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# Comparative Evaluation of Safety and Efficacy of Pioglitazone versus Voglibose on Lipid Level in Prediabetes Patient Add on Metformin

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**Original Research Article**

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**Abstract:** ADA has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes. Due to progressive nature of prediabetes to diabetes, 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 FDC of Metformin with Pioglitazone Versus FDC of Metformin with Voglibose on Lipid levels as an add-on drug in obese with prediabetes patients whose dyslipidemia status was uncontrolled with metformin alone. Methods: 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 obese with prediabetes, with FBG: 100-125 mg/dl and PPBG: 140-200 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). Results: At the end of 3rd and 6th months it was observed that though both FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose reduced Lipid levels significantly but Metformin with Pioglitazone caused a statistically significantly greater amount change in Lipid levels as compared with Metformin with Voglibose. Few side effects were observed with Metformin with Voglibose but not with Metformin with Pioglitazone. Conclusions: Though Metformin with Pioglitazone and Metformin with Voglibose were equally effective in lowering Lipid levels yet Metformin with Pioglitazone showed better results in improving dyslipidemia, as compared to Metformin with Voglibose. Pioglitazone had minimal side effects as compared to Metformin with Voglibose.
**Keywords:** Prediabetes, Metformin, Pioglitazone, Voglibose

## INTRODUCTION

The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 6.1-6.9 mmol/L (110 to 125 mg/dL) and impaired glucose tolerance (IGT) defined as 2-hours plasma glucose of 7.8-11.0 mmol/L (140-200 mg/dL) after ingestion of 75 g of oral glucose load or a combination of the two based on a 2 hrs oral glucose tolerance test (OGTT) [1]. On the other hand, the American Diabetes Association (ADA), has the same cut-off value for IGT (140-200 mg/dL) but has a lower cut-off value for IFG (100-125 mg/dL) and has additional hemoglobin A1c (HbA1c) based criteria of a level of 5.7% to 6.4% for the definition of prediabetes [2].

The overall prevalence of prediabetes in all 15 states of India was 10.3% [3]. The world-wide prevalence of IGT in 2010 was estimated to be 343 million (7.8%) ranging from 5.8% in South East Asia to 11.4% in North American and Caribbean Countries of the nation's population. International Diabetes Federation projects an increase in prevalence of prediabetes to 471 million globally by 2035 [4]. Several studies have shown an association of increased risk of chronic kidney disease and early nephropathy with prediabetes [5]. While prediabetes has been associated with an increased risk of diabetic retinopathy, macrovascular disease but whether this elevated risk is due to prediabetes itself or due to development of diabetes remains unclear [6].

Pioglitazone, an insulin-sensitizing Thiazolidinedione (TZDs), is widely used for the

treatment of type 2 diabetes. TZDs 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, 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 prediabetes and 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 Prediabetes. In addition, unlike their relatively lean counterparts, the obese with Prediabetes patients require specific dosing for a curative response to treatment. On these lines, we hypothesized that weight control with prediabetes interventions in conjunction with Fixed dose combination (FDC) of Metformin with Pioglitazone versus Metformin with Voglibose therapy could have a significant positive impact on the management of obesity with Prediabetes. By implicating pharmacological and dietary interventions to control adiposity, we have explored the therapeutic outcome of obese with Prediabetes Patients.

Therefore, the prevention and improvement of obesity with Prediabetes, particularly decrease of visceral fat is important in the control of these metabolic diseases. In the present study, we were targeted obese with Prediabetes subjects and confirmed the antiobesity effects of Metformin, Pioglitazone and Voglibose 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 FDC of Metformin with Pioglitazone, and Metformin with Voglibose which group improves obesity with Prediabetes compared with each other and its impact on dyslipidemia. We used six markers that are commonly used to evaluate dyslipidemia in obesity:

## MATERIAL AND METHODS

### Study design and settings

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

### Inclusion criteria

Patients with Prediabetes diagnose according to ADA criteria (FBG: 100-125 mg/dl and 2hrs PPBG 140-200 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 study, Patients willing to take medications as directed & willing to come for the follow-ups.

### Exclusion criteria

Patients with history of Type I and Type II 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

