**Journal Of Medical Science And Clinical Research**
IGM Publication          An Official Publication Of IGM Publication

# Comparative evaluation of Pioglitazone versus Voglibose on glycemic control in patients with Type 2 Diabetes Mellitus on Metformin

Authors
**Md Faheem Mubeen, Dr Deepak Bhosle, Dr Abhijeet Bhagat, Dr Zubair Quazi**
Corresponding Author
**Md Faheem Mubeen**
Department of Pharmacology, MGM Medical College and Hospital, Aurangabad, India

**Abstract**
**Background:** *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 glycemic control as an add-on drug in patients with Type 2 DM whose glycemic 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 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 i.e. FBG and PPBG.*
**Results:** *At the end of 6 months it was observed that though both pioglitazone and voglibose reduced FBG and PPBG significantly but pioglitazone caused a significantly greater percentage change in FBG but voglibose caused a significantly greater percentage change in PPBG. Few side effects were observed with voglibose and not with pioglitazone.*
**Conclusions:** *Though pioglitazone and voglibose were equally effective in lowering Blood glucose levels yet pioglitazone showed better results in improving FBG, as compared to voglibose. Furthermore, voglibose presented better results in controlling PPBG, as compared to Pioglitazone. 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 non-ketosis 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]

The presence of Type 2 DM is associated with adverse effects on health including metabolic complications in which numerous cytokines and hormones are involved. Furthermore, Type 2 DM are associated with a higher risk of developing chronic diseases which includes kidney disease, hypertension, osteoarthritis, and coronary artery disease (CAD) due to dyslipidaemia and low levels of high density lipoproteins and moreover epidemiologic studies have found that obese with Type 2 DM adults have significantly higher mortality as compared with non-obese with Type 2 DM adults. [7]

Pioglitazone, an insulin-sensitizing 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. [8] 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. [9] 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. [10] 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. [11]

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. [12, 13]

Metformin, a biguanide class of oral hypoglycemic agents, is the first line drug for the treatment of type 2 diabetes mellitus. [14] Metformin is used clinically for the treatment of 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. [15] Additionally, metformin has a variety of pleiotropic effects including improved lipid and cholesterol metabolism, decreased inflammation and inhibition of cell growth.[16] (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.[17]

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 Type 2 DM. In addition, unlike their relatively lean counterparts, Type 2 DM patients require specific dosing for a curative response to treatment. On

these lines, we hypothesized that glycemic control in diabetes interventions in conjunction with Metformin and Pioglitazone versus Metformin and Voglibose therapy could have a significant positive impact on the management of Type 2 DM. By implicating pharmacological and dietary interventions to contain adiposity, we have explored the therapeutic outcome of Type 2 DM Patients.

Therefore, in the present study, we were targeted Glycemic control in Type 2 DM subjects and confirmed the effects of Metformin, where a reduction in the blood glucose level was the primary outcome of these metabolic diseases.

The secondary 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 Type 2 DM compared with each other and its impact on Glycemic control. We used two markers that are commonly used to evaluate Blood glucose level in Type 2 DM: Fasting blood Glucose level and Post-prandial blood glucose level.

**Material 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 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. The total duration of study was 1 Year.

**Inclusion criteria:** Type 2 DM Patients diagnose according to American Diabetes Association (ADA) criteria (FBG ≥ 126 mg/dl and 2hrs PPBG 200 mg/dl) in the age group of 30-60 years of either sex, all patients provided written, vernacular, witnessed, informed consent to participate in the study, Patients willing to take medications as directed and willing to come for the follow-up.

