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Original article

Comparison of the Effect of Pioglitazone and Metformin on HOMA IR In Patient of Prediabetes

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Abstract:

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. . 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 Hence in the present study we plan to compare the effect of pioglitazone and metformin on HOMA –IR IN obese prediabetic patients.AIMS Comparison of the effect of pioglitazone and metformin on HOMA IR in patient of prediabetes.

Objectives : To study the effect of Metformin and pioglitazone on HOMA IR and HbA1c. Patient reported ADR of pioglitazone and metformin **.**

Results: There was a statistically HIGHLY significant decrease in HOMA –IR and HbA1c levels in Group I (Metformin), and groupll pioglitazone after 6 months of treatment as compared to baseline**.**

Conclusion: Our study showed pioglitazone was superior in reducing HOMA-IR when compared with metformin

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 (in the absence of impaired glucose tolerance – IGT) and IGT defined as postload plasma glucose of 140-199mg/dl based on 2-h 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 haemoglobin A1c levels of 5.7–6.4% as a new category of high diabetes risk.[2]

The term prediabetes itself has been critised on the basis that many people with prediabetes do not progress to diabetes, the term may imply that no intervention is necessary as no disease is present, and finally diabetes risk does not necessarily differ between people with prediabetes and those with a combination of other diabetes risk factors. Indeed, the WHO used the term '*Intermediate Hyperglycaemia*' and an International Expert Committee convened by the ADA the '*High Risk State of Developing Diabetes*' rather than 'prediabetes'.[3]

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.[4-11]

The use of metformin to treat prediabetic 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]

Thiazolidinediones, 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. Presently pioglitazone is the only drug approved while Rosiglitazone is banned because of increased cardiovascular risk. Hence in the present study we plan to compare the effect of pioglitazone and metformin on HOMA –IR IN obese prediabetic patients.

AIMS OF STUDY:

Comparison of the effect of pioglitazone and metformin on HOMA IR in patient of prediabetes.

OBJECTIVES OF STUDY

- To study the effect of pioglitazone on HOMA IR.
- To study the effect of Metformin on HOMA IR
- To study the effect of pioglitazone on HbA1c.
- To study the effect of Metformin on HbA1c.
- Patient reported ADR of pioglitazone and metformin

MATERIALS AND METHOD

DESIGN-

Open label, randomized, parallel group, comparative and prospective study.

1. 60 cases with prediabetes for calculating HOMA IR with cut off of1.8.
2. Informed written consent was obtained from all the patients. .
3. Group I received Metformin 500 mg SR BD,
4. Group II Pioglitazone 7.5mg BD

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. Written informed consent was obtained from each patient

INCLUSION CRITERIA

- Male or female patients aged 18 to 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
- Clinically significant cardiovascular diseases, including h/o CCF
- Angina pectoris within 1 year and h/o MI with in 1 year
- Convulsive disorder
- Clinically significant G.I disease, including active peptic ulcer with in the preceding 5 years.
- Renal disease.
- Hepatic disease, hematological disease
- Known infection with human immunodeficiency virus.
- Pregnant or lactating female.
- Smokers, alcoholic patients

DURATION OF STUDY:

Six month randomised open label single centre prospective clinical study

Sample : The present study was carried out in collaboration with the Department of medicine , MGM medical College and Department of Pharmacology, MGM Medical College, Aurangabad. A total 60 patients were enrolled and evaluated between September 2014 to November 2016.

Patients were randomly divided into two groups of 30 each

Group I Metformin 500 mg SR BD,

Group II Pioglitazone 7.5 mg BD,

Sample technique

They were randomly allocated into 2 groups of 30 each by **chit method**

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Study visits included clinic visits on day 0, day 90 and day 180. Patients under went the same investigations during each visit as above.

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OBSERVATION AND RESULT:

A total of 60 subjects were enrolled in this study. Patients were randomly divided into two groups of 30 each

- **GROUP I** : METFORMIN 500 SR MG BD.
- **GROUP II** : PIOGLITAZONE 7.5 MG BD.

The data was analysed by paired t test and unpaired student t test using SPSS version 20

Table No.1: Age and sex wise distribution of the subjects under study:

Age in years	Group I [MET]		Group II [pioglitazone]	
Gender	**M**	**F**	**M**	**F**
18-40	**12**	**18**	**9**	**21**
TOTAL	**30**		**30**	
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 30 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 HOMA-IR in patients of Group I using paired t test and unpaired t test :-

Group I metformin	Mean ± SD	Change from baseline Mean	p-value	Pioglitazone vs metformin p-value
Before	3.82 ± 0.574			
After six Months	3.20 ± 0.474	- 0.6	0.0001	0.001

If p > 0.05 Not Significant, p < 0.05 Significant

There was a statistically HIGHLY significant decrease in HOMA –IR levels in Group I (Metformin), after 6 months of treatment as compared to baseline.

