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Comparative study to evaluate the efficacy and safety of Pioglitazone and Metformin on HOMA IR and HbA1c in patient of prediabetes

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Abstract---In India, the number of people with diabetes is increasing day-by-day. Due to a sole “Asian Indian Phenotype,” Indians develop diabetes an era earlier and have an earlier onset of complications. Hence, it is essential to evaluate earlier stage of disease progression. Prediabetes, typically defined as blood glucose levels above normal but below the thresholds of diagnosis of diabetes, is a risk state that defines a high chance of developing diabetes. The present study was Prospective, open label, comparative, randomized, parallel group, single center study. Comparison of two active treatment groups over a period of six months. Sixty patients of either sex in the age of more than 40 years with prediabetes, with HbA1c in the range of 5.7 to 6.4 % at screening as per ADA. The effect of metformin and pioglitazone were observed on various parameters i.e. Serum Insulin, FBG, HbA1c, HOMA-IR. In metformin group the mean change in HOMA-IR from baseline to 6 months was 3.44 to 2.21 (-1.23); on the other hand, in Pioglitazone group from baseline to 6 months was 3.30 to 1.91 (-1.39). Whereas, serum insulin from 35.58 to 26.73 (-8.85) in metformin group; in Pioglitazone group from 35.13 to 21.77 (-13.36). Pioglitazone statistically highly significant than metformin group in improving glycemic indices. Though metformin and pioglitazone were equally effective in improving glycemic indices yet pioglitazone showed better

results in improving Serum Insulin, FBG, HbA1c, HOMA-IR as compared with Metformin. Pioglitazone had minimal side effects as compared to Metformin.

Keywords---blood glucose, serum insulin, glycosylated hemoglobin.

Introduction

Prediabetes, typically defined as blood glucose levels above normal but below the thresholds of diagnosis of diabetes, is a risk state that defines a high chance of developing diabetes. According to the World Health Organization (WHO), high risk for developing diabetes relates to two distinct states, impaired fasting glucose (IFG) defined as fasting plasma glucose (FPG) of 110-125mg/dl (impaired glucose tolerance (IGT) and IGT defined as post-glucose load plasma glucose of 140-199mg/dl based on 2-hours oral glucose tolerance test (OGTT) or a combination of both.[1] The American Diabetes Association (ADA), although applying the same thresholds for IGT, uses a lower cut-off value for IFG (FPG 100-125 mg/dl) and has additionally introduced hemoglobin Alc levels of 5.7-6.4% as a new category of high diabetes risk.[2,3]. The prevalence of IFG is more prevalent among men than women, although the reasons for this remain poorly understood. The International Diabetes Federation (IDF) estimates total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025. [4] According to the National Urban Diabetes Survey, the prevalence of diabetes and pre-diabetes were 12.1% and 14%, respectively. [5] The number of adults with IGT is expected to increase globally, reaching 472 million by 2030. The greatest absolute rises are expected in South-East Asia and the Western Pacific Region. [6]

Progression from prediabetes to diabetes

Around 5-10% of people with prediabetes become diabetic annually although conversion rate varies by population characteristics and the definition of prediabetes. In more recent major studies, progression estimates have been similar: the annualized incidence was 11% in the Diabetes Prevention Program (DPP) Outcomes Study. [7] Studies suggest that the risk of diabetes development on the basis of FPG and 2-hour post load glucose is broadly similar to that posed by HbA1c: According to an ADA expert panel, up to 70% of individuals with prediabetes will eventually develop diabetes. [8]

The most important factors that may explain the pathophysiology of prediabetes are increased insulin resistance and decreased insulin secretion. During glucose stimulation, pancreatic insulin secretion physiologically suppresses hepatic glucose production in the liver; however, glucose utilization is promoted in the peripheral tissues, including muscle and adipose tissue. Insulin resistance refers to a dysfunctional physiological response to insulin secretion *in vivo*. Despite normal or higher insulin levels, hepatic glucose production is not adequately suppressed, or a reduction in glucose utilization in peripheral tissue causes increased plasma glucose concentrations. Compared with Normal Glucose Tolerance subjects, there is a significantly higher tendency for insulin resistance

to increase in prediabetes subjects. [9,10]

Evaluation of insulin resistance or sensitivity and β -cell function is important for understanding the disease status and selection of pharmacologic treatment. The gold standard of evaluation of insulin sensitivity is glucose clamp test. However, the test is limited to research use and is difficult to perform at every medical institution. Although there are also other tests, they are often complex or inadequate. Homeostasis model assessment, first described by Matthews *et al.*, is hypothetical method for estimating insulin sensitivity. This model is based on the theory of a feedback loop between β cells and the liver. The homeostasis model assessment of insulin resistance (HOMA-IR), calculated from fasting plasma glucose level and fasting plasma insulin, is a simple method for evaluation of insulin sensitivity and correlates with the results of glucose clamp test in subjects with diabetes without significant hyperglycemia. [11]

