ORIGINAL ARTICLE

The Effectiveness and Safety of Fenofibrate and Saroglitazar in the Treatment of Diabetic Dyslipidemia

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of saroglitazar and fenofibrate in treating diabetic dyslipidemia.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Biochemistry, Nishtar Medical University and Hospital Multan, Pakistan over 12 months from January 2021 to January 2022.

Methods: Following a 4-week run-in phase, sixty newly diagnosed patients with a previous diagnosis of diabetes and dyslipidemia were included. Eligible participants were aged 18-65 years, with fasting triglyceride (TG) levels >200–400 mg/dL and documented type 2 diabetes mellitus (T2DM). Following baseline assessments, participants were randomised into two treatment groups: Saroglitazar 4 mg with 10 mg of Atorvastatin and Fenofibrate 200 mg with 10 mg of Atorvastatin. Lipid profiles, fasting blood glucose (FBG), and HbA1c were evaluated at baseline and after 12 weeks. Statistical analysis was conducted using appropriate tests with $p < 0.05$, which is considered significant.

Results: The study enrolled 60 participants, with comparable baseline characteristics between groups. While both treatments showed similar effects on lipid profiles, Saroglitazar showed exceptional effectiveness in lowering HbA1c and FBG levels compared to Fenofibrate. No significant differences in adverse effects were observed.

Conclusion: Saroglitazar may offer advantages in managing diabetic dyslipidemia and improving glycemic control compared to Fenofibrate in a larger sample size. More investigation is necessary to confirm these findings and evaluate long-term safety and efficacy.

Keywords: *Atorvastatin, Diabetes Mellitus, Dyslipidemias, Fenofibrate, Triglyceride.*

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Introduction

Diabetes mellitus (DM) is one of the leading chronic illnesses in the world that increases rates of morbidity and mortality.[1] It was estimated that 285 million persons globally suffered from diabetes in 2010. That figure is expected to increase to 439 million by 2030, representing a 7.7% prevalence. According to estimates, the proportion of adult diabetics in developing and wealthy nations would increase by 69 and 20 percent, respectively, between 2010 and 2030. In India, diabetes has become a national health crisis. The prevalence of type 2 diabetes mellitus in Pakistan is 11.77%, with a higher prevalence in males (11.20%) than females (9.19%). In Sindh province, the prevalence is 16.2% in males and 11.70% in females, while in Punjab province, it is

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12.14% in males and 9.83% in females. Baluchistan province reports a 13.3% prevalence among males and 8.9% among females, and in Khyber Pakhtunkhwa (KPK), it is 9.2% in males and 11.60% in females. Urban areas exhibit a higher prevalence of 14.81% compared to 10.34% in rural areas. These statistics underscore the urgency for Pakistan to incorporate diabetes preventive measures into its national health policy to mitigate the disease burden.[2] Diabetes mellitus (DM) is one of the leading chronic illnesses in the world that increases rates of morbidity and mortality.[3-5]

Diabetic dyslipidaemia represents a common and clinically significant metabolic disorder characterized by abnormal lipid profiles in individuals with diabetes mellitus.[6] The elevated likelihood of cardiovascular complications, such as coronary artery diseases and stroke, which are the primary causes of morbidity and death for individuals with diabetes, is further increased by this condition.[4] In managing diabetic dyslipidaemia, therapeutic interventions to control lipid levels are crucial for mitigating cardiovascular risk and improving overall patient outcomes.[7-9] Among the pharmacological agents commonly used for this purpose, Saroglitazar and Fenofibrate have emerged as promising options due to their efficacy in modulating lipid metabolism and reducing cardiovascular risk markers.[10]

The necessity to optimize therapeutic options for controlling this complicated metabolic condition is the driving force for the inquiry into the safety and effectiveness of fenofibrate and saroglitazar in treating diabetic dyslipidemia. Saroglitazar, a dual peroxisome proliferator-activated receptor (PPAR) agonist, exerts beneficial effects on lipid profiles by targeting multiple pathways involved in lipid metabolism, including improving insulin sensitivity and reducing triglyceride levels. Similarly,[11] While both Saroglitazar and Fenofibrate have demonstrated efficacy in improving lipid profiles in diabetic patients, a need to comprehensively evaluate their comparative efficacy and safety profiles in real-world clinical settings remains.[12,13] Furthermore, there is a lack of evidence directly comparing these two agents' impact on lipid parameters, glycaemic control, and safety outcomes. By conducting a comparative analysis of Saroglitazar and Fenofibrate in diabetic patients with dyslipidaemia, this study aims to elucidate their relative efficacy, safety, and tolerability profiles.

