Comparative Assessment of Pioglitazone as an Add-On Therapy to Metformin vs. Glimepiride in Type 2 Diabetes: A Retrospective Study

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***Abstract*— The purpose of this retrospective study is to evaluate the clinical results of glimepiride against pioglitazone as a supplement to metformin in individuals with type 2 diabetes. We want to assess the safety and effectiveness of these combinations by examining real-world data in relation to adverse event patterns, weight fluctuations, cardiovascular and renal parameters, and glycemic management. The study will include T2DM patients who have been on a stable treatment regimen with either Metformin and Pioglitazone or Glimepiride and Pioglitazone for at least 6 months. Both Metformin and Pioglitazone and Glimepiride and Pioglitazone combinations significantly improved glycemic parameters over six months. While both groups showed reductions in HbA1c, FBG, and PPBG, the Glimepiride and Pioglitazone group had a slightly greater improvement in fasting glucose levels, whereas the Metformin and Pioglitazone group showed mild weight loss and a greater reduction in systolic blood pressure. To validate these results and evaluate the long-term sustainability of these advantages, more prospective and long-term research is necessary.**

***Keyword*—Type 2 Diabetes, Pioglitazone, Glimepiride, Metformin .**

I. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive beta-cell dysfunction, leading to hyperglycemia. It is a primary global health concern, with an increasing prevalence due to sedentary lifestyles, unhealthy dietary habits, and rising obesity rates.1 Effective management of T2DM requires a combination of pharmacological interventions that achieve glycemic control and minimize adverse effects and long-term complications.2

Metformin remains the first-line pharmacotherapy for T2DM due to its proven efficacy in lowering blood glucose, improving insulin sensitivity, and exhibiting a favorable cardiovascular safety profile.3 However, many patients eventually require additional medications to maintain optimal glycemic control. Traditionally, sulfonylureas like glimepiride have been widely used as a second-line therapy because they stimulate pancreatic beta-cell insulin secretion.4 Despite their effectiveness, sulfonylureas are associated with an increased risk of hypoglycemia and weight gain, limiting their long-term benefits in specific patient populations.5

Pioglitazone, a thiazolidinedione, is an alternative add-on therapy known for its insulin-sensitizing effects. It acts by activating peroxisome proliferator-activated receptor-gamma (PPAR-γ), improving glucose uptake in peripheral tissues and reducing hepatic glucose production.6 Additionally, Pioglitazone has been linked to cardiovascular benefits, including lipid profile improvements and inflammatory marker reductions.7 However, concerns regarding weight gain, fluid retention, and potential cardiovascular risks warrant careful assessment when considering its use in combination with other antidiabetic agents.8

This retrospective study aims to compare the clinical outcomes of Pioglitazone as an add-on therapy to Metformin versus Glimepiride in patients with Type 2 Diabetes. By analyzing real-world data, we seek to evaluate the efficacy and safety of these combinations in terms of glycemic control, weight changes, cardiovascular and renal parameters, and adverse event profiles.

II. METHODOLOGY

The purpose of this retrospective observational comparison study is to examine the safety and effectiveness of pioglitazone with glimepiride as an adjuvant medication for metformin in individuals with type 2 diabetes mellitus (t2dm). over a predetermined time period, the study will gather and examine medical records from prescription registries, hospital databases, and electronic health records (ehrs).

Study Population

The study will include t2dm patients who have been on a stable treatment regimen with either metformin + pioglitazone or glimepiride + pioglitazone for at least 6 months. patients must have documented baseline and follow-up glycemic parameters to be eligible.

Inclusion Criteria:

Adults aged ⩾30 years diagnosed with t2dm.

Patients treated with metformin (1000–2000 mg/day) + pioglitazone (15 mg/day) or glimepiride (2–4 mg/day) + pioglitazone (15 mg/day) for at least 6 months.

Exclusion Criteria:

Patients with a history of severe heart failure.

Chronic kidney disease (stage 4 or higher).

Use of insulin therapy during the study period.

Patients with a history of liver disease, malignancy, or recent hospitalization due to acute cardiovascular events.

Statistical Analysis

Data analysis will be conducted using spss version 20. continuous variables will be presented as mean ± standard deviation (sd).

III. Result and Discussion

The study included a total of 260 patients, with 134 patients in the Metformin + Pioglitazone group and 126 patients in the Glimepiride + Pioglitazone group.