The use of metformin to treat prediabetes patients is based on the results of the US Diabetes Prevention Program. Randomized, controlled trial studies have shown improvement in fasting serum glucose, fasting insulin, and homeostasis model assessment-estimated insulin resistance (HOMA-IR) on metformin therapy associated with insulin resistance. According to many studies the major effect of metformin may be through inhibition of appetite probably by increasing the levels of GLP- 1 and by interacting with signaling of hormones such as ghrelin, leptin and insulin leading to reduction of excessive weight gain having favorable effect on HOMA IR, and glycemic control. [12]

Thiazolidinedione, including troglitazone, rosiglitazone, and pioglitazone have consistently been shown to be twice as effective as metformin in preventing IGT/IFG conversion to type 2 diabetes and in inducing reversion to normal glucose tolerance. Benefit of thiazolidinedione is related both to their insulin-sensitizing effect and their ability to augment and/or preserve β -cell function. [13] Although thiazolidinedione has not been approved for the treatment of prediabetes, they have been shown to prevent the progression of IGT/IFG to type 2 diabetes, and many physicians have begun to use these antidiabetic agents to slow or prevent the progression of prediabetes to diabetes in persons at high risk. Hence in the present study we plan to compare the effect of pioglitazone and metformin on Serum insulin, Blood glucose level, HbA1c, HOMA -IR in obese prediabetes patients.

Materials and Methods

Design

Prospective, open label, comparative, randomized, parallel group, single center study. Total number of 120 patients with prediabetes and having HOMA-IR cutoff >1.8 . After taking informed written consent patients are randomized into two groups. Group I received Metformin 500 mg SR BD for 6 months and group II has received Pioglitazone 7.5 mg BD for 6 months. The subjects enrolled for this study were selected from the Out-Patient Department of Medicine, MGM medical College, Aurangabad according to the inclusion and exclusion criteria.

Inclusion criteria

- Male or female patients aged more than 40 years with prediabetes.
- HbA1c in the range of 5.7 to 6.4 % at screening.
- HOMA IR of more than 1.8.

Exclusion criteria

- Known cases of type 1 and type 2 diabetes mellitus.
- HOMA -IR of less than 1.8
- Cardiovascular diseases.
- Renal disease, Hepatic disease, GIT disease, hematological disease.
- Pregnant or lactating female.
- Smokers, alcoholic patients

Statistical Analysis

The data was compiled in excel sheet and data analyzed by using SPSS 20th version. Student Paired t test and unpaired t test was used to measure the differences between inter and intra group variations.

Results

Baseline characteristics

A total of 120 subjects were enrolled in this study. Patients were randomly divided into two groups of 60 each

Table 1
Age and sex wise distribution of the subjects under study

| Age in years | Group I (MET) | | Group II (PIO) | |
|--------------|---------------|----|----------------|----|
| Gender | M | F | M | F |
| 18-40 | 24 | 36 | 18 | 42 |
| Total | 60 | | 60 | |
| p-value | P=0.0466 | | | |

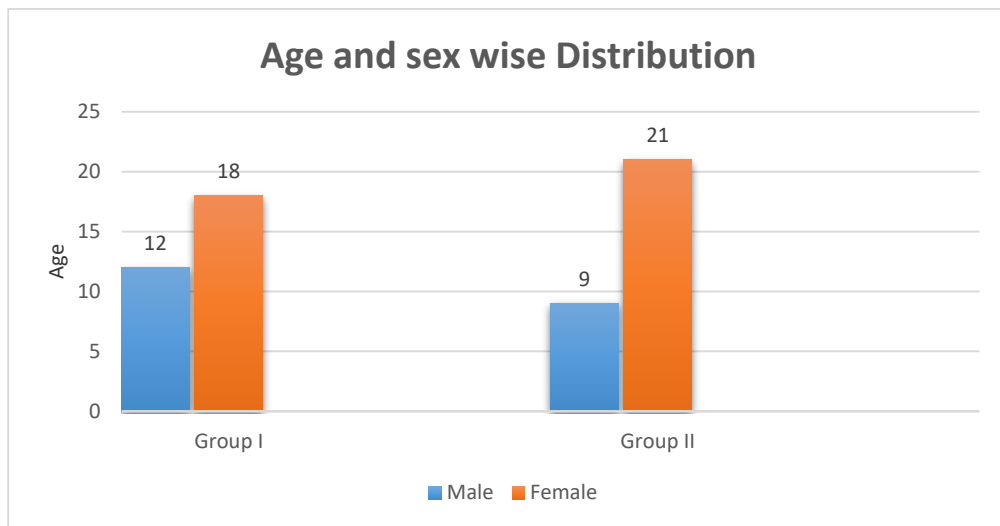


Figure 1. Age and sex wise distribution of the subjects under study

Table no. 1 shows the age and sex wise distribution of the subjects in 2 groups under study. Two groups consisted of 60 subjects each. Group I consisted of 40% male and 60% female patients. Male patients in Group II were 30% and female were 70%.