**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 Gastrointestinal disease (GIT), concomitant with steroid therapy and history of hypersensitivity to test drug, pregnant and lactating women also excluded from the study.
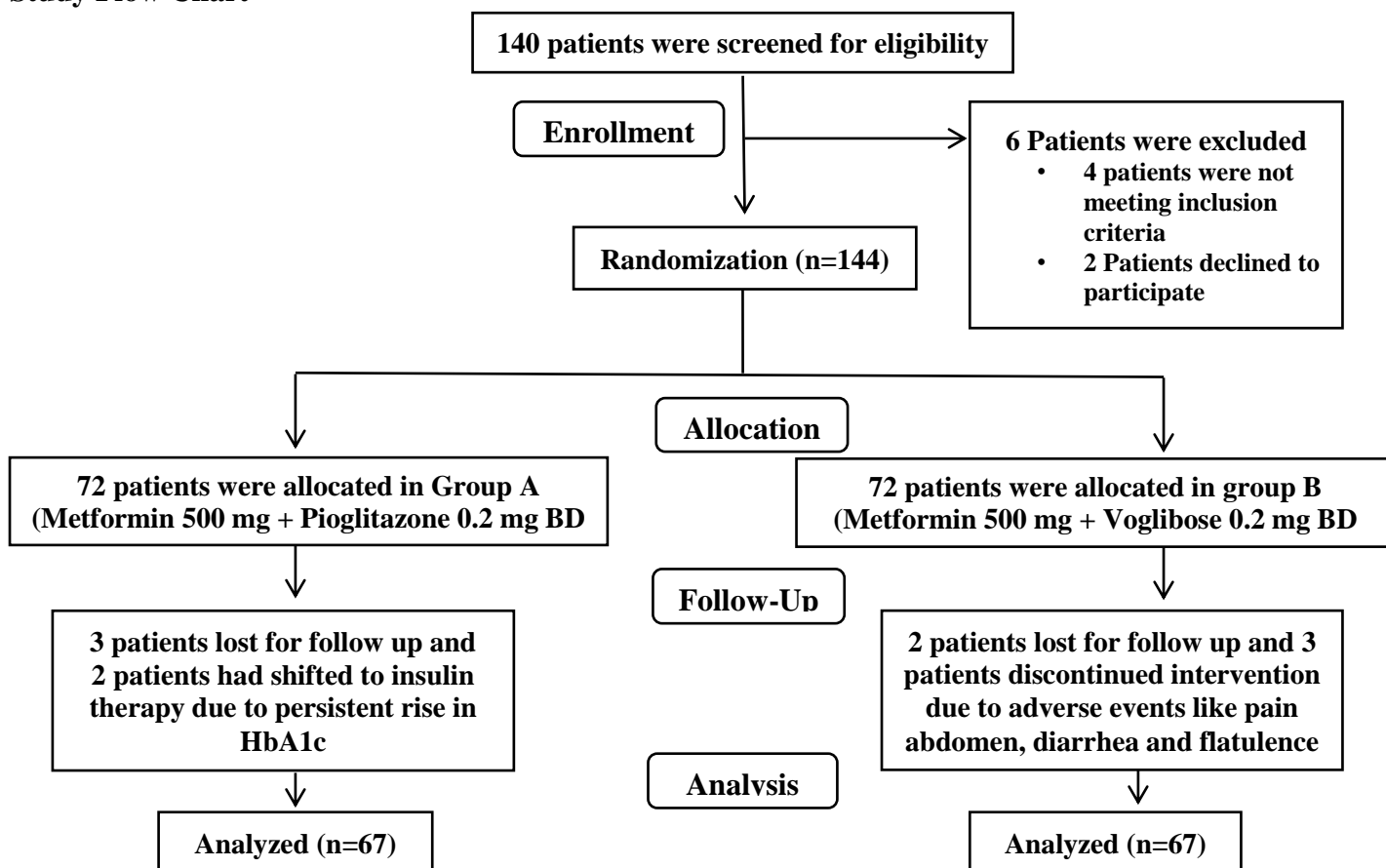
**Intervention Drugs**
After meeting the inclusion criteria, patients were randomized by a computer generated randomization sequence into two groups, each consist of 63 patients. In group A: Tab. Metformin 500 mg + Tab. Pioglitazon 7.5 mg combination BD orally was given for 6 months and group B: Tab. 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) 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.

**Study Flow Chart**

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                    ┌─────────────────────────────────────┐
                    │ 140 patients were screened for       │
                    │ eligibility                          │
                    └─────────────────────────────────────┘
                                    │
              ┌──────────────┐      │        ┌──────────────────────────────┐
              │  Enrollment  │──────┼───────▶│ 6 Patients were excluded      │
              └──────────────┘      │        │  • 4 patients were not        │
                                    ▼        │    meeting inclusion          │
                    ┌─────────────────────┐  │    criteria                   │
                    │ Randomization (n=144)│  │  • 2 Patients declined to     │
                    └─────────────────────┘  │    participate                │
                                             └──────────────────────────────┘
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| 72 patients were allocated in Group A (Metformin 500 mg + Pioglitazone 0.2 mg BD | **Allocation** | 72 patients were allocated in group B (Metformin 500 mg + Voglibose 0.2 mg BD |

| 3 patients lost for follow up and 2 patients had shifted to insulin therapy due to persistent rise in HbA1c | **Follow-Up** | 2 patients lost for follow up and 3 patients discontinued intervention due to adverse events like pain abdomen, diarrhea and flatulence |

| **Analyzed (n=67)** | **Analysis** | **Analyzed (n=67)** |

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

## Statistical Analysis

The collected data was compiled in MS Excel sheet for analysis in Statistical Package for the Social Sciences (SPSS) version 20$^{th}$ was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram. 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 patient. A unpaired 't' test was applied for two different groups and paired 't' test was applied for same group/ within group 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 study. Both the groups were similar in demographic profile at baseline as shown in Figure 1.

