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# Evaluation of Efficacy and Tolerability of Fixed Dose Combination of Metformin with Voglibose Versus Metformin with Pioglitazone in Prediabetics: An Open label, prospective, RCT

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## ABSTRACT

**Background:** ADA has 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, 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 voglibose in comparison to pioglitazone on glycemic control as an add-on drug in prediabetes patients 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 prediabetes, with FBG: 100-125 mg/dl and PPBG:140-200 mg/dl as per ADA were selected at randomly. The effect of FDC of Voglibose with Metformin and Pioglitazone with Metformin were observed on various parameters of Glycemic Triad (FBG, PPBG, HOMA-IR, HbA1c and Serum Insulin).

**Results:** At the end of 6 months it was observed that though both FDC of Voglibose with Metformin and Pioglitazone with Metformin reduced Glycaemia Statistically significantly but Pioglitazone with Metformin caused a significantly greater percentage change in Glycaemia as compared with Voglibose with Metformin. Few side effects were observed with Voglibose but not with Pioglitazone.

**Conclusions:** Though Voglibose with Metformin and Pioglitazone with Metformin were equally effective in lowering Glycemia yet Pioglitazone with Metformin showed better results in improving glycaemia, as compared to Voglibose with Metformin. Pioglitazone with Metformin had minimal side effects as compared to Voglibose with Metformin.

**Keywords**: Voglibose, Metformin, Pioglitazone, Prediabetes, Glycemia

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## INTRODUCTION:

Prediabetes is defined according to American Diabetes Association (ADA) criteria an impaired fasting glucose (IFG; fasting glucose of 100–125 mg/dL), impaired glucose tolerance (IGT; two-hour postprandial glucose of 140–199 mg/dL), or both. There is substantial evidence to suggest that even at these blood glucose levels, significant risk exists for both micro- and macrovascular complications. [1]

The overall prevalence of prediabetes in all 15 states of India was 7.3%. Overall, the prevalence in urban areas 11.2% was about double that in rural areas 5.2%. Compared with their rural counterparts, men in urban areas had prediabetes of 1.84 and women in urban areas had an odds ratio of 1.58, after adjustment for age, BMI, systolic blood pressure, socioeconomic status (SES), and smoking status. [2]

Insulin resistance, a major abnormality underlying prediabetes and type 2 diabetes mellitus (T2DM) and obesity, is defined as the pathophysiological condition of reduced insulin responsiveness in liver, muscle, and adipose tissue. [3] Insulin resistance plays a key role in the pathogenesis of diseases by causing an imbalance between factors that favour hepatic lipid accumulation, such as lipid influx and de novo lipogenesis (DNL), and factors that

ameliorate lipid accumulation, such as lipid export or oxidation. [4]

Pioglitazone, is an insulin-sensitizing (Thiazolidinedione's) TZDs, is widely used for the treatment of type 2 diabetes. TZDs are known to activate peroxisome proliferator-activated Receptor- γ (PPAR- γ). [5] 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. [6] 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. [7] 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. [8]

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. [9,10]

Metformin, a biguanide class of oral hypoglycemic agents, is the first line drug for the treatment of type 2 diabetes mellitus. [11] 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. [12] Additionally, metformin has a variety of pleiotropic effects including improved lipid and cholesterol metabolism, decreased inflammation and inhibition of cell growth. [13] (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. [14]

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 prediabetes. In addition, unlike their relatively lean counterparts, prediabetes patients require specific dosing for a curative response to treat. On these lines, we hypothesized that glycemic control in prediabetes interventions in conjunction with Fixed Dose Combination (FDC) of Voglibose with Metformin versus Pioglitazone with Metformin therapy could have a significant positive impact on the management of prediabetes. We believe that, in FDC, these modalities represent the most effective means for delaying or even preventing the onset of diabetes in a prediabetes population. This paper concludes with a brief example in which these principles are applied to a hypothetical patient.

Therefore, in the present study, we were targeted Glycemic control in prediabetes subjects and confirmed the effects of combined drugs, which group reduces blood glucose level, HOMA-IR, HbA1c, Serum Insulin was the primary outcome of these metabolic diseases.