Table 2

Comparison of Fasting Blood Glucose in both groups at baseline and after 3rd and 6th months using unpaired t-test

| FBG | Group I Mean±SD | Group II Mean±SD | p-value |
|----------------|--------------------|---------------------|-------------|
| Baseline | 119.38± 9.20 | 120.05±5.10 | P=0.322 NS |
| After 3 Months | 95.50±3.93 | 89.60±3.40 | P<0.0001 HS |
| After 6 Months | 88.20±2.70 | 74.58±4.73 | P<0.0001 HS |

If $p > 0.05$ Not Significant, $p < 0.05$ Significant, NS= Not significant, HS= Highly Significant

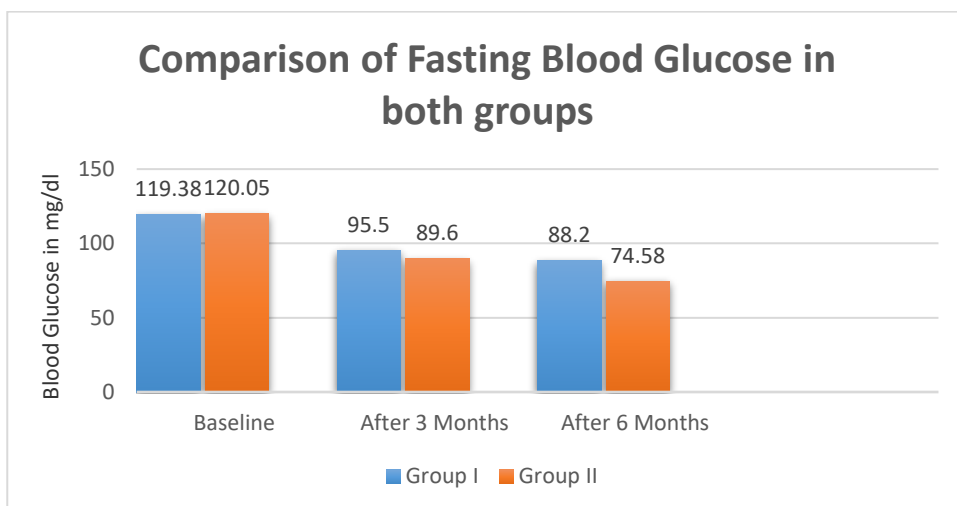


Figure 2. Comparison of Fasting Blood Glucose in both groups at baseline and after 3rd and 6th months

There was a statistically HIGHLY significant decrease in Fasting Blood Glucose levels in Group I and II, after 3rd and 6th months of treatment as compared to baseline.

Table 3

Comparison of Mean Differences of Fasting Blood Glucose at baseline Vs After 6 months in Groups analyzed by paired “t” test

| FBG | Mean Difference | P-value |
|--|-----------------|------------|
| Baseline Vs After 6 months in Group I | 31.18 | P<0.0001 S |
| Baseline Vs After 6 months in Group II | 45.47 | P<0.0001 S |

P value < 0.05 is significant & P value > 0.05 is not significant

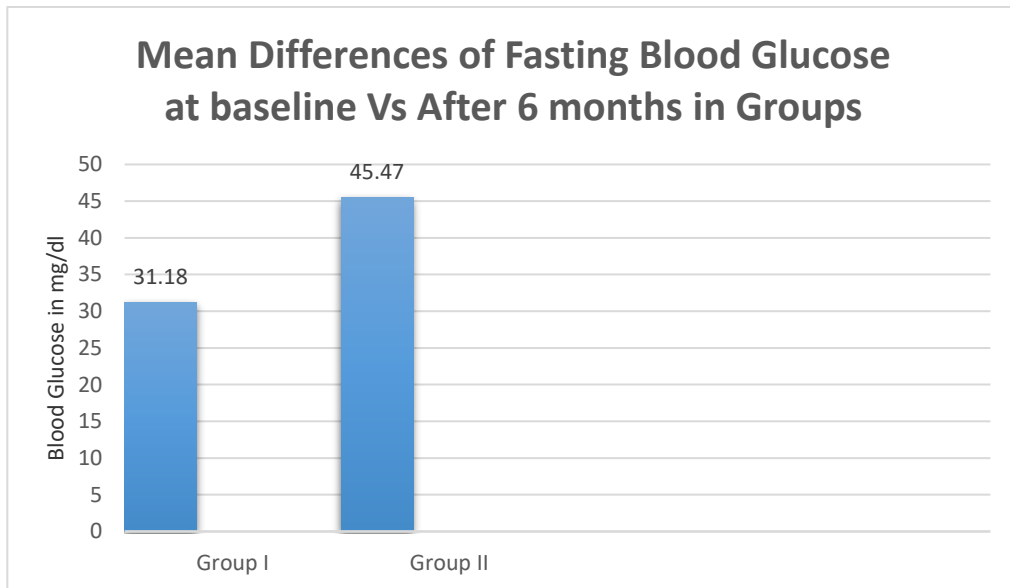


Figure 3. Comparison of Mean Differences of Fasting Blood Glucose at baseline Vs After 6 months in Groups