In table 1 and figure 2: In both the groups, maximum number of patients was in the age group of 51-60 years and least number of patients were within ≤40 years of age. Mean age in group A was $51.10 \pm 6.62$ and in group B was $52.29 \pm 6.55$. 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 | |

**Figure 2:** Distribution of Age-group in Group A and B
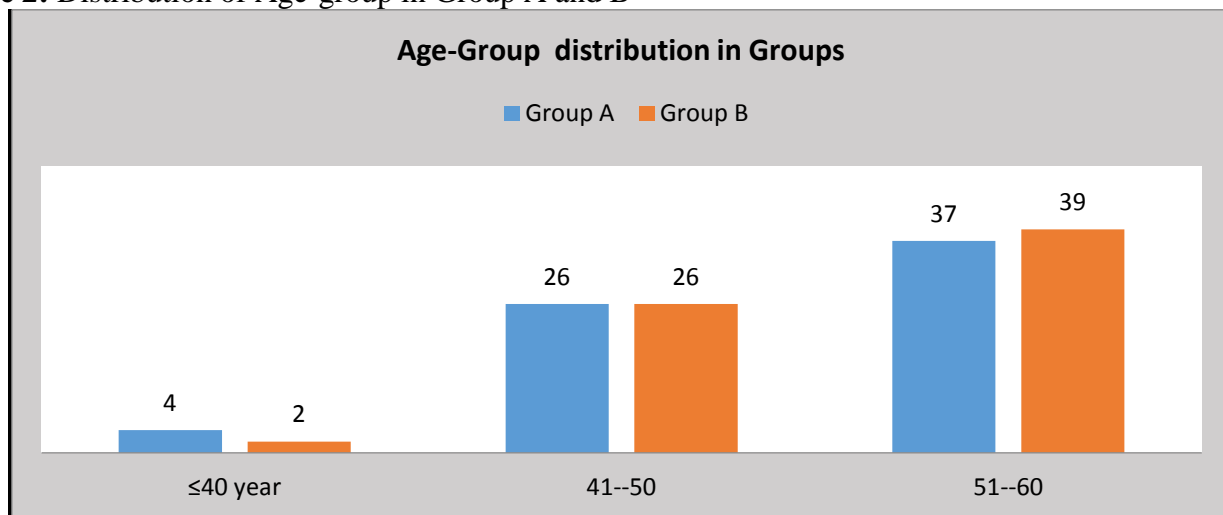


**Table 2:** Comparison of Mean Fasting Blood Glucose level (mean ± SD in mg/dl (Unpaired t-test)) during treatment with Group A and Group B over six months' period

| | | Group A Mean±SD | Group B Mean±SD | t-value | p-value |
|---|---|---|---|---|---|
| FBS | Baseline | 156.09±14.48 | 153.05±15.08 | 1.19 | P=0.235 NS |
| | After 1 Months | 153.04±13.39 | 149.77±14.96 | 1.27 | P=0.208 NS |
| | After 2 Months | 131.51±10.57 | 135.23±14.23 | 1.72 | P=0.087 NS |
| | After 3 Months | 118.42±10.69 | 124.73±10.80 | 3.39 | P=0.001 S |
| | After 4 Months | 108.29±9.38 | 117.81±10.81 | 5.42 | P<0.0001 HS |
| | After 5 Months | 92.98±7.35 | 103.35±12.45 | 5.87 | P<0.0001 HS |
| | After 6 Months | 74.59±4.73 | 87.59±10.50 | 9.23 | P<0.0001 HS |

