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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

Introduction: 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. ***Methods:*** The present study was Prospective, open label, comparative, randomized, parallel group, single center study conducted at Department of General Medicine, Shadan Institute of Medical Sciences, Teaching Hospital & Research Centre, Hyderabad. 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 HbAlc 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. ***Results:*** 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 37.65 to 28.75 (-8.9) in metformin group; in Pioglitazone group from 37.43 to 23.75 (-13.68). Pioglitazone statistically highly significant than metformin group in improving glycemic indices. ***Conclusions:*** 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

Insulin Resistance and relative insulin deficiency contribute to the pathogenesis of type 2 diabetes. Insulin resistance, which plays the major role early in the evolution of the disease, is associated with clusters of cardiovascular risk factors (e.g. hypertension and dyslipidemia) that contribute to increased risk for coronary heart disease.[1] Presently, objectives for treatment of type 2 diabetes include not only normalization of hyperglycemia, but also reduction of hypertension and correction of dyslipidemia.[2] Directly targeting underlying insulin resistance in the periphery is a relatively new approach for treating 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. [3] Thus, oral antihyperglycemic medication (OAM) therapies that target elevated insulin resistance are rational treatment strategies that also improve the cardiovascular risk profile.

Pioglitazone is a thiazolidinedione (TZD) insulin sensitizer.[5] As a nuclear peroxisome proliferator-activated receptor (PPAR-) agonist, it improves blood glucose and plasma lipoprotein profiles by modulating the transcription of genes that play key roles in carbohydrate and lipid metabolism, respectively. Pioglitazone may also improve endothelial dysfunction and other inflammatory conditions in the vasculature. Similar to other TZDs, including troglitazone and rosiglitazone, pioglitazone has been shown to enhance insulin sensitivity in the peripheral organs and the liver, resulting in improved glycemic control in patients with type 2 diabetes.[6] In these patients, pioglitazone also lowers elevated plasma free fatty acids and improves diabetic dyslipidemia [low HDL-cholesterol (HDL-C) and high triglycerides (TGs); Ref. 13].

Metformin improves glycemic control primarily by sensitizing the liver to the effects of

insulin, thus decreasing hepatic insulin resistance and glucose output through a reduction in gluconeogenesis. Metformin also increases glucose use as a consequence of its insulin-sensitizing effect in the periphery. [7]In addition, metformin has been found to improve the lipoprotein profile and induce weight reduction. The benefits of metformin have been associated with a reduction in both microvascular and macrovascular complications in an overweight subset of patients in the United Kingdom Prospective Diabetes Study (UKPDS; Ref. 18)

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 in recently diagnosed OAM-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 glycemic control, as defined by change in hemoglobin A1C (A1C).

MATERIALS AND METHODS:

Prospective, open label, comparative, randomized, parallel group, single center study conducted at Department of General Medicine, Shadan Institute of Medical Sciences, Teaching Hospital & Research Centre, Hyderabad. Total number of 140 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.
- HbAlc 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 140 subjects were enrolled in this study. Patients were randomly divided into two groups of 70 each

Table No. l: 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	**29**	**41**	**23**	**47**
Total	**70**		**70**	
p-value	**P=0.0466**			

Table no. 1 shows the age and sex wise distribution of the subjects in 2 groups under study. Two groups consisted of 70 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	121.48± 9.20	123.05±5.10	P=0.462 NS
After 3 Months	97.50±3.93	91.60±3.40	P<0.0001 HS
After 6 Months	91.20±2.70	76.68±4.73	P<0.0001 HS

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

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	30.28	P<0.0001 S
Baseline Vs After 6 months in Group II	46.37	P<0.0001 S

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

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

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

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	9.27 ± 0.31	9.13 ± 0.42	P=0.410 NS
After 6 Months	7.57 ± 0.25	7.55 ± 0.20	P<0.0001 HS

If p > 0.05 Not Significant, p < 0.05 Significant

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	**1.7**	**P<0.0001 S**
Baseline Vs After 6 months in Group II	**1.5**	**P<0.0001 S**

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

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	37.65 ± 3.49	37.43 ± 2.85	P=0.441 NS
After 6 Months	28.75 ± 3.21	23.75 ± 2.52	P<0.0001 HS

If p > 0.05 Not Significant, p < 0.05 Significant

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	8.9	P<0.0001 S
Baseline Vs After 6 months in Group II	13.68	P<0.0001 S