Table 4

Comparison of HOMA-IR in both groups at baseline and after 6th months using unpaired t-test

| HOMA-IR | Group I Mean±SD | Group II Mean±SD | p-value |
|----------------|--------------------|---------------------|-------------|
| Baseline | 3.44 ± 0.46 | 3.30 ± 0.45 | P=0.062 NS |
| After 6 Months | 2.21 ± 0.30 | 1.91 ± 0.32 | P<0.0001 HS |

If $p > 0.05$ Not Significant, $p < 0.05$ Significant

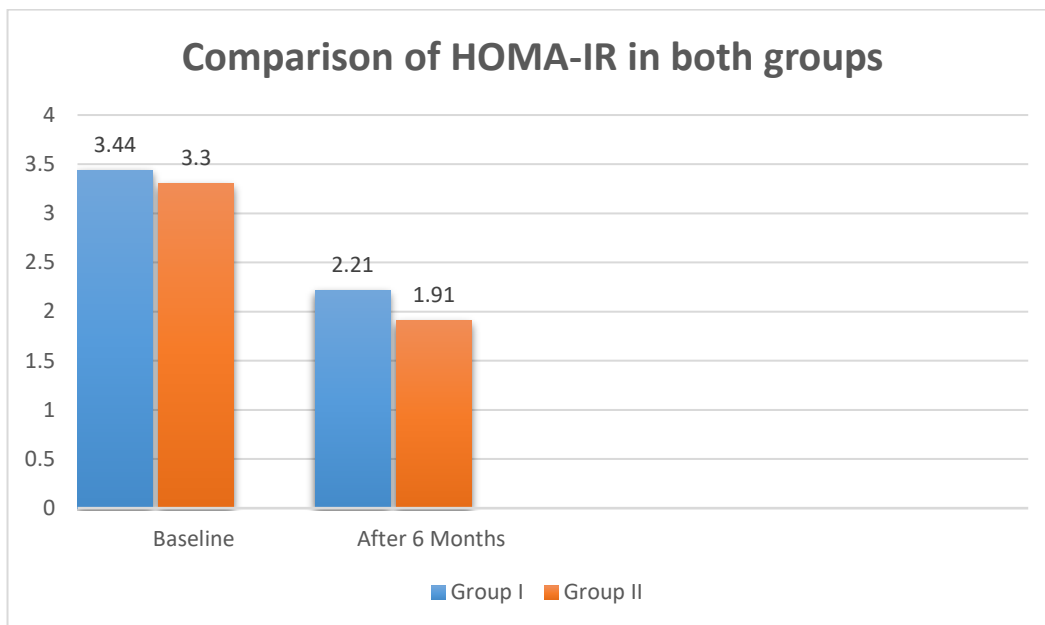


Figure 4. Comparison of HOMA-IR in both groups at baseline and after 6th months

There was a statistically HIGHLY significant decrease in HOMA-IR in Group I and II, after 6th months of treatment as compared to baseline

Table 5

Comparison of Mean Differences of HOMA-IR at baseline Vs After 6 months in Groups analyzed by paired "t" test

| HOMA-IR | Mean Difference | P-value |
|--|-----------------|------------|
| Baseline Vs After 6 months in Group I | 1.23 | P<0.0001 S |
| Baseline Vs After 6 months in Group II | 1.39 | P<0.0001 S |