The secondary end point of the study was to evaluate the safety of FDC which group has fewer side effects.

## 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 Pioglitazone with Metformin combination versus Voglibose with Metformin in Prediabetes with obese patients over a period of six months in outpatient department of Medicine in MGM Hospitals and College, Aurangabad. This 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 2 Years.

**Inclusion criteria:** Prediabetes Patients diagnose according to American Diabetes Association (ADA) criteria (IGT; two-hour postprandial glucose of 140–199 mg/dL and HbA1c 5.7-6.4%) 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 and Type 2 DM, with acute medical emergencies like Diabetic Ketoacidosis, Polycystic ovarian disease, Liver disease, Kidneys disease, Cardiovascular disease, any Microvascular complication, with chronic Gastrointestinal disease, concomitant with steroid therapy and history of hypersensitivity to test drug, pregnant and lactating women also excluded from the study.

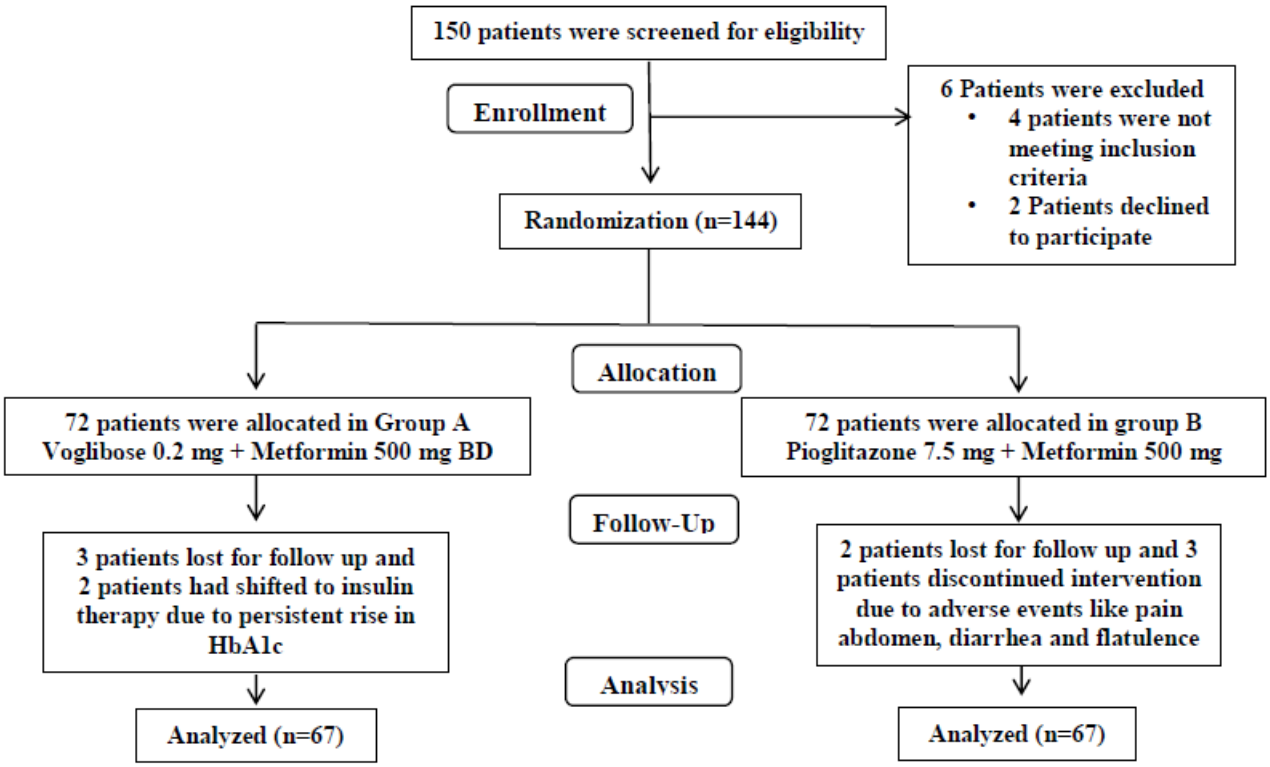
### Intervention drugs:

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: FDC of Tab. Voglibose 0.2 mg + Metformin 500 mg BD orally was given for 6 months and Group B: FDC of Tab. Pioglitazone 7.5 mg + Metformin 500 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 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), Serum insulin, HbA1c and Homeostasis model assessment-insulin resistance (HOMA-IR) 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.