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Table 3: Comparison of HOMA-IR in patients of Group II using Paired t test and unpaired t test.

Group II pioglitazone	Mean ± SD	Change from baseline Mean	P value	Piogltizone vs metformin p-value
Baseline	4.04 ± 0.781	- 1.01	0.0001	0.0001
After six Months	3.03 ± 0.487			

If p > 0.05 Not Significant, p < 0.05 Significant There was a statistically HIGHLY significant decrease in HOMA –IR levels in Group II (poiglitazone), after 6 months of treatment compared to baseline

Table 4: Comparison of HbA1c in patients of Group I using paired T test and unpaired I test :-

Group I metformin	Mean ± SD	Change from baseline Mean	P value	Piolgitazone vs metformin p-value
Before	6.05 ± 0.252	- 0.5	0.0001	0.0001
After six Months	5.49 ± 0.227			

If p > 0.05 Not Significant, p < 0.05 Significant

There was a statistically HIGHLY significant decrease in HbA1c levels in Group I (Metformin), after 6 months of treatment compared to baseline.

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Table 5: Comparison of HbA1c in patients of Group II using paired t test and unpaired t test :-

Group II pioglitazone	Mean ± SD	Change from baseline Mean	P value	Pioglitazone vs metformin p-value
Before	6.07 ± 0.239	- 0.8	0.0001	0.001
After six Months	5.23 ± 0.223			

If p > 0.05 Not Significant, p < 0.05 Significant

There was a statistically HIGHLY significant decrease in HbA1c levels in Group II (poiglitazone), after 6 months of treatment compared to baseline.

Table 6 : 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 buy two patients in group I.

DISCUSSION

INSULIN RESISTANCE and relative insulin deficiency contribute to the pathogenesis of prediabetes[12] 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.[13] Thus, oral antihyperglycemic medication therapies that target elevated insulin resistance are rational treatment strategies that also improve the cardiovascular risk profile.

Pioglitazone is a thiazolidinedione (TZD) insulin sensitizer . As a nuclear peroxisome proliferator-activated receptor (PPAR- γ) agonist, it improves blood glucose by modulating the transcription of genes that play key roles in carbohydrate metabolism respectively

Metformin (a biguanide) 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.

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 prediabetic 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 haemoglobin 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 3.82 to 3.20 from baseline which was statistically highly significant [-0.62, p< 0.0001] in metformin group 1**. MP van der Aa et al** [14] showed mean HOMA IR reduction from baseline (-1.0, p< 0.02) with metformin which is comparable with our study. Mean HOMA-IR was reduced from 4.04 to 3.03 from baseline which was statistically highly significant [-1.01 p <0.0001] in pioglitazone group 2. **Silvio E. Inzucchi et al** [15] 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 (-1.01 vs -0.6). Our finding is similar to the study done by **IMRE PAVO *et al*** [16] which showed statistically significant reduction in mean HOMA-IR (14.9, p < 0.002) with poiglitazone 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. There was statistically significant difference between the two groups in HbA1c change from baseline. Metformin group I had significant decreases from baseline in HbA1c (-0.5, *P* <0.001) after six month of treatment. Our result matches with the study done by BARRY J. GOLDSTEIN et al [17] who showed reduction of HbA1c with metformin (-.0.82, p<0.005). Similarly in pioglitazone group II there was a significant mean decrease in HbA1c from baseline(-0.8 , p<0.0001). Ours finding correlate with study done by Aronoff S et al **[18]** 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* [19] which showed statistically significant reduction in HbA1c (-1.3, p < 0.001) with poiglitazone 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 diarrohea with metformin. IMRE PAVO *et al* [20] reported weight gain with pioglitazone and nausea , diarrhoea with metformin in his study. No treatment was needed for this adverse effect. 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.*[16] 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. Because insulin resistance prevails in these patients, insulin-sensitizing agents represent viable treatment options. Hepatic function in prediabetes is of particular interest. A recent study has shown that pioglitazone decreased hepatic fat content in patients with type 2 diabetes, and this decrease correlated with enhanced hepatic insulin sensitivity. 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.

More consistently, increased body weight has been reported after treatment with PPAR-γ agonists.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 iv glucose tolerance test. Quon et al [17] 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.*[23] have concluded that HOMA is a reliable indicator of insulin sensitivity in large-scale 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 A1C 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.

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