P value < 0.05 is significant & P value > 0.05 is not significant

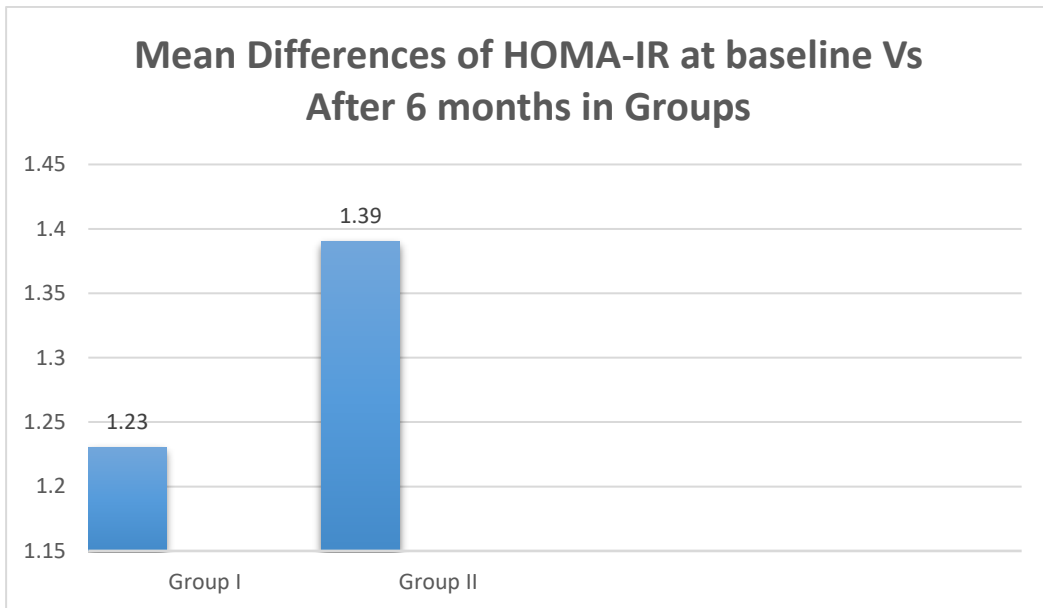


Figure 5. Comparison of Mean Differences of HOMA-IR at baseline Vs After 6 months in Groups

Table 6

Comparison of HbA1c in both groups at baseline and after 6th months using unpaired t-test

| HbA1c | Group I Mean±SD | Group II Mean±SD | p-value |
|----------------|--------------------|---------------------|-------------|
| Baseline | 6.17 ± 0.31 | 6.13 ± 0.42 | P=0.310 NS |
| After 6 Months | 5.47 ± 0.25 | 4.95 ± 0.20 | P<0.0001 HS |

If $p > 0.05$ Not Significant, $p < 0.05$ Significant

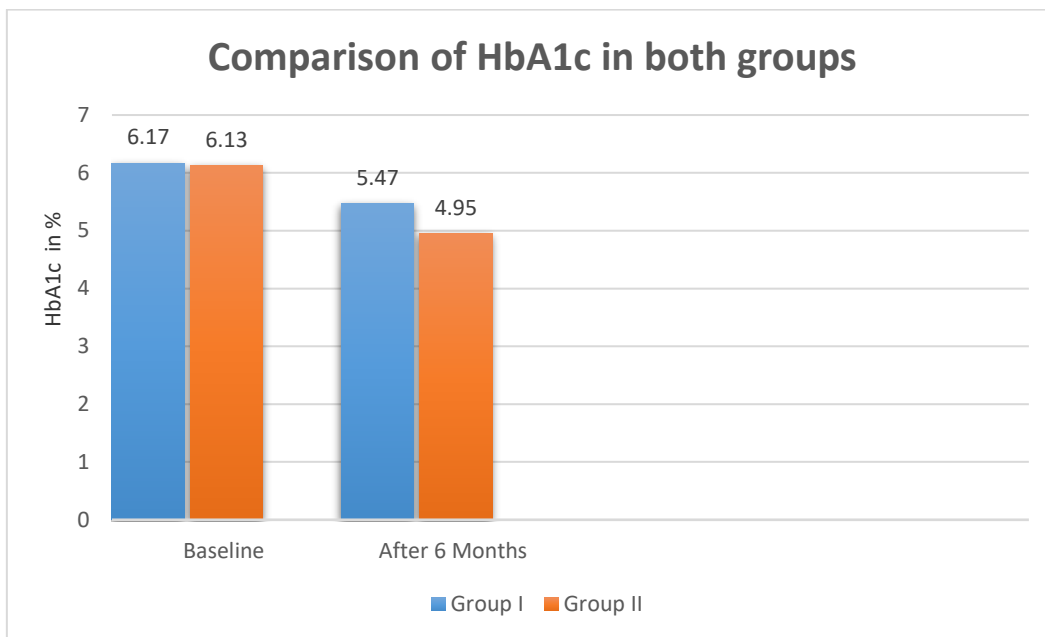


Figure 6. Comparison of HbA1c in both groups at baseline and after 6th months

There was a statistically HIGHLY significant decrease in HbA1c in Group I and II, after 6th months of treatment as compared to baseline.

Table 7
Comparison of Mean Differences of HbA1c at baseline Vs After 6 months in Groups analyzed by paired “t” test

| HbA1c | Mean Difference | P-value |
|--|-----------------|------------|
| Baseline Vs After 6 months in Group I | 0.7 | P<0.0001 S |
| Baseline Vs After 6 months in Group II | 1.1 | P<0.0001 S |

