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Comparative study of Study of Safety, Efficacy of Metformin versus Pioglitazone on Lipid Levels in prediabetes patients

[1]M. Sangeetha
Research Scholar
Department of Pharmacology Index Medical College Hospital and Research Center
Malwanchal University

[2]Dr. Abhay John
Professor Department of Pharmacology Index Medical College Hospital and Research Center
Malwanchal University

Corresponding Author: Dr. Abhay John

Abstract

Introduction: 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) from 100-125mg/dl and impaired glucose tolerance (IGT) defined as post-glucose plasma level from 140- 199mg/dl based on 2-hours oral glucose tolerance test (OGTT). Metformin has pleiotropic effects leading to improved lipid and cholesterol metabolism, reduced inflammation and inhibition of cell growth. Pioglitazone is dependent on the presence of insulin to exert its advantageous effects and preserve β-cells of the islets of Langerhans, but does not act same as an insulin secretagogue. Improved glycaemic control results in lowering of circulating HbA1C and insulin levels in type 2 DM patients. **Material and Methods:** Present study is Comparative, Prospective, randomized, Open-label, Single Center, Parallel group study conducted at Index Medical college. Study was conducted in prediabetes patients for assessment of effects of Metformin and Pioglitazone. All patients were evaluated at baseline, 3 months for clinical and physical examination and laboratory investigation. Present Study was conducted in prediabetes Patients for assessment of effect of Metformin and Pioglitazone on lipid levels attending the outpatient department of Medicine in Index Hospitals and College. **Results:** In the lipid profile, both groups showed a decrease at three months in serum total cholesterol (30 mg/dl decrease from baseline to 3 months in the PGZ group versus 20 mg/dl decrease from baseline to 3 months in the MF group). The PGZ group achieved a significant decrease in serum triglyceride levels 45 mg/dl from baseline to 3 months and 11 mg/dL from baseline to 3 months in the MF group. Moreover, HDL showed an Increase at three months (5 mg/dl from baseline in the PGZ group versus 4 mg/dl from baseline in the MF group and low-density lipoprotein (LDL) cholesterol levels (30 mg/dl from baseline to 3 months in the PGZ group versus 30 mg/dl from the baseline to 3 months in the MF group). **Conclusion**: After 3 months' treatment with Metformin and Pioglitazone, showed statically significant reduction in Lipid Profile values. Whereas, after 3 months of treatment with Metformin and Pioglitazone caused reduction in Lipid Profile values statistically significant decreased compare with Metformin and Pioglitazone. On the hand,

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Metformin reduced PPBG level, statistically highly significant compared with Pioglitazone group.

Keywords: Lipid Levels, Metformin, Pioglitazone

INTRODUCTION:

Prediabetes defined as blood glucose levels above the normal but below thresholds for diagnosis of diabetes, is a risk state that defines a high chance of developing diabetes. [1] 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) from 100-125mg/dl and impaired glucose tolerance (IGT) defined as post-glucose plasma level from 140- 199mg/dl based on 2-hours oral glucose tolerance test (OGTT). [2]

Whereas, around 5-10% of people with prediabetes become diabetic annually although conversion rate varies by population characteristics. [3] In Diabetes Prevention Program (DPP) Outcomes Study states that the annualized incidence of prediabetic to diabetic was 11%. [4] In addition, DDP study also revealed that the risk of diabetes development on the basis of above the normal range of FPG and 2-hour post load glucose is broadly similar to an ADA criteria, up to 70% of individuals with prediabetes will eventually develop diabetes. [5]

The most important factors that may explain the pathophysiology of prediabetes are increased insulin resistance and decreased insulin secretion. [6] Normally, during glucose stimulation, pancreatic insulin secretion occur, physiologically suppresses hepatic glucose production in the liver, and also glucose utilization is promoted in the peripheral tissues, including muscle and adipose tissue. [7] Whereas, insulin resistance refers to a dysfunctional physiological response to insulin secretion. [8]

Metformin has pleiotropic effects leading to improved lipid and cholesterol metabolism, reduced inflammation and inhibition of cell growth. (4) Metformin activates AMPK, which primarily and secondarily decreases mammalian target of rapamycin (mTOR) complex levels, playing a main role in governing cell growth, production, and breakdown which act as an anticancer agent. [9] (5) Increases plasma levels of glucagon-like peptide 1 (GLP-1) which is a member of the incretin family of peptide hormones which is released from the gut in response to ingested glucose thereby leading to retardation of gastric emptying, inhibiting glucagon release from α cell, and produces a feeling of satiety. [10]