The results of this study should help guide the choice of the best pharmaceutical treatments for managing diabetic dyslipidemia and lead clinical choice-making. Ultimately, this should lower the risk of cardiovascular disease and improve patients' health in this high-risk group.

Methods

The study was conducted at the Department of Biochemistry, Nishtar Medical University and Hospital Multan, Pakistan, over 12 months from January 2021 to January 2022 after taking permission from the Institutional Review Board (IRB) of hospital vide letter No: 42/198, dated 03rd January 2021 to ensure compliance with ethical norms and patient confidentiality. The research was conducted at the Multan Institute of Child Health in Multan, Pakistan. Eligible participants for this study were individuals aged between 18 and 65 years who had been previously diagnosed with type 2 diabetes mellitus (T2DM) and dyslipidemia. Specifically, participants must have had fasting triglyceride (TG) levels ranging from >200 to 400 mg/dL. Patients with newly diagnosed dyslipidemia were also considered, provided they had a confirmed diagnosis of T2DM and were receiving treatment with sulfonylurea or metformin for at least three months. Additionally, individuals who did not improve their dyslipidemia following a four-week regimen of 10 mg atorvastatin were eligible for inclusion in the study. The exclusion criteria encompassed patients using specific medications, those with a history of cardiac abnormalities, thyroid or hepatic dysfunction, renal impairment, comorbid serious illnesses, drug or alcohol misuse, drug allergies, and pregnant or nursing women. Eligibility assessments involved comprehensive physical examinations and baseline laboratory evaluations, with individuals displaying abnormal kidney, liver, and thyroid hormone levels being ineligible for participation. A standardized form documenting relevant history and investigations was completed for all participants. The study spanned three months, during which lipid profiles, fasting blood glucose (FBG), and HbA1c

were evaluated at baseline and after 12 weeks. Regular monitoring of adverse events was conducted, including monthly follow-up calls to ensure patient adherence and well-being.

A total of sixty patients were included in the research, allocated into two groups of thirty patients each using computer-generated random numbers. One group received Fenofibrate 200 mg and Atorvastatin 10 mg, while the other group received Saroglitazar 4 mg and Atorvastatin 10 mg. Lipid profiles, FBG, and HbA1c were assessed at follow-up appointments in weeks 4, 8, and 12, with participants reporting any adverse effects experienced. The primary outcome measure was the absolute difference in blood TG levels between the start and end of the treatment period. Secondary outcomes included changes in glycemic fluctuations, safety evaluation, and other lipid markers (total cholesterol, VLDL-C, HDL-C, LDL-C, FBG, and HbA1c).

Data collection involved transforming information into variables using statistical analysis, followed by coding and input into a data management program such as Microsoft Excel. Initial data were presented as percentages, while final data were expressed as mean ± standard deviation. Statistical tests, including Student's t-test, Mann-Whitney U test, Chi-square test, or Fisher's exact test, were employed to compare groups, with significance set at $p < 0.05$. Given the pilot nature of the study, sample size computation was not performed, and 60 participants were deemed appropriate for analysis.

Results

The study aims to evaluate the safety and effectiveness of two therapy groups: Saroglitazar 4 mg and Atorvastatin 10 mg versus Fenofibrate 200 mg and Atorvastatin 10 mg in the management of diabetic dyslipidemia. Regarding demographics, the gender distribution is presented as percentages for each treatment group, with 56.7% females and 43.3% males in the Saroglitazar

group and 60% females and 40% males in the Fenofibrate group (Figure-1).