P value < 0.05 is significant & P value > 0.05 is not significant

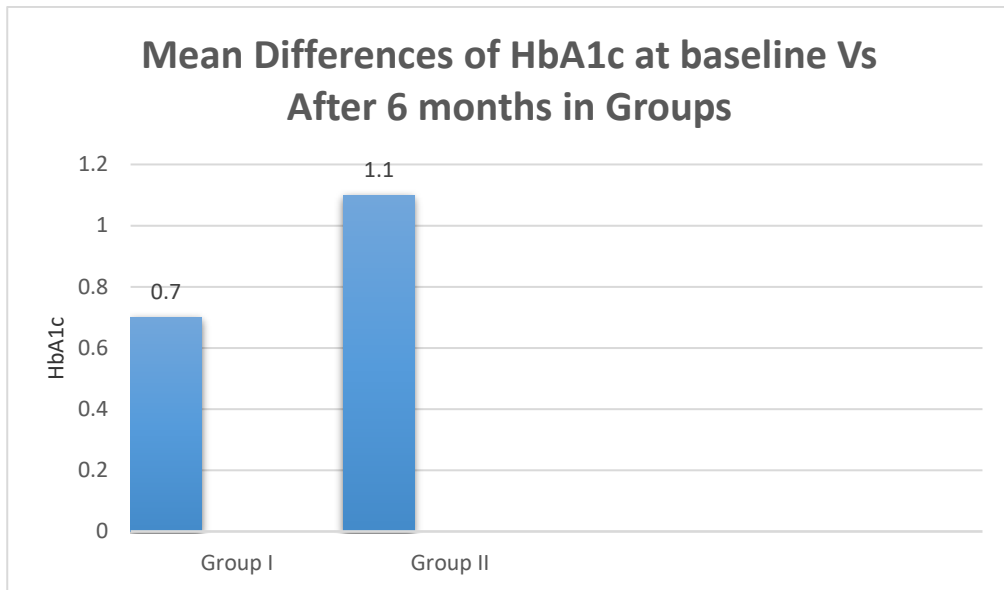


Figure 7. Comparison of Mean Differences of HbA1c at baseline Vs After 6 months in Groups

Table 8

Comparison of Serum insulin in both groups at baseline and after 6th months using unpaired t-test

| Serum Insulin | Group I Mean±SD | Group II Mean±SD | p-value |
|----------------|--------------------|---------------------|-------------|
| Baseline | 35.58 ± 3.49 | 35.13 ± 2.85 | P=0.441 NS |
| After 6 Months | 26.73 ± 3.21 | 21.77 ± 2.52 | P<0.0001 HS |

If $p > 0.05$ Not Significant, $p < 0.05$ Significant

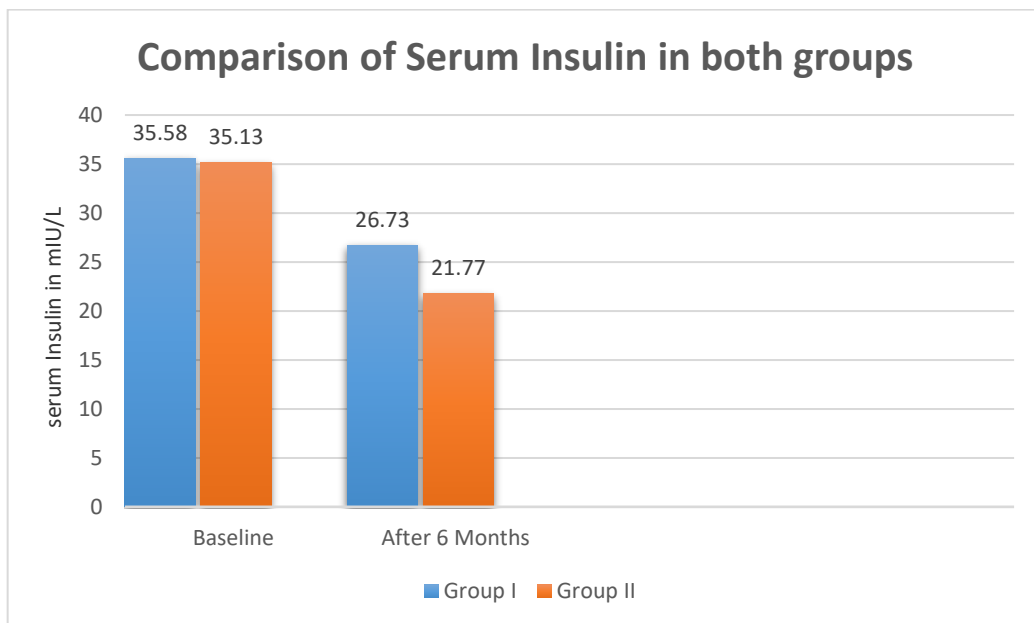


Figure 8. Comparison of Serum insulin in both groups at baseline and after 6th months

There was a statistically HIGHLY significant decrease in Serum insulin in Group I and II, after 6th months of treatment as compared to baseline.