**Study Flow Chart:**




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

**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. Quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline, after three months and six months effect of Group A Versus Group B in prediabetes patient. An 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 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 study. Both the Groups were similar in demographic profile at baseline as shown in flowchart 1.

In table 1 and figure 1: 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 ± 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 | |
| Z-value | 1.04 | | | |

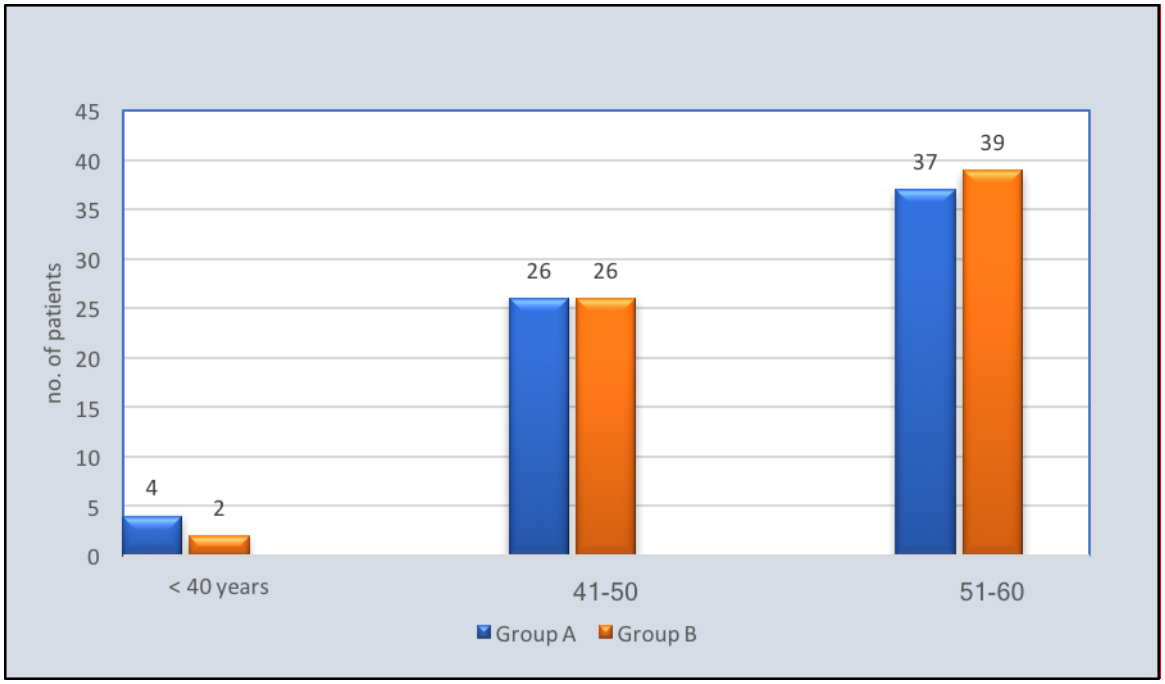
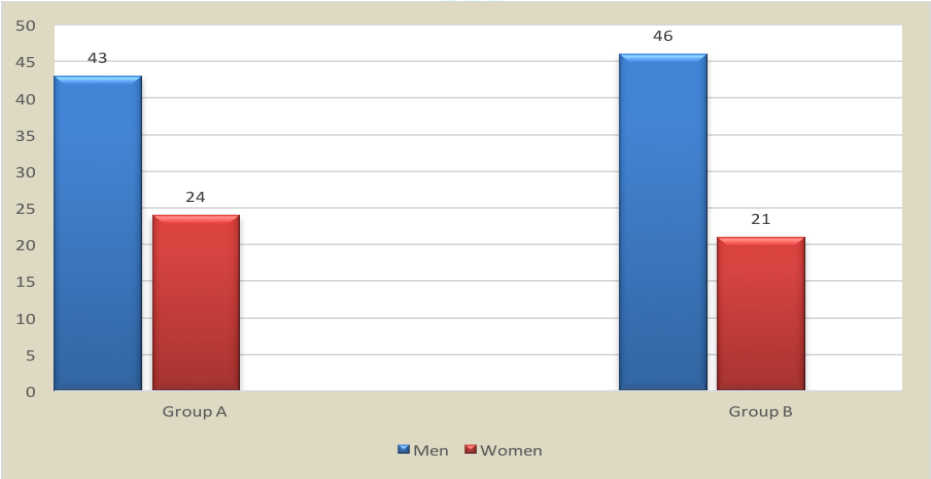