The mean age of participants in the Saroglitazar group was 46.55 years (SD = 7.74), while in the Fenofibrate group, it was 48.25 years (SD = 7.12). Additionally, the mean BMI (Body Mass Index) was comparable between the two groups, with values of

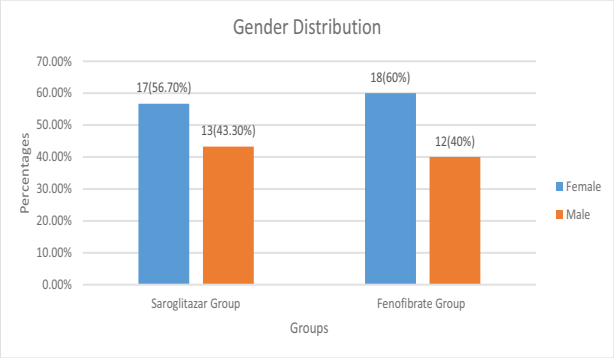

Fig.1: Distribution of gender between the groups (n=60)

26.1 (SD = 3.62) and 26.4 (SD = 3.12) for the Saroglitazar and Fenofibrate groups, respectively. Regarding laboratory data, lipid profile parameters, including TG (Triglycerides), LDL (Low-Density Lipoprotein), HDL (High-Density Lipoprotein), VLDL (Very Low-Density Lipoprotein), and total cholesterol levels, were measured. The mean levels of these values were comparable among the two treatment groups, indicating comparable baseline lipid profiles. Additionally, fasting blood sugar (FBS) levels were recorded, with participants in the Saroglitazar group having a mean FBS of 155.90 mg/dL (SD = 22.32) and those in the Fenofibrate group having a mean FBS of 140.65 mg/dL (SD = 27.14). Furthermore, HbA1c levels, a marker of long-term glucose control, were assessed, showing mean values of 8.01% (SD = 0.57) in the Saroglitazar group and 7.93% (SD = 0.57) in the Fenofibrate group. (Table-1).

Table-2 compares mean changes in laboratory parameters between the two treatment groups after the intervention. The mean changes in Total Cholesterol, TG level, LDL level, HDL level, and VLDL level were not appreciably different across the Saroglitazar and Fenofibrate groups, as indicated by p-values greater than 0.05. However, the mean change in HbA1c levels among both groups was statistically significant ($p<0.01$), suggesting that the interventions had differential effects on glycaemic control. Specifically, the Saroglitazar group demonstrated a more profound decrease in HbA1c compared to the Fenofibrate group. Additionally, the mean change in FBS level was statistically significant ($p=0.01$), with the Saroglitazar group showing a more substantial decrease in FBS than the Fenofibrate group.

Table-1: Demographics of study population (n=60)

Characteristic	Saroglitazar with Atorvastatin (n=30)	Fenofibrate with Atorvastatin (n=30)
Demographics	**(Mean ± SD)**	**(Mean ± SD)**
Female (%)	17 (56.7%)	18 (60%)
Male (%)	13 (43.3%)	12 (40%)
Age (years)	46.55 ± 7.74	48.25 ± 7.12
BMI	26.1 ± 3.62	26.4 ± 3.12
Laboratory Data		
TG (mg/dL)	284.75 ± 50.06	283.60 ± 46.12
LDL (mg/dL)	103.05 ± 33.43	100.90 ± 33.49
HDL (mg/dL)	34.15 ± 6.24	34.10 ± 5.79
VLDL (mg/dL)	51.90 ± 6.77	52.45 ± 7.31
Cholesterol (mg/dL)	207.85 ± 23.13	213.50 ± 17.67
Fasting Blood Sugar (FBS) (mg/dL)	155.90 ± 22.32	140.65 ± 27.14
HbA1c	8.01 ± 0.57	7.93 ± 0.57

Table-2: Comparison of mean change in Laboratory parameters (n=60)