Table 9

Comparison of Mean Differences of Serum insulin at baseline Vs After 6 months in Groups analyzed by paired “t” test

| Serum Insulin | Mean Difference | P-value |
|--|-----------------|------------|
| Baseline Vs After 6 months in Group I | 8.85 | P<0.0001 S |
| Baseline Vs After 6 months in Group II | 13.36 | P<0.0001 S |

P value < 0.05 is significant & P value > 0.05 is not significant

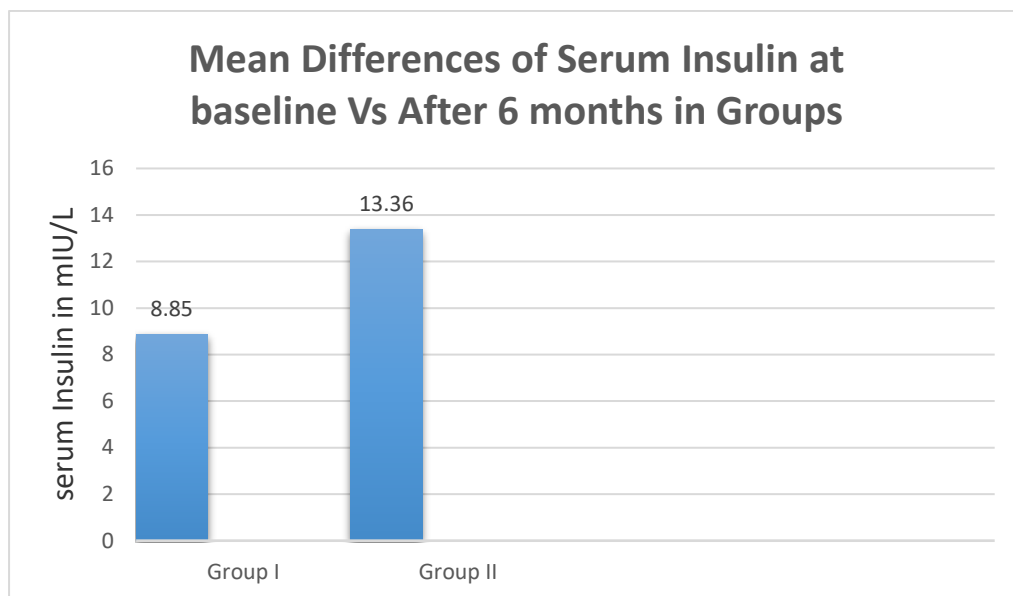


Figure 9. Comparison of Mean Differences of Serum insulin at baseline Vs After 6 months in Groups

Table 10
Adverse Drug Reaction

| Groups | Weight gain | Diarrhea | Nausea/ vomiting | Abdominal Pain |
|----------------|-------------|----------|---------------------|----------------|
| Group I (MET) | | 2 | 2 | 2 |
| Group II (PIO) | 1 | | | |
| Total | 1 | 2 | 2 | 2 |

Weight gain was reported in group II in one patient only while diarrhea and abdominal pain was seen in two patients in group I nausea/vomiting was reported by two patients in group I.

Discussion

Presently, objectives for treatment of prediabetes include not only normalization of hyperglycemia, but also reduction of complication associated with insulin resistance. Directly targeting underlying insulin resistance in the periphery is a relatively new approach for treating prediabetes and type 2 diabetes. Beyond enhancements in glycemic control, reduction of insulin resistance may confer beneficial changes in additional components of insulin resistance syndrome, independent of improvements in glucose metabolism. [14,15] Thus, oral antihyperglycemic medication therapies that target elevated insulin resistance are rational treatment strategies that also improve the cardiovascular risk profile. Both pioglitazone and metformin are first-line therapeutic interventions in the management of type 2 diabetes patients, but their mechanisms of action are different and there are no data that directly compare their antihyperglycemic efficacy, their effects on insulin resistance, or their tolerability on recently

diagnosed prediabetes Oral Antidiabetic Medication naive patients. Therefore, we compared the efficacy and tolerability of monotherapy with pioglitazone to metformin in this population. The primary objective of the study was to compare the effect of each treatment on HOMA IR and hemoglobin A1C (A1C).

Effects on HOMA IR

Both groups showed significant reduction in HOMA-IR level at the end of study period. After six months of treatment mean HOMA-IR was reduced from 3.44 to 2.21 from baseline which was statistically highly significant [-1.23, $p < 0.0001$] in metformin group L MP van der Aa et al [16] showed mean HOMA IR reduction from baseline. (-1.0, $p < 0.02$) with metformin which is comparable with our study. On the other hand, mean HOMA-IR was reduced from 3.30 to 1.91 from baseline which was statistically highly significant [-1.39, $p < 0.0001$] in pioglitazone group. Silvio E. Inzucchi et al [17] showed mean HOMA IR reduction from baseline. (-1.3, $p < 0.0001$) with pioglitazone. However, mean difference change from baseline was greater with pioglitazone treated group when compared with metformin group (-1.39 vs -1.23). Our finding is similar to the study done by IMRE PAVO et al [18] which showed statistically significant reduction in mean HOMA-IR (4.9, $p < 0.002$) with pioglitazone when compared with metformin. (-0.9, $p < 0.003$).