Pioglitazone is dependent on the presence of insulin to exert its advantageous effects and preserve β-cells of the islets of Langerhans, but does not act same as an insulin secretagogue. [11] Improved glycaemic control results in lowering of circulating HbA1C and insulin levels in type 2 DM patients. [12] Through agonistic action of PPAR- α, activation of genes regulating fatty acid metabolism and lipogenesis in adipose tissue, results in Lipolysis and plasma fatty acid levels are reduced. [13]

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Material and Methods

Present study was conducted in Department of pharmacology in collaboration with department of Medicine, Index Medical College. Study was conducted over a period of 2 years after taking approval from ethical Committee. Study was conducted as per ICH-GCP guidelines.

Present study is Comparative, Prospective, randomized, Open-label, Single Center, Parallel group study conducted at Index Medical college. Study was conducted in prediabetes patients for assessment of effects of Metformin and Pioglitazone. All patients were evaluated at baseline, 3 months for clinical and physical examination and laboratory investigation.

Present Study was conducted in prediabetes Patients for assessment of effect of Metformin and Pioglitazone on lipid levels attending the outpatient department of Medicine in Index Hospitals and College.

Inclusion Criteria:

- Patients with prediabetes diagnose according to ADA criteria (IFG: 100 -125mg/dl, 2hrs post glucose plasma level 140- 199 mg/dl) and with Indian obesity (BMI > 25 kg/m^2) as per Indian Endocrine Society.
- Patients of either gender between age group 30 to 60 years.
- HbA1c between levels of 5.7-6.4% %.
- Patient willing to give informed written consent.

Exclusion Criteria:

- Patients with history of Type I DM and Type II DM.
- Patients with history of cardiac, liver and renal disease.
- Patients with history of Gastrointestinal Tract diseases (IBD).
- Patients with history of hypothyroidism and hyperthyroidism
- Patients with history of Alcohol intake & Smoking.
- Patients taking steroid, oral contraceptives & hormone replacement therapy
- Pregnant and lactating females.

Follow-up Visits:

Follow-up visits were scheduled at the end of three months and six months for assessment, including measurement of weight and general and systemic examination and laboratory parameters (Serum Insulin, HOMA-IR, HbA1c, Blood glucose and Lipid levels).

Biochemical Parameters:

The following laboratory investigation was performed on sample of prediabetes patients before and at the end of 3^{rd} month and 6^{th} month of therapy.

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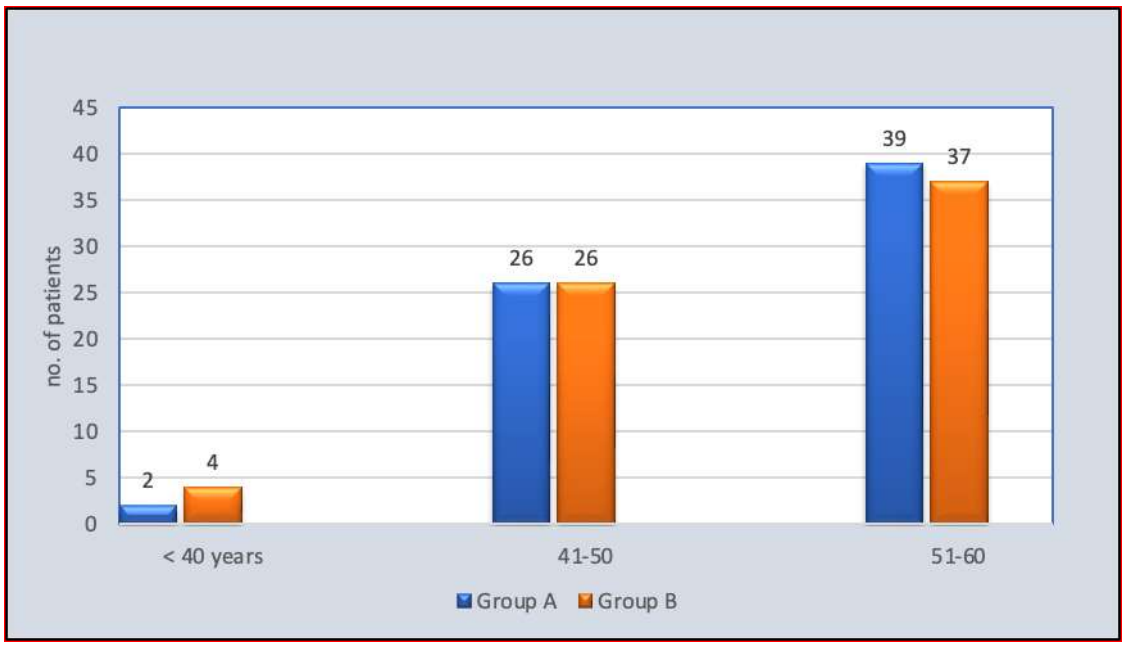
1. Postprandial Blood Glucose
2. Total cholesterol
3. Triglycerides
4. HDL
5. LDL
6. VLDL