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

**Figure 3:** Comparison of Mean FBG levels (mg/dl) during treatment with Group A and Group B over a period of six months
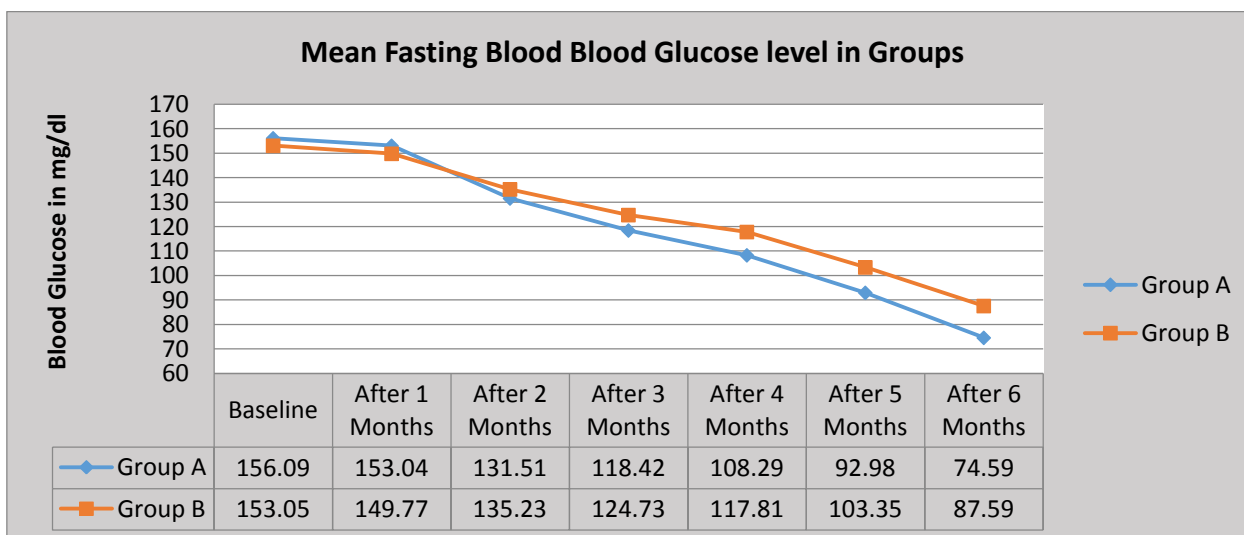
FBG levels during treatment with Pioglitazone and Voglibose over a period of six months are shown in Table 2 and Figure 3. Fasting blood glucose levels within both the groups showed significant reduction over a period of 6 months. But o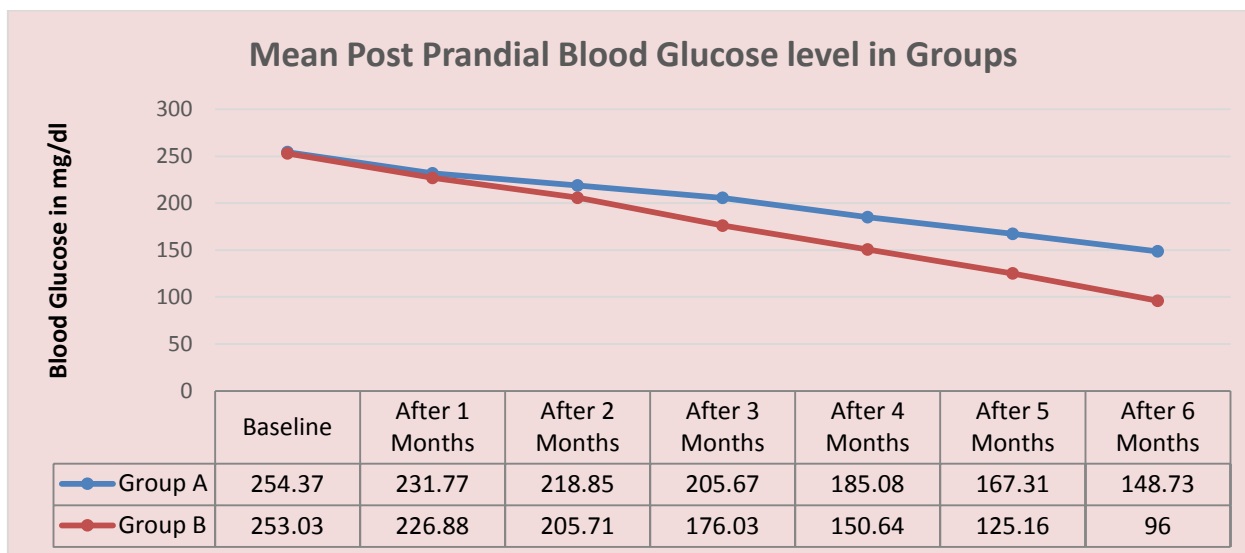n comparison between group A versus group B patients, there was a significant difference in mean percentage change in FBG levels at the end of $3^{rd}$ month ($p= 0.05$) and this difference was highly significant at $4^{th}$, $5^{th}$ and $6^{th}$ month of study period ($p< 0.001$).

