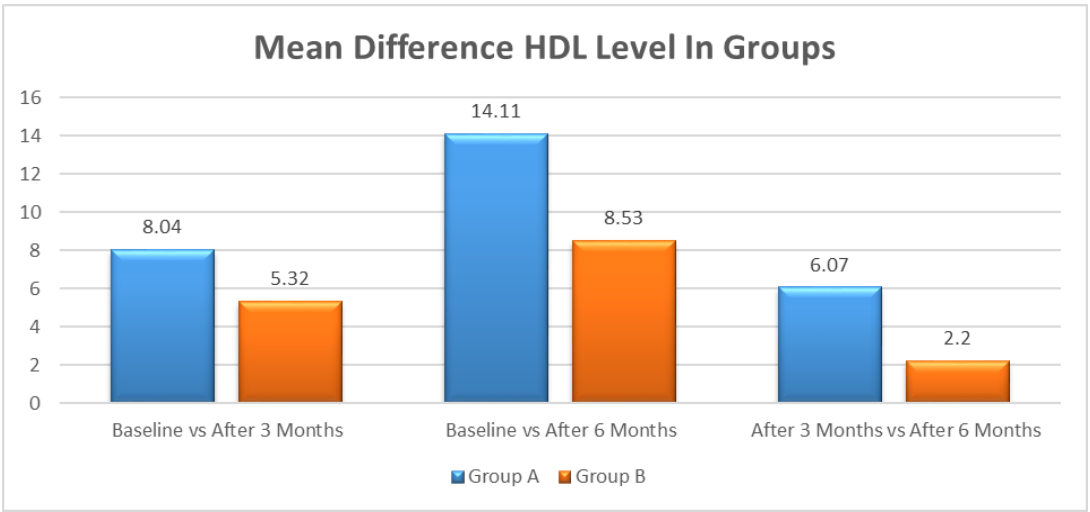


Fig-7: Comparison of Mean Difference HDL (mg/dl) level during treatment with Group A and Group B

Table-8: Comparison of Mean LDL Cholesterol (mean ± SD in mg/dl) during treatment with Group A and Group B over six months' period:

		Group A Mean±SD	Group B Mean±SD	t-value	p-value
LDL	Baseline	174.58±17.09	175.47±14.71	0.325	P=0.743 NS
	After 3 Months	144.93±28.09	149.03±27.33	0.846	P=0.394 NS
	After 6 Months	97.89±14.96	144.05±24.48	13.17	P<0.0001 HS

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, S: Significant, HS: Highly Significant, Unpaired t-test.

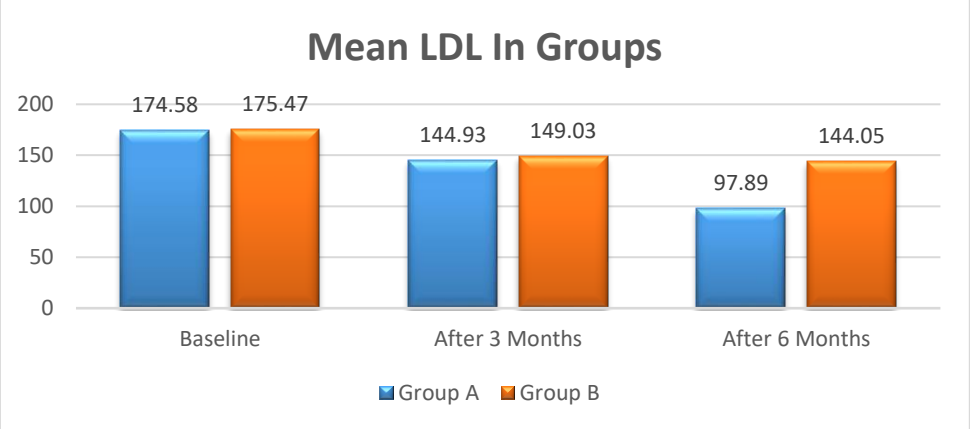


Fig-8: Comparison of Mean LDL (mean ± SD in mg/dl) levels during treatment with Group A and Group B over a period of six months

LDL levels during treatment with pioglitazone and voglibose over a period of six months are shown in Table 8 and figure 8. LDL within both the groups showed significant increase over a period of 6 months. On comparison between the patients of group A versus group A, there was a significant difference in mean percentage change in serum LDL levels at the end of 3rd month ($p< 0.05$) and highly significant difference 6th month of study period ($p< 0.001$).