Safety parameters:
The safety was evaluated objectively by recording the ADR in the standard format of ADR reporting form and further reported to PvPi Medical college.

Statistical Analysis:
Data analyzed in Statistical Package for the Social Sciences (SPSS) version 25th was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram. A paired 't' test was applied for same group/within group and also quantitative data was represented in the form of pie diagram and bar diagram. An unpaired 't' test was applied for two groups and also quantitative data was represented in the form of pie diagram and bar diagram.

Results
Graph 1: Distribution of Age-group in Pioglitazone and Metformin



In both the groups, maximum number of patients were in the age group of 51-60 years and least number of patients were ≤40 years of age. Mean age in Pioglitazone patients were **53.13±6.41** and in Metformin patients were **56.11±5.36**. There was no statistically significant difference in mean age of patient from Pioglitazone and Metformin patients

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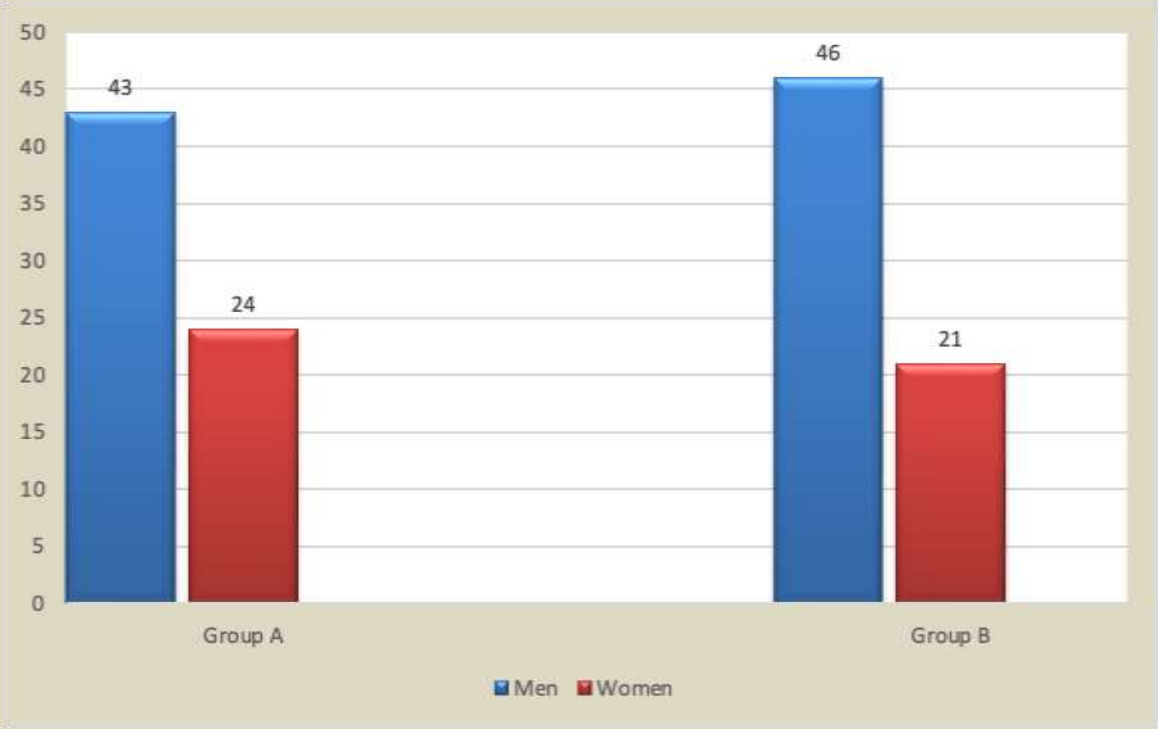
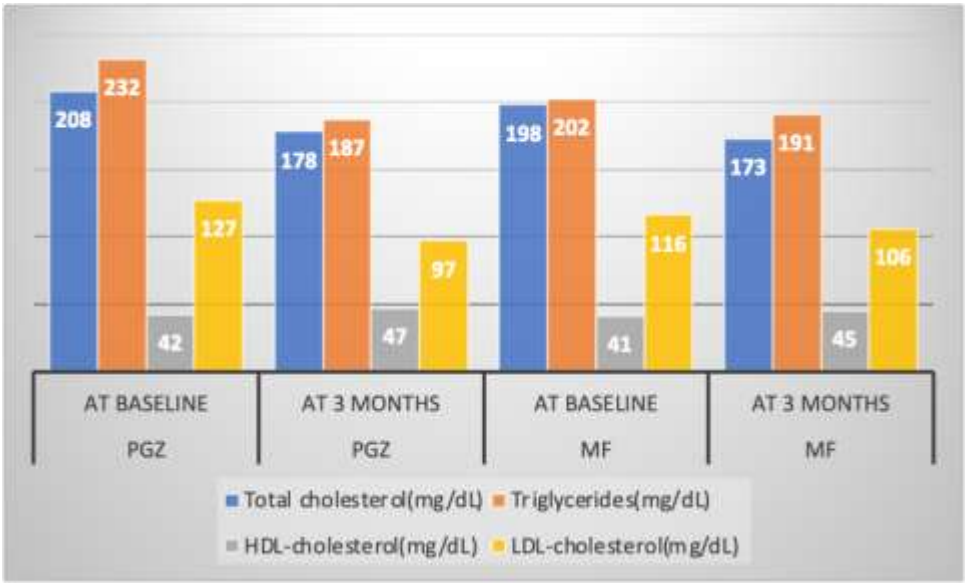
Graph 2: Gender difference between Pioglitazone and Metformin



The table 2 and graph 2 reflects those 167 diabetic patients selected, in Pioglitazone: 106 were male (63.47%) while 61 were female patients (36.52%). In Metformin consisted of 101 male patients (60.47%) and 66 female patients (39.52%). There was no statistically significant difference in number of patients from Pioglitazone and Metformin patients (0.112).

Graph 3: Distribution of Lipid Profile