**Figure 1: Distribution of Age-group in Group A and B**

**Table 2: Gender difference between Group A and Group B**

| | Group A | | Group B | | Chi-Square test p=value |
|---|---|---|---|---|---|
| | n=67 | (%) | n=67 | (%) | |
| Male | 43 | 64.17 | 46 | 68.65 | 0.112 |
| Female | 24 | 35.83 | 21 | 31.35 | |
| Total | 67 | 100 | 67 | 100 | |




**Graph 2: Gender difference between Group A and Group B**

The table 2 and graph 2 reflects that 134 prediabetes patients selected, in Group A: 43 were male (64.17%) while 24 were female patients (35.83%). In Group B consisted of 46 male patients (68.65%) and 21 female patients (31.35%). There was no statistically significant difference in number of patient from Group A and Group B patients (0.112).

**Table 3: Comparison of FBG between Group A and Group B at baseline, after 3 months and after 6months (Unpaired test):**

| | | Group A Mean±SD | Group B Mean±SD | z-value | p-value |
|---|---|---|---|---|---|
| **FBS** | Baseline | 103.14±3.38 | 104.15±4.38 | 0.07 | P=0.150 ns |
| | After 3 Months | 92.41±5.42 | 89.92±6.70 | 2.72 | P=0.016 * |
| | After 6 Months | 80.85±7.51 | 78.47±7.20 | 3.01 | P=0.029 * |

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

**Table 4: Comparison of Mean Differences of Fasting Blood glucose level (mg/dl) at baseline, after 3 months and after 6 months in Groups analyzed by paired 't' test**

| FBS | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs After 3 Months | 10.73 | 12.87 | P<0.0001 ** | 14.22 | 14.46 | P<0.0001 ** |
| After 3 Months vs. After 6 Months | 11.56 | 13.26 | P<0.0001 ** | 11.44 | 12.75 | P<0.0001 ** |
| Baseline vs After 6 Months | 22.29 | 21.86 | P<0.0001 ** | 25.67 | 25.49 | P<0.0001 ** |

**NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

Fasting Blood Glucose levels within both the groups showed statistically significant reduction over a period of 6 months. But on comparison between Group A versus Group B patients, there was a statistically significant difference in mean percentage change in FBG levels at the end of 3rd month ($p$< 0.05) and this difference was statistically highly significant at 6th month of study period (Table 3 and 4, $p$< 0.001).

**Table 5: Comparison of Mean Post Prandial Blood Glucose level between Group A and Group B at baseline, after 3 months and after 6months (Z- test):**

| | | Group A Mean±SD | Group B Mean±SD | Z-value | p-value |
|---|---|---|---|---|---|
| PPBG | Baseline | 174.85±15.22 | 174.44±16.62 | 0.14 | P=0.892 ns |
| | After 3 Months | 153.76±15.75 | 161.11±15.68 | 2.70 | P=0.017 * |
| | After 6 Months | 124.08±9.96 | 146.59±16.83 | 9.42 | P<0.0001 ** |

**Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant,**

*** p<0.05 significant, ** p<0.001 highly significant**

**Table 6: Comparison of Mean Differences of Post-Prandial Blood glucose level (mg/dl) at baseline, after 3 months and after 6 months in Groups analyzed by paired 't' test:**

| PPBG | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs After 3 Months | 21.08 | 25.15 | P<0.0001 ** | 13.32 | 12.51 | P<0.0001 ** |
| After 3 Months vs. After 6 Months | 29.67 | 12.80 | P<0.0001 ** | 27.85 | 22.09 | P<0.0001 ** |
| Baseline Vs After 6 Months | 50.76 | 22.40 | P<0.0001 ** | 22.44 | 10.83 | P<0.0001 ** |

**NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

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

**Table 7: Comparison of Mean HOMA-IR between Group A and Group B at baseline, after 3 months and after 6months (Z- test):**

| | | Group A Mean±SD | Group B Mean±SD | z-value | p-value |
|---|---|---|---|---|---|
| HOMA-IR | Baseline | 3.82±0.63 | 3.87±0.67 | 3.51 | P=0.63 ns |
| | After 3 Months | 3.16±0.52 | 2.87±0.47 | 5.86 | P<0.0001 ** |
| | After 6 Months | 2.38±0.44 | 2.12±0.39 | 9.14 | P<0.0001 ** |

**Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant,**

*** p<0.05 significant, ** p<0.001 highly significant**

**Table 8: Comparison of Mean Differences of HOMA-IR level at baseline, after 3 months and after 6 months in Groups analyzed by paired 't' test:**

| HOMA-IR | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs. After 3 Months | 0.65 | 14.13 | P<0.0001 ** | 1.00 | 9.63 | P<0.0001 ** |
| After 3 Months vs. After 6 Months | 0.78 | 16.60 | P<0.0001 ** | 0.74 | 20.40 | P<0.0001 ** |
| Baseline vs. After 6 Months | 1.44 | 26.33 | P<0.0001 ** | 1.74 | 17.46 | P<0.0001 ** |

**NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

Homeostasis model assessment-insulin resistance (HOMA-IR) within both the groups showed statistically significant reduction over a period of 6 months. On comparison between Group A versus Group B patients, a statistically highly significant difference in mean percentage change in HOMA-IR levels was observed at the end of 3rd and 6th month (Table 7 and 8, $p< 0.001$).

**Table 9: Comparison of Mean HbA1c between Group A and Group B at baseline, after 3 months and after 6months (Z-test):**

| | | Group A Mean±SD | Group B Mean±SD | z-value | p-value |
|---|---|---|---|---|---|
| HbA1c | Baseline | 6.25±0.14 | 6.24±0.14 | 0.22 | P=0.416 ns |
| | After 3 Months | 5.81±0.17 | 5.62±0.21 | 2.64 | P<0.0001 ** |
| | After 6 Months | 5.31±0.19 | 5.14±0.11 | 4.10 | P<0.0001 ** |

**Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

**Table 10: Comparison of Mean Differences of HbA1c level at baseline, after 3 months and after 6 months in Groups analyzed by paired 't' test**

| HbA1C | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs. After 3 Months | 0.44 | 16.13 | P<0.0001 ** | 0.61 | 19.36 | P<0.0001 ** |
| After 3 Months vs. After 6 Months | 0.50 | 15.49 | P<0.0001 ** | 0.48 | 16.69 | P<0.0001 ** |
| Baseline vs. After 6 Months | 0.94 | 31.07 | P<0.0001 ** | 1.09 | 49.87 | P<0.0001 ** |

**NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

HbA1c levels within both the groups showed statistically significant reduction over a period of 6 months. But on comparison between Group A versus Group B patients, there was statistically highly significant difference in mean percentage change in HbA1C at the end of 3rd and 6th month of study period (Table 9 and 10, $p< 0.001$).