**Table 3:** Comparison of Mean Post Prandial Blood Glucose 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 |
|---|---|---|---|---|---|
| PPBG | Baseline | 254.37±12.89 | 253.03±13.74 | 9.23 | P<0.0001 S |
|  | After 1 Months | 231.77±14.28 | 226.88±14.08 | 0.538 | P=0.561 NS |
|  | After 2 Months | 218.85±11.73 | 205.71±15.37 | 1.99 | P=0.048 S |
|  | After 3 Months | 205.67±15.37 | 176.03±18.47 | 5.05 | P<0.0001 HS |
|  | After 4 Months | 185.08±15.50 | 150.64±12.37 | 9.88 | P<0.0001 HS |
|  | After 5 Months | 167.31±16.50 | 125.16±8.99 | 14.21 | P<0.0001 HS |
|  | After 6 Months | 148.73±12.89 | 96.00±9.36 | 18.35 | P<0.0001 HS |

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

**Figure 4:** Comparison of Mean PPBG levels (mg/dl) during treatment with Group A and Group B over a period of six months



| | Baseline | After 1 Months | After 2 Months | After 3 Months | After 4 Months | After 5 Months | After 6 Months |
|---|---|---|---|---|---|---|---|
| Group A | 254.37 | 231.77 | 218.85 | 205.67 | 185.08 | 167.31 | 148.73 |
| Group B | 253.03 | 226.88 | 205.71 | 176.03 | 150.64 | 125.16 | 96 |

PPBG levels during treatment with Pioglitazone and Voglibose over a period of six months are shown in Table 3 and Figure 4. PPBG levels within both the groups showed significant reduction over a period of 6 months. But on comparison between group A versus group B patients, there was a significant difference in mean percentage change in PPBG levels at the baseline, and at the end of $2^{nd}$ month ($p= 0.05$) and this difference was highly significant at $3^{rd}$, $4^{th}$, $5^{th}$ and $6^{th}$ month of study period ($p< 0.001$).

**Table 4:** Comparison of Mean Difference Fasting Blood glucose level (mg/dl, Paired t-test) in Group A and Group B:

| FBS | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs After 1 Months | 9.41 | 16.79 | P<0.0001 S | 3.26 | 1.960 | P=0.054 NS |
| Baseline vs After 2 Months | 24.58 | 25.10 | P<0.0001 S | 17.80 | 8.702 | P<0.0001 S |
| Baseline vs After 3 Months | 37.67 | 27.77 | P<0.0001 S | 28.31 | 12.004 | P<0.0001 S |
| Baseline vs After 4 Months | 47.79 | 32.04 | P<0.0001 S | 35.23 | 14.886 | P<0.0001 S |
| Baseline vs After 5 Months | 63.10 | 40.03 | P<0.0001 S | 49.68 | 23.930 | P<0.0001 S |
| Baseline Vs  After 6 Months | 81.49 | 44.61 | P<0.0001 S | 65.44 | 35.721 | P<0.0001 S |

NS: Not significant, S: Significant, HS: Highly Significant.

**Figure 5:** Comparison of Mean Difference Fasting Blood Glucose level (mg/dl) during treatment with Group A and Group B
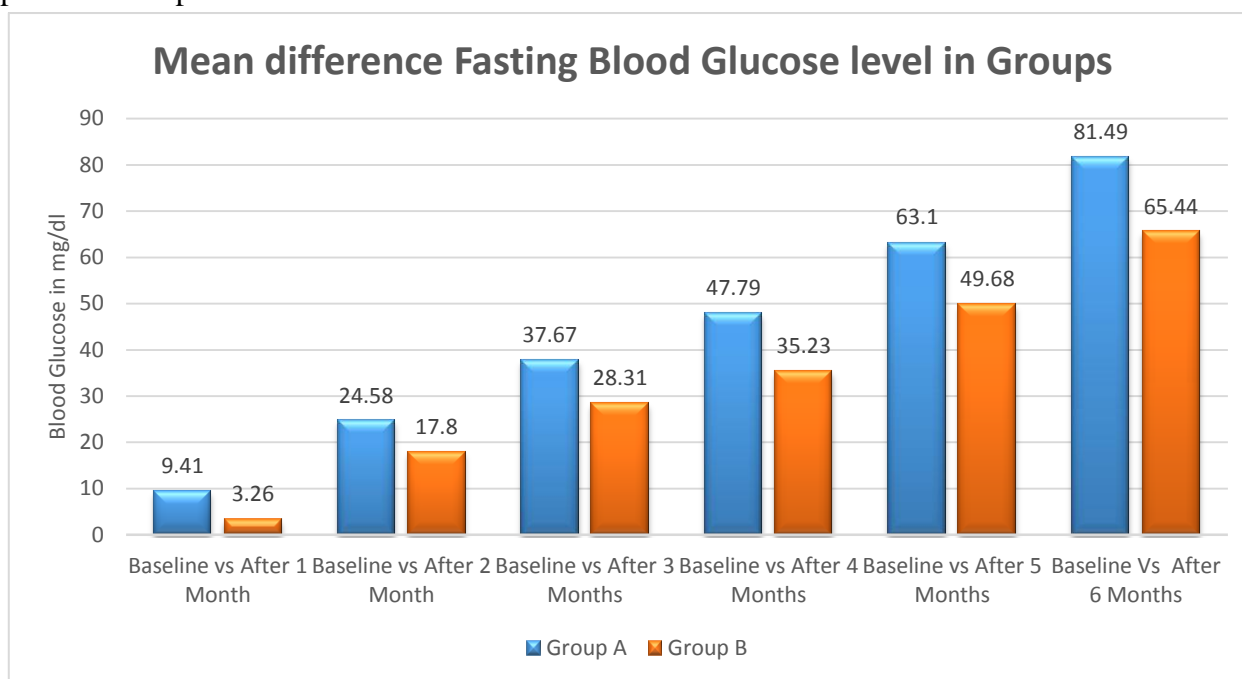