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In the lipid profile, both groups showed a decrease at three months in serum total cholesterol (30 mg/dl decrease from baseline to 3 months in the PGZ group versus 20 mg/dl decrease from baseline to 3 months in the MF group). The PGZ group achieved a significant decrease in serum triglyceride levels 45 mg/dl from baseline to 3 months and 11 mg/dL from baseline to 3 months in the MF group. Moreover, HDL showed an Increase at three months (5 mg/dl from baseline in the PGZ group versus 4 mg/dl from baseline in the MF group and low-density lipoprotein (LDL) cholesterol levels (30 mg/dl from baseline to 3 months in the PGZ group versus 30 mg/dl from the baseline to 3 months in the MF group).

DISCUSSION

Results from after 3 months of assessment of efficacy and safety in Group A (Pioglitazone) and Group B (Metformin) following were outcomes.

Similarly, two groups showed a significant reduction in Lipid profile at the end of 3 months. In our study Pioglitazone: Total cholesterol level was decreased from baseline value 285.97±11.05 to 267.40±15.00 mg/dl after 3 months of treatment. On the other hand, Metformin: Mean Total cholesterol was decreased in mean baseline value from 285.89±9.88 to 261.55±15.92 mg/dl after 3 months of treatment.

In our study Pioglitazone: Serum Triglycerides level was decreased from baseline value 189.94±7.52 to 175.17±8.66 mg/dl after 3 months of treatment. Furthermore, Metformin: Serum Triglycerides was decreased in mean baseline value from 189.37±10.67 to 170.10±11.54 mg/dl after 3 months of treatment.