Effects on HbA1c.

There was statistically significant difference between the treatment groups in HbA1c change from baseline. Metformin group had significant decreases from baseline in HbA1c (-0.7, $p < 0.001$) after six months of treatment. Our result matches with the study done by BARRY J. GOLDSTEIN et al [19] who showed reduction of HbA1c with metformin (-0.82, $p < 0.005$). Similarly, in pioglitazone group there was a significant mean decrease in HbA1c from baseline (-1.1, $p < 0.0001$). Ours finding correlate with study done by Aronoff S et al [20] which showed significant mean decrease in HbA1c (-1.0, $p < 0.05$). Mean difference change from baseline was greater with pioglitazone treated group when compared with metformin group (-0.8 vs -0.5). Our finding is similar to the study done by IMRE PAVO et al [18] which showed statistically significant reduction in HbA1c (-1.3, $p < 0.001$) with pioglitazone when compared with metformin. (-1.2, $p < 0.001$).

Both treatments were generally well tolerated. In our study, most common adverse effects reported were weight gain with pioglitazone and nausea, vomiting and diarrhea with metformin. IMRE PA VO et al [18] reported weight gain with pioglitazone and nausea, diarrhea with metformin in his study. No treatment was needed for these adverse effects. There was no drop out in our study. The present study clearly shows a difference in HOMA-IR and HbA1c between treatment groups (in favor of pioglitazone). Furthermore, the significant difference between HOMA-IR and HbA1c results for the two drugs in the current study is in accordance with a glucose disposal rate for pioglitazone that is two to four times higher than that observed with metformin, as measured by clamp techniques used in the previously cited studies. [21,22] Both metformin and pioglitazone have been shown to improve glycemic control as well as insulin resistance; therefore, a direct comparison of these two drugs is of particular clinical interest. This is an innovative head-to-head comparison of the effects of pioglitazone and metformin,

and, together with the recent publication of Hallsten et al. [23] is one of the first trials to compare the effects of TZD and metformin monotherapy both in general and specifically in patients of prediabetes who are also naive to glucose-lowering medication.

Whereas, insulin resistance prevails in these patients, insulin-sensitizing agents represent viable treatment options. Hepatic function in prediabetes is of particular interest. In addition to different effects on insulin sensitivity, pioglitazone and metformin had different effects on body weight; pioglitazone treatment resulted in weight gain, whereas metformin treatment resulted in weight loss. Weight reduction in patients treated with metformin has been shown in a vast majority of previous studies.^[24] Because obesity often contributes to the etiology of prediabetes, weight reduction with metformin therapy may be an additional benefit. Weight loss in patients who are obese may be particularly beneficial in terms of the associated risk reduction of both microvascular and macrovascular complications.

More consistently, increased body weight has been reported after treatment with PPAR- γ agonists. Previous studies have shown a shift of fat distribution from visceral to subcutaneous adipose tissue during treatment with thiazolidinedione, including pioglitazone suggesting this shift as a potential explanation for the seemingly paradoxical simultaneous improvement in glycaemia and insulin resistance observed with increase in body weight.^[25] Because visceral adiposity was not assessed in the present study, we could not determine whether relationships existed between body fat distribution and the differential effects of pioglitazone and metformin on glycemic control and insulin sensitivity.

Limitations of this study include the use of indirect measures of insulin sensitivity as indicators of insulin resistance, instead of more invasive and logistically challenging techniques, such as the hyperinsulinemic-euglycemic clamp, or a frequently sampled i.v glucose tolerance test. Quon et al [26] has emphasized greater clinical utility of HOMA as compared with less predictive indirect measures of insulin sensitivity such as the fasting glucose to insulin ratio, especially when glucose levels are abnormal. Based on the ability of HOMA to accurately mimic the results of glucose clamp techniques, Bonora et al. [27] have concluded that HOMA is a reliable indicator of insulin sensitivity in large-scale studies in which procedures such as clamp techniques may be impractical. Thus, the indirect measures of insulin sensitivity used in this study are considered as surrogates for insulin resistance measured using the diagnostic gold standard of clamp studies.

Results of our study confirm that both pioglitazone and metformin represent effective and safe first-line pharmacological treatment options in recently diagnosed, Oral Antidiabetic Medication -naive patients of prediabetes. The present study demonstrates that pioglitazone and metformin monotherapies are equally effective in lowering A 1C and HOMA-IR, but improvements were more pronounced in patients on pioglitazone therapy. Further clinical investigations are indicated to clarify to what degree insulin sensitivity contributes to the efficacy of pioglitazone or metformin monotherapy in the early stages of prediabetes.

Conclusion

Our study showed pioglitazone was superior in reducing HOMA-IR when compared with metformin. If combination of pioglitazone and metformin is used far superior reduction will be achieved on HOMA- IR. Limitation of our study was short duration of study and small sample size.

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