In table 4 and Figure 5, in Group 'A' the mean difference of FBG level at baseline and after 1$^{st}$ month was 9.41 mg/dl. These mean difference was found to be highly statistically significant (p<0.0001). In a Group 'B' the mean difference of FBG level at baseline and after 1$^{st}$ month was 3.26 mg/dl. These mean difference was not statistically significant (p<0.05). Furthermore, in Group 'A' the mean d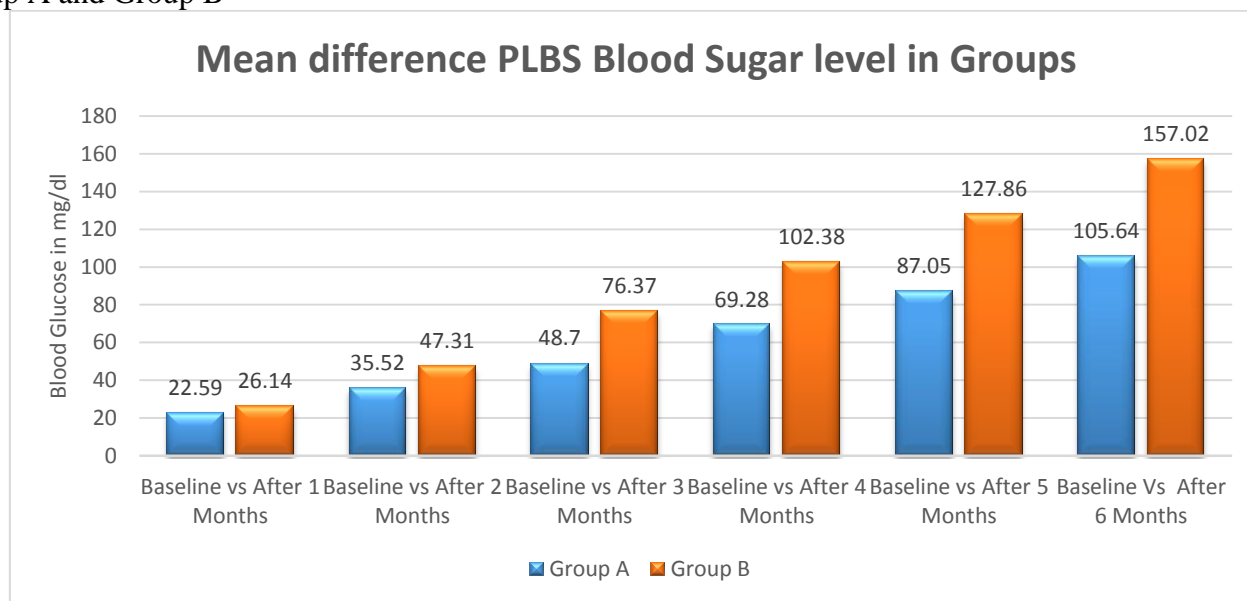ifference of FBG level at baseline and after 6$^{th}$ month was 81.49 mg/dl. These mean difference was found to be highly statistically significant (p<0.0001). In a Group 'B' the mean difference of FBG level at baseline and after 6$^{th}$ month was 65.44 mg/dl. These mean difference was highly statistically significant (p<0.0001). The major changes in mean difference of baseline to after six months was occurred in occurred in Group A as compared with Group B.