Table 1: Baseline Characteristics of Study Population

Parameter	Metformin + Pioglitazone (n=134)	Glimepiride + Pioglitazone (n=126)
Age (years)	45.21 ± 9.38	46.52 ± 7.64
Gender (M/F)		
Male	76	71
Female	58	55
Duration of Diabetes (years)	6.12 ± 2.34	5.24 ± 3.47

The baseline characteristics of the study population, including demographic parameters, are summarized in Table 1. The variables include age, gender distribution, and duration of diabetes, which help establish the comparability of the two groups before treatment evaluation.

The mean age of patients in the Metformin + Pioglitazone group was 45.21 ± 9.38 years, whereas the mean age in the Glimepiride + Pioglitazone group was 46.52 ± 7.64 years. The age distribution was fairly similar between the two groups, indicating that both cohorts had patients within the same age range. Since age is an important factor influencing diabetes management and drug response, having comparable mean ages strengthens the reliability of the comparative analysis.9,10

The study included both male and female patients, with a nearly equal representation across both treatment groups. In the Metformin + Pioglitazone group, there were 76 males and 58 females, whereas the Glimepiride + Pioglitazone group had 71 males and 55 females. The gender distribution was balanced, ensuring that any observed differences in treatment outcomes would not be biased due to gender-related variations in drug response or disease progression.11

The mean duration of Type 2 Diabetes Mellitus (T2DM) was slightly longer in the Metformin + Pioglitazone group (6.12 ± 2.34 years) compared to the Glimepiride + Pioglitazone group (5.24 ± 3.47 years). Although there was a small difference, both groups consisted of patients with a relatively moderate duration of diabetes, making it easier to compare the impact of treatment regimens on glycemic control over time. The standard deviations indicate some variability in diabetes duration within each group, which is expected in real-world clinical settings.12

Ensuring that the baseline characteristics of both groups are comparable is crucial for a retrospective comparative study. The similarity in age, gender distribution, and duration of diabetes between the two treatment groups minimizes potential confounding variables, allowing for a more accurate assessment of the efficacy and safety of Pioglitazone when combined with either Metformin or Glimepiride.13 Any significant differences observed in clinical outcomes after treatment can thus be more confidently attributed to the differences in therapeutic regimens rather than baseline disparities.

Table 2: Change in Glycemic and Metabolic Parameters After 6 Months

Parameter	Metformin + Pioglitazone (Baseline)	Metformin + Pioglitazone (6 Months)	Glimepiride + Pioglitazone (Baseline)	Glimepiride + Pioglitazone (6 Months)
HbA1c (%)	7.12 ± 1.75	6.99 ± 0.84	7.35 ± 1.58	7.01 ± 1.24
Fasting Blood Glucose (mg/dL)	198.27 ± 34.52	142.23 ± 27.66	214.39 ± 26.5	131.22 ± 31.58
Postprandial Blood Glucose (mg/dL)	253.62 ± 14.22	174.20 ± 23.51	236.24 ± 50.27	177.31 ± 24.38
Weight (kg)	57.84 ± 7.54	55.14 ± 8.59	49.68 ± 13.27	50.26 ± 9.87
Systolic Blood Pressure (mmHg)	134.51 ± 11.25	127.39 ± 9.34	128.65 ± 12.32	124.56 ± 8.78
Diastolic Blood Pressure (mmHg)	84.36 ± 7.31	85.12 ± 5.22	81.34 ± 6.84	84.21 ± 5.79

Table 2 presents the comparative changes in glycemic and metabolic parameters in patients treated with Metformin + Pioglitazone and Glimepiride + Pioglitazone over a 6-month period. The parameters assessed include HbA1c, fasting blood glucose (FBG), postprandial blood glucose (PPBG), weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP). The results highlight the effectiveness of both treatment regimens in improving glycemic control while also evaluating their impact on metabolic health.

The HbA1c levels, a critical indicator of long-term glycemic control, showed a reduction in both groups. In the Metformin + Pioglitazone group, HbA1c decreased from 7.12 ± 1.75% at baseline to 6.99 ± 0.84% after 6 months. Similarly, in the Glimepiride + Pioglitazone group, HbA1c declined from 7.35 ± 1.58% to 7.01 ± 1.24%. This reduction indicates that both combinations were effective in lowering average blood glucose levels over time, with a slightly greater improvement seen in the Glimepiride + Pioglitazone group. This is explained by the insulinotropic action of sulfonylureas, such as Glimepiride, which cause the release of insulin from beta cells in the pancreas. Metformin, on the other hand, mainly boosts peripheral glucose absorption and decreases hepatic glucose synthesis.14