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

DISCUSSION

Due to variations in mechanisms and sites of action, all existing AD drugs possess comparative differences in their glucose lowering efficacy. In our meta-analysis, pioglitazone monotherapy produced similar efficacy as other AD drugs in HbA1c reduction but greater efficacy with statistical significance in FBS reduction. Subgroup analysis with specific comparator drugs revealed pioglitazone to be a good choice of treatment in reducing HbA1c and FBS which was not inferior to metformin, SUs and DPP-4 inhibitors. This findings are supported by several previously published reports on patients with T2DM39–44. However, as only one study each comparing pioglitazone vs acarbose and pioglitazone vs repaglinide lead to opposite findings, it is difficult to judge which monotherapy was more efficacious. Subgroup analysis on geographical locations showed variable glycemic response of T2DM patients with pioglitazone treatment, indicating variable drug response due to patients' ethnic difference, age, sex, baseline weight and HbA1c45. Comparing studies in terms of duration of diabetes revealed a more pronounced efficacy of pioglitazone on FBS reduction in patients' having long-term T2DM than in naïve T2DM patients'. It is plausible that prior AD treatment of a portion of patients before enrollment might have influenced the efficacy of pioglitazone. However, this scenario was not observed in the context of HbA1c reduction, therefore warranting further investigations. In subgroup analysis following trial duration, pioglitazone was efficacious in reducing HbA1c and FBS levels than comparators when the trials were conducted for >12 weeks duration suggesting a slower onset action of pioglitazone to give maximal effect. A few long-term (52-week) studies evaluating pioglitazone monotherapy also supported the sustained antihyperglycaemic effect of pioglitazone.[8] Subgroup analysis based on dosage revealed a higher efficacy of fixed-dose pioglitazone in improving glycemic response than variable-dose which again suggests the gradual increase in therapeutic action by pioglitazone when given at a fixed-dose than in variable-dose.

In line with earlier findings in T2DM patients,[9] we also observed significant mean increase in patients' BW (2.06 kg) following pioglitazone use. It is believed that increased BW with pioglitazone is due to fluid retention and fat accumulation in the body. Although previous studies reported BW gain in a higher rate, a few but contradictory findings exist where the use of pioglitazone without or with lower BW gain were also reported. [10] Nonetheless, BW gain is a major problem among pioglitazone users, which may limit its utility. However, numerous studies have shown the benefits of adjuvant strict dietary restriction with exercise intervention to attenuate pioglitazone-induced BW gain.[11]

Te HOMA-IR method is widely used for assessing insulin resistance in clinical trials and epidemiological studies, improvement of which indicates enhanced insulin sensitivity. Since pioglitazone is an insulin sensitizer which improves insulin sensitivity by acting on peripheral and liver cells; it is anticipated that pioglitazone would improve HOMA-IR compared with comparator. [12] In this meta-analysis however, pioglitazone had similar efficacy as comparators on HOMA-IR. However, interestingly detailed analysis of individual studies revealed that studies (n=3) conducted in Iran appear to favor the comparators rather than pioglitazone indicating the possible influence of genetic makeup in the pharmacodynamics of pioglitazone. Apart from the Iranian studies, other studies (n=7) favored pioglitazone with statistical significance (p=0.05)

Consistent with previous observations, this meta-analysis confirmed the positive influence of pioglitazone on the lipid profile of T2DM patients with significant decrease in TGs and increase in HDL (although mean HDL increase was similar to comparators.[13] Several studies have reported the effect of pioglitazone in increasing TC and LDL, but pioglitazone appeared to be associated with TC and LDL reduction in this meta-analysis which was also supported by other evidences.[14] It is plausible that variations in treatment duration, pioglitazone dosage as well as patients' compliance to pioglitazone are responsible for the contradictory findings of individual studies. Large number of clinical studies have reported pioglitazone as a good regulator of BP. [15] Our meta-analysis results also support the contribution of pioglitazone in reducing BP, particularly SBP, in patients with T2DM, although changes in BP from baseline were not significantly associated with pioglitazone use. Since hypertension is frequently diagnosed as a co-morbidity in patients with T2DM which could lead to long-term vascular and renal complications, BP-lowering efficacy of pioglitazone may be helpful in preventing the development of hypertension and its associated complications in T2DM patients.

Similar to prior studies, [16] the incidences of oedema were significantly higher with pioglitazone, while the incidences of hypoglycaemia were significantly lower than comparators. Although limited number of studies were included in these analyses, the presence of low heterogeneity indicates reliability of the results. The low hypoglycemic risk associated with pioglitazone monotherapy was reported to be beneficial for T2DM patients with CV disease, especially in preventing mortality after severe hypoglycemia.[17] Two meta-analyses investigated the association of pioglitazone with CV risk reported pioglitazone with no relevant effect on CV events among a diverse population of diabetes patients, significantly lower risk of death and reduced all-cause mortality, thereby further supporting our meta-analysis results.[18] Despite the favorable effect, pioglitazone treatment in patients with underlying heart disease may be harmful since pioglitazone-mediated peripheral oedema can progress into congestive heart. Apart from the aforementioned adverse events, analysis of other reported adverse events during pioglitazone treatment did not reach statistical significance due to insufficient included studies and therefore, these results were not able to evaluate the safety profile of pioglitazone. However, the incidence of bladder cancer during pioglitazone treatment was not reported in any of the included studies supporting the conclusion of a recent meta-analysis. [19] Which suggested that other factors but not pioglitazone may contribute to the risk of bladder cancer.

CONCLUSIONS

Based on the findings of this meta-analysis, we concluded that pioglitazone monotherapy showed overall favorable risk-benefit balance. Specifically, pioglitazone is an effective treatment option in managing T2DM patients due to its potential of ameliorating hyperglycemia, adverse lipid metabolism and BP. Improvement of these CV risk factors is crucial in terms of CV protection and stroke prevention in T2DM patients. Pioglitazone monotherapy can also be used as an alternative to metformin monotherapy if metformin cannot be tolerated or as a combination therapy if metformin alone fails to achieve target HbA1c level. Since hypoglycemia is recognized as a potential cause of death70, particularly due to cerebral damage, the low hypoglycaemic risk of pioglitazone over other AD drugs will be advantageous in preventing mortality in T2DM patients

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