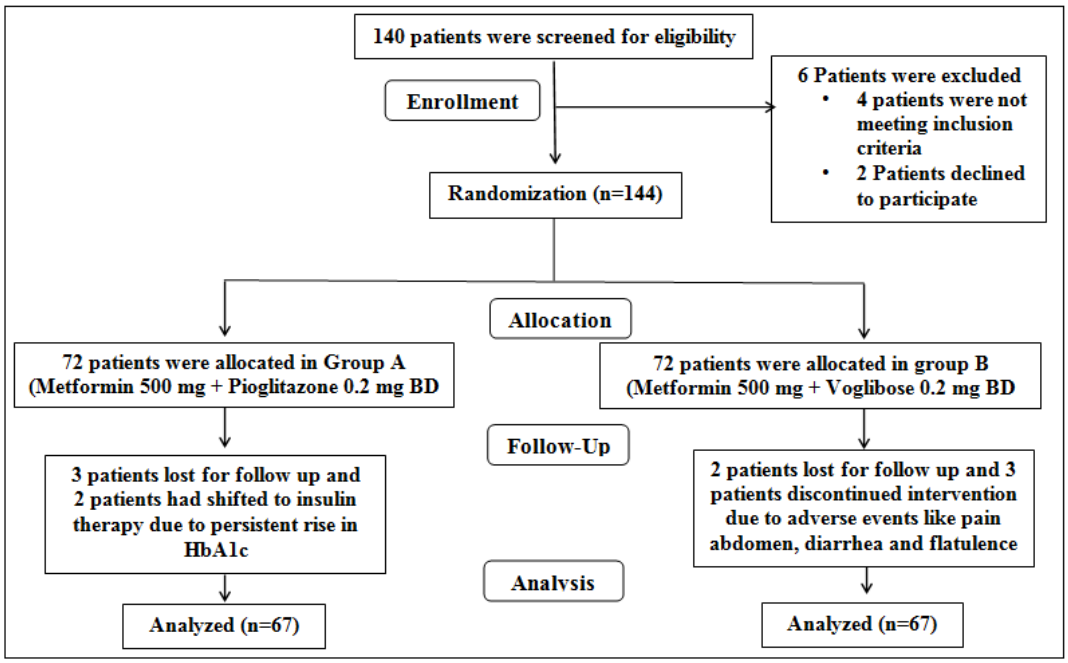
After meeting the inclusion criteria, patients were randomized by a Chit method into two groups,

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) 24th version was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram, pie diagram etc. Quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline and after three months and after six months effect of Group A Versus Group B in obese with Prediabetes patient. A paired 't' test was applied and also quantitative data was represented in the form of pie diagram and 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 Prediabetes 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 | |

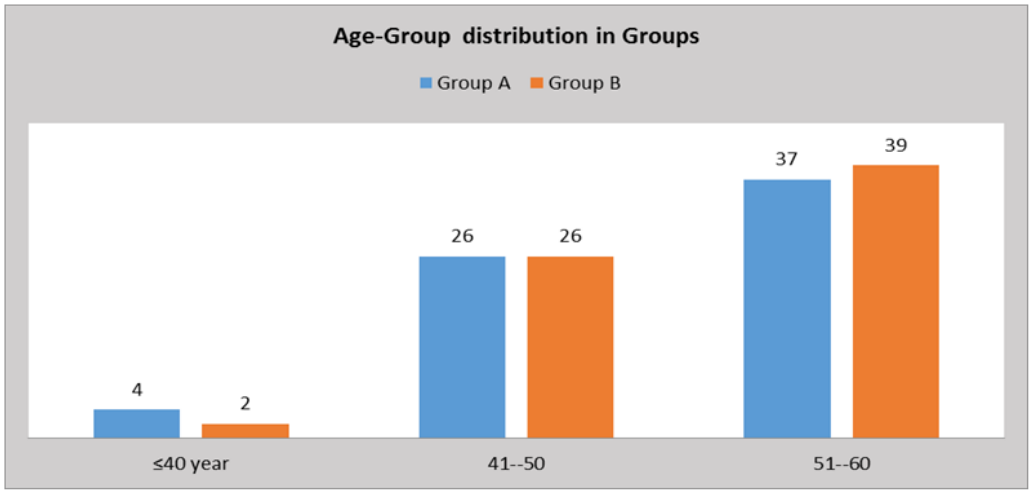



**Fig-1: Distribution of Age-group in Group A and B**

**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 | 287.31±18.58 | 287.58±19.37 | 0.387 | P=0.700 NS |
| | After 3 Months | 252.26±25.43 | 269.85±28.13 | 0.522 | P=0.603 * |
| | After 6 Months | 234.79±23.71 | 244.88±14.53 | 11.74 | P<0.0001 ** |

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

Serum total cholesterol (TC) levels during treatment with Group A and Group B over a period of six months are shown in Table 2. Serum total cholesterol within both the groups showed a statistically significant reduction over a period of 6 months. On comparison between Groups A versus Group B patients, there was a statistically 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 statistically 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 | p-value | Mean Difference | p-value |
| Baseline vs After 3 Months | 35.05 | P<0.0001 ** | 17.73 | P<0.0001 ** |
| Baseline vs After 6 Months | 52.52 | P<0.0001 ** | 42.70 | P<0.0001 ** |
| After 3 Months vs After 6 Months | 17.47 | P<0.0001 ** | 24.97 | P<0.0001 ** |

**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 A Mean±SD | Group B Mean±SD | t-value | p-value |
|---|---|---|---|---|---|
| TG | Baseline | 189.80±14.98 | 189.48±17.36 | 1.67 | P=0.114 NS |
| | After 3 Months | 159.67±12.92 | 167.55±13.37 | 1.06 | P=0.289 * |
| | After 6 Months | 136.22±12.05 | 147.26±8.19 | 10.66 | P<0.0001 ** |