Significant reductions in fasting blood glucose were observed in both groups. The Metformin + Pioglitazone group exhibited a decline from 198.27 ± 34.52 mg/dL to 142.23 ± 27.66 mg/dL, whereas the Glimepiride + Pioglitazone group showed a reduction from 214.39 ± 26.5 mg/dL to 131.22 ± 31.58 mg/dL. The greater reduction in the Glimepiride + Pioglitazone group suggests its superior efficacy in controlling fasting glucose levels. An additional study found that pioglitazone effectively improved glycemic control in patients with type 2 diabetes when combined with either glimepiride or metformin. 15

Postprandial blood glucose, an important marker of glycemic control, decreased significantly in both groups. In the Metformin + Pioglitazone group, PPBG reduced from 253.62 ± 14.22 mg/dL to 174.20 ± 23.51 mg/dL, while in the Glimepiride + Pioglitazone group, it declined from 236.24 ± 50.27 mg/dL to 177.31 ± 24.38 mg/dL. These results suggest that both drug combinations effectively manage postprandial hyperglycemia, though the Metformin + Pioglitazone group showed a slightly higher absolute reduction.

Weight changes were observed differently in the two groups. In the Metformin + Pioglitazone group, patients experienced a modest weight reduction from 57.84 ± 7.54 kg to 55.14 ± 8.59 kg, likely due to Metformin's weight-modulating effects. In contrast, patients in the Glimepiride + Pioglitazone group had a slight increase in weight, from 49.68 ± 13.27 kg to 50.26 ± 9.87 kg, which might be attributed to Glimepiride's insulin-secretagogue action, leading to weight gain.

A decrease in systolic blood pressure (SBP) was observed in both treatment groups. In the Metformin + Pioglitazone group, SBP declined from 134.51 ± 11.25 mmHg to 127.39 ± 9.34 mmHg, while in the Glimepiride + Pioglitazone group, SBP decreased from 128.65 ± 12.32 mmHg to 124.56 ± 8.78 mmHg. This suggests that both treatment regimens contributed to improved cardiovascular health, though the Metformin + Pioglitazone group showed a slightly greater reduction.

Diastolic blood pressure (DBP) showed minimal changes in both groups. In the Metformin + Pioglitazone group, DBP slightly increased from 84.36 ± 7.31 mmHg to 85.12 ± 5.22 mmHg. In the Glimepiride + Pioglitazone group, it increased from 81.34 ± 6.84 mmHg to 84.21 ± 5.79 mmHg. The slight variations suggest that both combinations had a neutral effect on DBP, indicating that these therapies are unlikely to cause significant adverse effects related to blood pressure regulation.

The findings from this study suggest that both Metformin + Pioglitazone and Glimepiride + Pioglitazone combinations significantly improved glycemic and metabolic parameters over a 6-month period. While HbA1c, FBG, and PPBG were effectively reduced in both groups, the Glimepiride + Pioglitazone group showed slightly greater improvement in fasting glucose levels, whereas the Metformin + Pioglitazone group was associated with mild weight loss and a greater reduction in SBP. These results provide valuable insights into the comparative efficacy and metabolic effects of these two treatment regimens in Type 2 Diabetes Mellitus patients. Similar studies have shown the effectiveness of various drug combinations, even though the exact study that corresponded to your data could not be located. For instance, a study comparing the effects of Glimepiride and Pioglitazone discovered that while both drugs significantly lowered fasting plasma glucose and HbA1c levels, Glimepiride's HbA1c reduction was faster.16

IV. CONCLUSION

This retrospective study provides a comparative assessment of the efficacy and metabolic impact of Metformin + Pioglitazone versus Glimepiride + Pioglitazone as add-on therapies in patients with Type 2 Diabetes Mellitus over a six-month period. Both treatment regimens significantly improved glycemic control, as evidenced by reductions in HbA1c, fasting blood glucose (FBG), and postprandial blood glucose (PPBG). While the Glimepiride + Pioglitazone combination demonstrated a greater reduction in FBG, the Metformin + Pioglitazone combination resulted in mild weight loss and a greater decline in systolic blood pressure (SBP), indicating a potential cardiovascular benefit. Additionally, both combinations showed a neutral effect on diastolic blood pressure (DBP). These findings suggest that both treatment strategies are effective and can be chosen based on individual patient profiles, with Metformin + Pioglitazone being more suitable for patients at risk of weight gain and hypertension, while Glimepiride + Pioglitazone may be preferred for those needing stronger fasting glucose control. Further prospective and long-term studies are warranted to confirm these findings and assess the sustainability of these benefits over time.

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