**Table 5:** Comparison of Mean Difference Post-Prandial Blood Glucose level (mg/dl) in Group A and Group B

| PPBG | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs After 1 Months | 22.59 | 17.04 | P<0.0001 S | 26.14 | 12.79 | P<0.0001 S |
| Baseline vs After 2 Months | 35.52 | 19.79 | P<0.0001 S | 47.31 | 17.79 | P<0.0001 S |
| Baseline vs After 3 Months | 48.70 | 21.16 | P<0.0001 S | 76.37 | 26.67 | P<0.0001 S |
| Baseline vs After 4 Months | 69.28 | 30.58 | P<0.0001 S | 102.38 | 46.96 | P<0.0001 S |
| Baseline vs After 5 Months | 87.05 | 36.65 | P<0.0001 S | 127.86 | 61.37 | P<0.0001 S |
| Baseline Vs  After 6 Months | 105.64 | 53.01 | P<0.0001 S | 157.02 | 88.50 | P<0.0001 S |

NS: Not significant, S: Significant, HS: Highly Significant.

**Figure 6:** Comparison of Mean Difference Post-Prandial Blood Glucose level (mg/dl) during treatment with Group A and Group B



In table 5 and Figure 6, in Group 'A' the mean difference of PPBG level at baseline and after 1st month was 22.59 mg/dl. These mean difference was found to be highly statistically significant (p<0.0001). In a Group 'B' the mean difference of PPBG level at baseline and after 1st month was 26.14 mg/dl. These mean difference was highly statistically significant (p<0.0001). Moreover, in Group 'A' the mean difference of PPBG level at baseline and after 6th month was 105.64 mg/dl. These mean difference was found to be highly statistically significant (p<0.0001). In a Group 'B' the mean difference of FBG level at baseline and after 6th month was 157.02 mg/dl. These mean difference was highly statistically significant (p<0.0001). The major changes in mean difference of baseline to after six months was occurred in occurred in Group B as compared with Group A.

**Discussion**

The result of add on therapy with Voglibose or Pioglitazone as a third agent was detected on various parameters. [18-22] The controlling of Glycemic level in Type 2 DM consist of diet control, exercise and pharmacological therapy. [23, 24] The present comparative study was conducted to assess the efficacy of Pioglitazone with Metformin versus Voglibose with Metformin based regimen in urban patients with type 2 diabetes in India. 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. There were no cases of hypoglycemia, weight gain and edema reported in the present study. It is not so costly as compared with other drugs. It is easily available even in remote areas. No significant drug interactions are there and usually well tolerated.

No dose adjustment was needed and they improve glycemic control.

Long-term data from major studies like Prospective Diabetes Study has already established the importance of tight and early glucose control to prevent complications of diabetes. [25] A significant decrease in FBG and PPBG was found with both Pioglitazone and Voglibose. The reduction in FBG and PPBG was perceived in consecutive sequence commiserating with duration of study i.e. at 1st, 2nd, 3rd, 4th, 5th and 6th months. But on contrast, arrangement of pioglitazone with metformin resulted in greater decline in FBG but PPBG level greater decline in Metformin and Voglibose combination.

These guidelines await outcome validation but offer a strong rationale for combination therapy in a high risk population.[26] Rational behind combination of this two drugs are impact on beta cells, increases insulin sensitivity, further reduction of insulin resistance with these 2 drugs could enhance durability of glycemic control, additionally decreasing the intestinal absorption of glucose and preserve β-cells of the islets of Langerhans

Among the side effects, weakness was perceived with both the drugs whereas abdominal pain, flatulence, diarrhea, headache, sweating and hot flushes were perceived only with voglibose and not with pioglitazone, thereby presenting that pioglitazone is a safer drug because it causes fewer side effects as compared with Voglibose. So, Pioglitazone may be the ideal add on drug along with metformin in the treatment of type 2 diabetes mellitus. It is found quite effective in patients of urban setting. If there is no question of affordability, then it could be good alternative options as combination anti-diabetic drugs.

## Conclusion

Though pioglitazone showed better results in controlling glycemic profile (FBG, PPBG) as compared with Voglibose. Moreover, pioglitazone had minimal side effects as compared to voglibose.

## Reference

1. Reaven GM, Role of insulin resistance in human disease. Diabetes; 1988; 37: 1595–607

2. Peter H, Troels KH, Lise T, Steffen T, Rudi S, Allan F, Hans-Henrik. Mannose-Binding Lectin as a Predictor of Microalbuminuria in Type 1 Diabetes. Diabetes 2005, 54:1523.1527. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2004;27: 5-10.