**Table 11: Comparison of Mean Serum Insulin level between Group A and Group B at baseline, after 3 months and after 6months (Z- test):**

| | | Group A Mean±SD | Group B Mean±SD | z-value | p-value |
|---|---|---|---|---|---|
| S. Insulin | Baseline | 15.01±2.35 | 15.05±2.40 | 0.54 | P=0.913 ns |
| | After 3 Months | 13.88±2.09 | 12.99±2.09 | 6.24 | P<0.017 * |
| | After 6 Months | 11.94±1.90 | 10.97±1.67 | 8.19 | P<0.003 * |

**Mean ± SD in mg/dl, SD: Standard deviation, NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

**Table 12: Comparison of Mean Differences of Serum Insulin level at baseline, after 3 months and after 6 months in Groups analyzed by paired 't' test:**

| S. Insulin | Group A | | | Group B | | |
|---|---|---|---|---|---|---|
| | Mean Difference | t-value | p-value | Mean Difference | t-value | p-value |
| Baseline vs. After 3 Months | 1.13 | 8.55 | P<0.0001 ** | 2.07 | 5.04 | P<0.0001 ** |
| After 3 Months vs. After 6 Months | 1.94 | 13.32 | P<0.0001 ** | 2.01 | 14.88 | P<0.0001 ** |
| Baseline vs. After 6 Months | 3.07 | 18.77 | P<0.0001 ** | 4.08 | 11.03 | P<0.0001 ** |

**NS: Not significant, * p<0.05 significant, ** p<0.001 highly significant**

Serum Insulin levels within both the groups showed statistically significant reduction over a period of 6 months. But on comparison between Group A versus Group B patients, a statistically significant difference in mean percentage change in serum insulin levels was observed at the end of 3rd month ($p< 0.05$) and a statistically highly significant difference was observed at the end of 6th month (Table 11 and 12, $p< 0.001$).

## DISCUSSION:

The present comparative study was conducted to assess the efficacy and safety of fixed does Combination (FDC) of Voglibose and Metformin versus Pioglitazone and Metformin in urban prediabetes patients in India. In the present study 67 patients of prediabetes were given Voglibose and Metformin versus Pioglitazone 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.

Chronic hyperglycemia is an important predictor of the development of diabetic complications like microvascular, macrovascular and acute metabolic complications. Chennai urban population study (CUPS) and the Chennai Urban Rural Epidemiology Study (CURES) provided valuable data from India on diabetic complications. [15, 16] The Diabetes Prevention Program (DPP) was a 27-center randomized clinical trial to determine that both the lifestyle intervention and pharmacological therapy (metformin) were effective in preventing or delaying the onset of diabetes from prediabetes in individuals with impaired glucose tolerance (IGT) who are at high risk for the disease. [17]

In our study significant decrease in FBG, PPBG, HOMA-IR, HbA1c and Serum Insulin was found in both Voglibose and Metformin versus Pioglitazone with Metformin. The reduction in various parameters was perceived in consecutive sequence commiserating with duration of study i.e. at baseline, 3rd and 6th months. But on contrast, arrangement of FDC of Pioglitazone with Metformin resulted in greater decline in FBG, HOMA-IR, HbA1c, and Serum Insulin than Voglibose with Metformin. Whereas only PPBG was reduced significantly in FDC of Voglibose with Metformin than Pioglitazone with metformin. Similarly, study conducted by Amita Jindal et al. supports with our study. [18]

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

On the other hand, fixed does Combination (FDC) of two drugs are mainly used to reduce numbers of pill burden, preferably offer synergistic effect, reduced side effects, to optimize the target of diseases, offers increased bioavailability of antidiabetic drugs in relevant to their simultaneous administration as separated pills, thus reduced the number of pills to take at a time. [19-24] It is cheaper to acquire a FDC drug than to acquire single drug individually. [25] This article examines the use of FDC's therapy for the treatment of prediabetes and it gives ideas to prescribers, payers and patients.

Among the side effects, weakness was perceived with both the drugs whereas abdominal pain, flatulence, diarrhea, headache, sweating and hot flushes were perceived only in Voglibose with Metformin not in Pioglitazone with Metformin, 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 prediabetes and 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 FDC of Prediabetes and anti-diabetic drugs.

## CONCLUSION

Though Pioglitazone with Metformin showed better results in controlling glycemic profile (FBG HOMA-IR, HbA1c, and Serum Insulin) as compared with Voglibose with Metformin. Moreover, Pioglitazone had minimal side effects as compared to Voglibose group.

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**Conflict of interest:** *None declared*

*Ethical approval: The study was approved by the institutional ethics committee*

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