In Pioglitazone: HDL cholesterol level was increased from baseline value 41.13±1.89 to 44.92±2.44 mg/dl after 3 months of treatment. Moreover, in Metformin: HDL cholesterol level was increased in mean baseline value from 41.23±1.36 to 46.17±2.08 mg/dl after 3 months of treatment.

In Pioglitazone: LDL cholesterol level was decreased from baseline value 206.84±11.28 to 187.44±14.88 mg/dl after 3 months of treatment. In addition, in Metformin: LDL cholesterol was decreased in mean baseline value from 206.78±10.17 to 181.56±16.66mg/dl after 3 months of treatment.

In Pioglitazone: VLDL cholesterol level was decreased from baseline value 37.98±1.50 to 35.03±1.73 mg/dl after 3 months of treatment. On the other hand, in Metformin: VLDL cholesterol was decreased in mean baseline value from 37.87±2.13 to 34.02±2.30 mg/dl after 3 months of treatment. According to a study done by Amita Jindal et al., pioglitazone in combination with Metformin, there was decreased level of TC, TG, LDL,

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VLDL and improves HDL levels, which support with our study. [14]

When a comparison was done in two groups using an unpaired t-test, reduction in Total Cholesterol in Pioglitazone Vs Metformin, i.e mean difference from baseline to after 3 months was –9.44 Vs -13.64.

Moreover, metformin-induced insulin-stimulated glucose disposal in the skeletal muscle, reduction in appetite and anorectic component, decrease in leptin levels, and rise in GLP-1 levels with Metformin contribute to improving dyslipidaemia. [15]

Pioglitazone control dyslipidemia (lowers TC, TG, LDL, VLDL and raises HDL level) in prediabetes patients through agonist of PPAR- α. PPAR in adipose tissue reduces the flux of fatty acid into muscle, thereby lowering insulin resistance. It also causes activation of adiponectin which leads to increases insulin sensitivity by elevating AMP kinase, which stimulates glucose transport into muscle and increases fatty acid oxidation. Because both metformin and Pioglitazone apparently converge on AMP kinase this is a very important target for drug development. These agents mobilize fat from muscle and liver thereby improving lipotoxicity. [16]

In our study, the most common adverse drug reaction reported in the two groups were related to gastrointestinal disturbances. In Pioglitazone, gastrointestinal adverse drug reactions were Nausea in 3 (4.4%) patients, Abdominal blotting in 5 (7.4%) patients, Flatulence in 7 (10.4%) patients, Diarrhea in 4 (5.9%) patients, Abdominal pain in 5 (7.4%) patients.

On the other hand, in Metformin gastrointestinal adverse drug reactions and headache experienced by patient, Nausea in 2 (2.9%) patients, Abdominal blotting in 4 (5.9%) patients, Diarrhea in 3 (4.4%) patients, and Abdominal pain in 4 (5.9%) patients and weight gain in 6 (8.9%). While comparing both groups, in Metformin had minimal side effects, thereby showing that pioglitazone is a safer drug. No treatment was needed for this side effect in both groups.

The mechanism of GI intolerance caused by metformin are different hypothesis includes stimulation of intestinal secretion of serotonin, alteration in incretin and metabolism of glucose, and malabsorption of bile salts. It has been found that metformin structure has some similarities with 5-hydroxytryptamine (5-HT) receptor-selective agonists and, is transported by Serotonin Reuptake Transporter (SERT). The release of serotonin (5-hydroxytryptamine (5-HT)) from the intestine results in the symptoms nausea, vomiting and diarrhoea which are similar to those as linked with metformin intolerance. Within the intestine, the bile acid pool is increased by metformin, mainly through decreased ileum absorption. This could also account for metformin intolerance through changes in the microbiome and stool consistency which in turn causes flatulence. [17]

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CONCLUSION

After 3 months' treatment with Metformin and Pioglitazone, showed statically significant reduction in Lipid Profile values. Whereas, after 3 months of treatment with Metformin and Pioglitazone caused reduction in Lipid Profile values statistically significant decreased compare with Metformin and Pioglitazone. On the hand, Metformin reduced PPBG level, statistically highly significant compared with Pioglitazone group.

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