Table-9: Comparison of Mean Difference LDL levels (mg/dl) in Group A and Group B

LDL	Group A			Group B		
	Mean Difference	t-value	p-value	Mean Difference	t-value	p-value
Baseline vs After 3 Months	29.64	7.29	P<0.0001 S	26.44	6.29	P<0.0001 S
Baseline vs After 6 Months	76.68	25.26	P<0.0001 S	31.41	9.37	P<0.0001 S
After 3 Months vs After 6 Months	47.04	13.98	P<0.0001 S	4.98	3.56	P=0.003 S

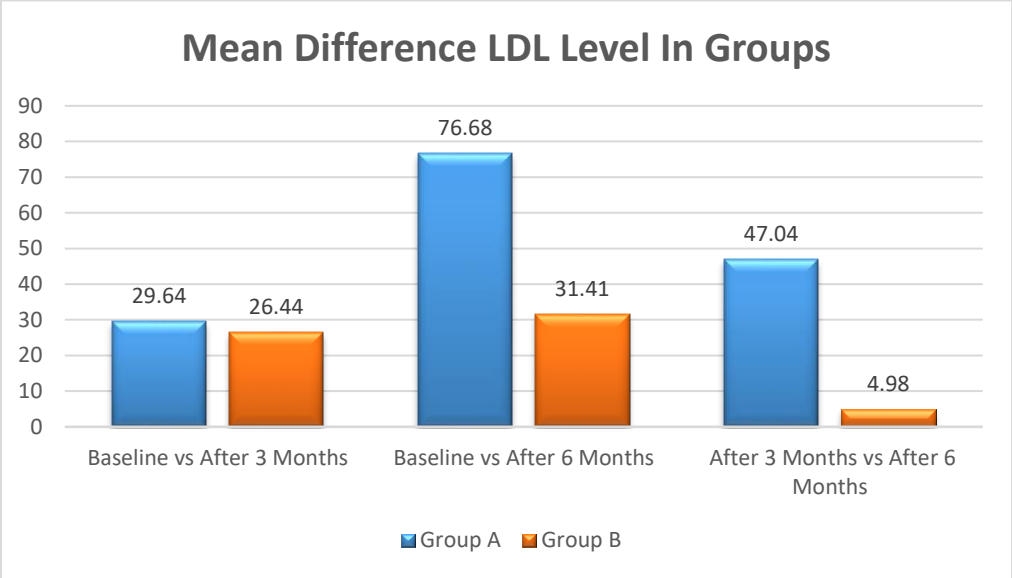


Fig-9: Comparison of Mean Difference LDL (mg/dl) level during treatment with Group A and Group B

Table-10: Comparison of Mean VLDL during treatment with Group A and Group B over six months' period:

		Group A Mean±SD	Group B Mean±SD	t-value	p-value
VLDL	Baseline	30.31±4.01	29.36±3.48	1.06	P=0.289 NS
	After 3 Months	27.45±2.67	28.16±2.57	1.34	P=0.316 NS
	After 6 Months	23.42±1.63	25.79±2.37	4.21	P=0.004 S

Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, S: Significant, HS: Highly Significant, Unpaired t-test.

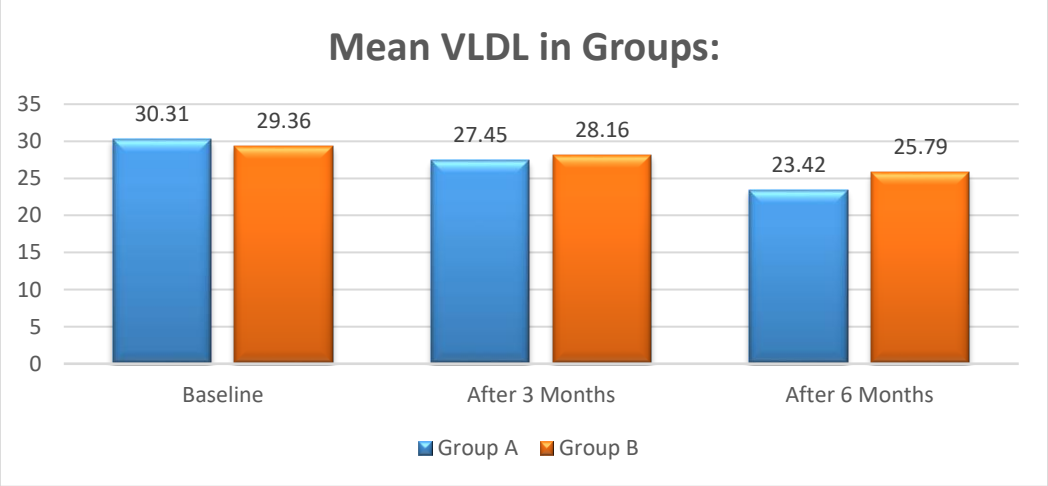


Fig-10: Comparison of Mean VLDL levels during treatment with Group A and Group B over a period of six months:

VLDL levels during treatment with pioglitazone and voglibose over a period of six months are shown in Table 10 and figure 10. Serum VLDL within both the groups showed significant reduction over a period of 6 months. On comparison between the patients of group A versus group B, there was no significant difference in mean percentage change in VLDL levels at the end of 3rd month ($p > 0.05$) but the difference was significant at the end of 6th month of study period ($p < 0.001$).

Table-11: Comparison of Mean Difference VLDL levels in Group A and Group B:

VLDL	Group A			Group B		
	Mean Difference	t-value	p-value	Mean Difference	t-value	p-value
Baseline vs After 3 Months	2.86	5.05	P<0.0001 S	1.19	1.45	P=0.164 NS
Baseline vs After 6 Months	6.86	12.59	P<0.0001 S	4.67	9.76	P<0.0001 S
After 3 Months vs After 6 Months	4.00	10.62	P<0.0001 S	2.56	4.39	P<0.0001 S

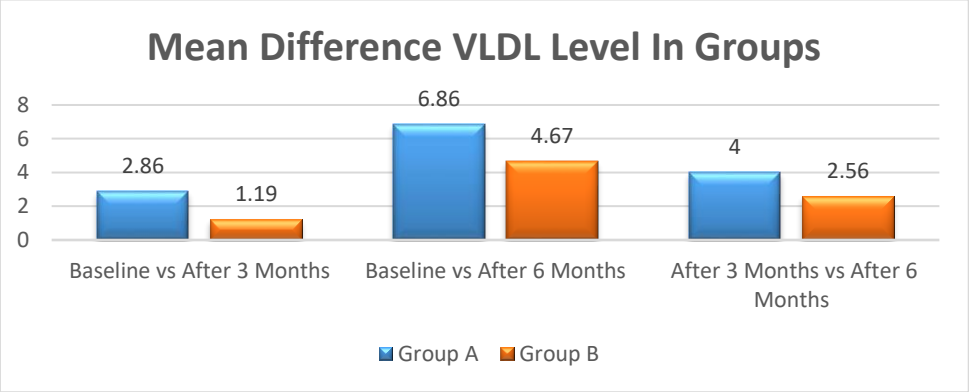


Fig-11: Comparison of Mean Difference VLDL level during treatment with Group A and Group B:

DISCUSSION

The controlling of Type 2 DM consist of diet control, exercise and pharmacological therapy. In the present study 67 patients of Type 2 DM were given pioglitazone with metformin and voglibose with metformin in group A and group B respectively. The result of add on therapy with voglibose or pioglitazone as a third agent was detected on various parameters.

Moreover, Pioglitazone with Metformin and Voglibose with Metformin has been stated that have an impact on serum lipids. i.e. TC, TG, LDL and VLDL and these were reduced significantly with both pioglitazone and voglibose group. The decrease in these parameters was commiserating with period of observation i.e. 3rd and 6th month with both drugs. On contrast, addition of pioglitazone caused in superior decrease in TC, TG and LDL than voglibose at the end of 3rd and 6th month of study. However, decrease in VLDL was equal with both groups at 3rd month of observation but at 6th month, the decrease in VLDL was superior with pioglitazone than with voglibose.

Various studies stated that significant decrease in TC, TG and LDL with pioglitazone and increase in HDL [17-20]. Reports about voglibose on lipids are contrary. One more study showed by Mughal *et al.* [21], there was significant decrease in TG and VLDL but there was no significant result on TC and LDL with voglibose. Another study about voglibose has been stated to cause increase in TC and LDL and decrease in HDL in type 2 diabetic patients by Iwamoto *et al.* [22].

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

CONCLUSION

Though pioglitazone showed better results in controlling lipid profile as compared to voglibose. Moreover, pioglitazone had minimal side effects as compared to voglibose.

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