3. CDC diabetes. National Diabetes Fact Sheet, general information. CDC Division of Diabetes Translation Public Inquiries/Publications, US 2005.

4. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India. 2007;55:323–4.

5. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J. 2013;6(10):524–31.

6. Anjana RM, Ali MK, Pradeepa R, Deepa M, Datta M, Unnikrishnan R, Rema M, Mohan V. The need for obtaining accurate nationwide estimates of diabetes prevalence in India - rationale for a national study on diabetes. Indian J Med Res. 2011;133:369–80.

7. National Heart, Lung, and Blood Institute; National Institute of Diabetes and Digestive and Kidney Diseases. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. Bethesda, MD: National Institutes of Health; 1998. NIH Publication No. 98-4083. Chapter 2, part C: Overweight and

obesity: background, Health risks of overweight and obesity.

8. Tachibana K, Yamasaki D, Ishimoto K, Doi T. The role of PPARs in cancer. PPAR Res 2008;10:27-37

9. Yki-Ja¨rvinen H. Thiazolidinediones. N Engl J Med 2004; 351 (11): 1106-18

10. Walter H, Lubben G. Potential role of oral thiazolidinedione therapy in preserving β-cell function in type 2 diabetes mellitus. Drugs 2005; 65 (1): 1-13.

11. Diani AR, Sawada G, Wyse B, et al. Pioglitazone preserves pancreatic islet structure and insulin secretory function in three murine models of type 2 diabetes. Am J Physiol Endocrinol Metab 2004; 286 (1): 116-22.

12. *Martindale*, The Complete Drug Reference, Pharmaceutical Press, Part 3: 334.

13. Abhishek Raj. Formulation and In-vitro evaluation of Voglibose Dispersible tablets. EJBPS, 2016;3(2): 226-30.

14. American Diabetes Association. Standards of medical care in diabetes2014. Diabetes Care. 2014; 37 (1): S14-80.

15. Liu W, Yang XJ: The Effect of Metformin on Adolescents with Type 1 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Int J Endocrinol 2016;385:40-71.

16. Pernicova I, Korbonits M. Metforminmode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol. 2014; 10: 143-56.

17. Maida A., Lamont BJ., Caox, Drucker DJ., Metformin regulates the incretin receptors axis via a pathway dependent on peroxisome proliferator-activated receptors alpha in mice. Diabetologia. 2011;54: 339-49.

18. Costa B, Pinol C. Acarbose in ambulatory treatment of non-insulin-dependent diabetes mellitus associated to imminent sulfonylurea failure: a randomised-

multicentric trial in primary health-care. Diabetes and Acarbose Research Group. Diabetes Res Clin Pract 1997; 38:33-40.

19. Shinozaki K, Suzuki M, Hirose J, Hara Y, Harano Y. Improvement of insulin sensitivity and dyslipidemia with a new glucosidase inhibitor, Voglibose in nondiabetic hyperinsulinemic subjects. Metabolism 1996;45:731-7.

20. Olansky L, Marchatti A, Lau H. Multicenter retrospective assessment of thiazolidinedione monotherapy and combination therapy in patients with type 2 diabetes mellitus: comparative subgroup analyses of glycaemic control and blood lipid levels. Clin Ther 2003;25 Suppl B:B64-80.

21. Boyle PJ, King AB, Olansky L, Marchetti A, Lau H, Magar R et al. Effects of pioglitazone and rosiglitazone on blood lipid levels and glycemic control in patients with type 2 diabetes mellitus: a retrospective review of randomly selected medical records. Clin Ther 2002;24:378-96.

22. Goldberg RB, Kandall DM, Deeg MA, Buse JB, Zagor AJ, Pinaire JA et al. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes mellitus and dyslipidemia. Diabetes Care 2005;28: 1547-54.

23. Mughal MA, Memon MY, Zardari MK, Tanwani RK, Ali M. Effect of acarbose on glycemic control, serum lipids and lipoproteins in type 2 diabetes. J Pak Med Assoc 2000;50:152-6.

24. Iwamoto Y, Kashiwagi A, Yamada N, Terao S, Mimori N, Suzuki M et al. Efficacy and safety of vildagliptin and voglibose in Japanese patients with type 2 diabetes; a 12 week, randomized, double blind, active controlled study. Diabetes Obes Metab 2010;12:700-8.

25. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359 (15):1577-89.

26. Diani AR, Sawada G, Wyse B. Pioglitazone preserves pancreatic islet structure and insulin secretory function in three murine models of type 2 diabetes. *Am J Physiol Endo Metab*. 2003;286:116–122.