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

Serum Triglycerides levels during treatment with Group A and Group B over a period of six months are shown in Table 4. Serum triglycerides within both the groups showed statistically significant reduction over a period of 6 months. On comparison between Group A versus Group B patients, there was a statistically significant difference in mean percentage change in serum triglycerides at the end of 3rd month ($p< 0.05$) and a statistically 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 A** | | **Group B** | |
|---|---|---|---|---|
| | Mean Difference | p-value | Mean Difference | p-value |
| Baseline vs After 3 Months | 30.13 | P<0.0001 ** | 22.23 | P<0.0001 ** |
| Baseline vs After 6 Months | 53.58 | P<0.0001 ** | 42.23 | P<0.0001 ** |
| After 3 Months vs After 6 Months | 23.45 | P<0.0001 ** | 20.29 | P<0.0001 ** |

**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 | 41.97±2.22 | 41.51±2.64 | 1.06 | P=0.290 NS |
| | After 3 Months | 44.29±3.45 | 43.46±3.85 | 3.42 | P=0.001 * |
| | After 6 Months | 46.49±2.60 | 45.54±3.53 | 3.49 | P<0.0001** |

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

HDL levels during treatment with Group A and Group B over a period of six months are shown in Table 6. HDL within both the groups showed statistically significant reduction over a period of 6 months. On comparison between Group A versus Group B patients, there was a statistically significant difference in mean percentage change in HDL at the end of 3rd month and a statistically 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 | p-value | Mean Difference | p-value |
| Baseline vs After 3 Months | 2.32 | P<0.0001 ** | 1.95 | P<0.0001 ** |
| Baseline vs After 6 Months | 4.52 | P<0.0001 ** | 4.03 | P<0.0001 ** |
| After 3 Months vs After 6 Months | 2.20 | P<0.0001 ** | 2.08 | P<0.0001 ** |

**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 | 207.38±17.09 | 208.18±14.71 | 0.325 | P=0.743 NS |
| | After 3 Months | 176.64±28.09 | 192.94±27.33 | 0.846 | P=0.394 * |
| | After 6 Months | 161.06±14.96 | 169.89±24.48 | 13.17 | P<0.0001 ** |

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

LDL levels during treatment with Group A and Group B over a period of six months are shown in Table 8. LDL within both the groups showed statistically significant reduction over a period of 6 months. On comparison between the patients of Group 1 versus Group 2, there was a statistically significant difference in mean percentage change in serum LDL levels at the end of 3rd month ($p< 0.05$) and statistically 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 | p-value | Mean Difference | p-value |
| Baseline vs After 3 Months | 30.74 | P<0.0001 ** | 15.24 | P<0.0001 ** |
| Baseline vs After 6 Months | 46.32 | P<0.0001 ** | 38.29 | P<0.0001 ** |
| After 3 Months vs After 6 Months | 15.58 | P<0.0001 ** | 23.05 | P=0.003 * |

**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 | 37.96±4.01 | 37.89±3.48 | 1.06 | P=0.289 NS |
| | After 3 Months | 31.33±2.67 | 33.45±2.57 | 1.34 | P=0.316 NS |
| | After 6 Months | 27.24±1.63 | 29.45±2.37 | 4.21 | P=0.004 * |

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

VLDL levels during treatment with Group A and Group B over a period of six months are shown in Table 10. Serum VLDL within both the groups showed statistically significant reduction over a period of 6 months. On comparison between the patients of Group A versus Group B, there was not statistically significant difference in mean percentage change in VLDL levels at the end of 3rd month ($p$> 0.05) but the difference was statistically 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 | p-value | Mean Difference | p-value |
| Baseline vs After 3 Months | 6.56 | P<0.0001 ** | 4.44 | P=0.164 NS |
| Baseline vs After 6 Months | 10.72 | P<0.0001 ** | 4.00 | P<0.0001 ** |
| After 3 Months vs After 6 Months | 4.09 | P<0.0001 ** | 4.00 | P<0.0001 ** |

## DISCUSSION

The controlling of obesity with Prediabetes consists of diet control, exercise and pharmacological therapy. In the present study 67 patients of obesity with Prediabetes were given FDC of Metformin with Pioglitazone and FDC of Metformin with Voglibose in group A and group B respectively. The result of add on therapy with Pioglitazone or Voglibose as a third agent was detected on various parameters.

Moreover, FDC of Pioglitazone with Metformin and Voglibose with Metformin 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, LDL and increase of HDL 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 but at end of 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]. 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 Prediabetes 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 with Voglibose and not with pioglitazone; thereby presenting that pioglitazone is a safer drug.

## CONCLUSION

Though FDC of Metformin with Pioglitazone showed better results in controlling lipid level as compared to FDC of Metformin with Voglibose. Moreover, Metformin with pioglitazone had minimal side effects as compared to Metformin with Voglibose.

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