Laboratory Parameters	Saroglitazar with Atorvastatin (n=30)	Fenofibrate with Atorvastatin (n=30)	*P*-value
Total Cholesterol (mg/dL)	59.77 ± 22.52	69.77 ± 15.52	0.91
TG level (mg/dL)	125.77 ± 46.27	110.77 ± 29.52	0.15
LDL level (mg/dL)	37.27 ± 15.02	44.27 ± 17.02	0.77
HDL level (mg/dL)	12.27 ± 7.52	10.27 ± 5.52	0.19
VLDL level (mg/dL)	14.77 ± 7.77	15.77 ± 7.77	0.89
HbA1C level (%)	2.27 ± 1.62	1.32 ± 1.52	<0.01
FBS level (mg/dL)	45.27 ± 22.52	28.77 ± 24.52	0.01

Table-3 presents the comparison of side effects between Group A (Saroglitazar 4 mg and Atorvastatin 10 mg) and Group B (Fenofibrate 200 mg and Atorvastatin 10 mg). The incidence of side effects, including body aches, nausea, gastritis, and weakness, was evaluated in each group. Overall, there were no statistically significant differences in the incidence of side effects between the two groups, as indicated by *p*-values greater than 0.05 for all side effects. However, it's notable that Group B exhibited a slightly higher incidence of body aches, nausea, and weakness than Group A, although these differences were not statistically significant. These findings suggest.

Table-3: Comparison of side effects (n=60)

Side Effects	Saroglitazar with Atorvastatin (n=30)	Fenofibrate with Atorvastatin (n=30)	*P*-value
Body ache	1(3.33%)	2(6.67%)	0.15
Nausea	0(0.0%)	1(3.33%)	0.99
Gastritis	1(3.33%)	1(3.33%)	0.89
Weakness	1(3.33%)	2(6.67%)	0.88

Discussion

Our investigation discovered that saroglitazar may have a place in managing dyslipidemia and hyperglycemia in individuals with diabetic dyslipidemia (DD). A much higher risk of premature atherosclerotic heart disease is linked to diabetes mellitus. Diabetes is frequently accompanied by dyslipidemia. Serum cholesterol levels and atherosclerotic cardiovascular disease are related. Patients with DD have a lipid profile that includes low HDL cholesterol levels and high TGs, as well as minor to substantial elevations in VLDL and VLDL fragment concentrations. Typically, there is no discernible rise in LDL-C values between patients with diabetes and those without the condition.[14,15]

In this 12-week trial, we found that, regarding glycemic control, Saroglitazar 4 mg and a low-dose Atorvastatin 10 mg performed better than Fenofibrate 200 mg and low-dose Atorvastatin 10 mg. Furthermore, the fact that no statistically significant variation was seen in the quantity of lipids that dropped indicates that the dyslipidemias in both groups were adequately treated. Comparable outcomes were observed in Saroglitazar's first prospective, randomised clinical trial, PRESS V. In the PRESS V trial, saroglitazar reduced TG levels at 2 mg and 4 mg in a dose-related manner.[16] In the effectiveness study, saroglitazar at doses of 2 mg and 4 mg considerably decreased plasma TG from the reference by 26.4 per cent and 45 per cent.

In week 24, the PRESS V study demonstrated a significant reduction in LDL (5 per cent), VLDL (45.5 per cent), and TC (7.7 per cent) compared to pioglitazone therapy.[16,17]

Our study's results were consistent with those of previously published research.[18] We also noticed that Saroglitazar reduced TC levels by 27%, whilst Fenofibrate reduced TC levels by 31%. Therefore, our investigation discovered that Saroglitazar was just as successful as Fenofibrate in lowering TC levels in DD patients. These results contrast with those of the PRESS-V trial, which revealed that the decline in TC concentrations was limited to 7.7%. The potential cause of this discrepancy may be the PRESS-V trial's lack of statin treatment.[18]

In the multi-centre, randomized, double-blind PRESS VI study, saroglitazar's safety and efficacy were evaluated against a placebo in individuals with type 2 diabetes for whom dyslipidemia was not managed with atorvastatin therapy.[19] Saroglitazar treatment was found to lower TG and TC levels significantly. Our study revealed similar results for the decline in TG and TC levels.

Our investigation discovered that the average decrease in LDL, VLDL, and HDL values was 36%, 27%, and 26%, respectively. In our investigation, HDL levels increased by 26%, whereas the mean increase in HDL levels observed in the PRESS-V experiment was 4%. The concurrent use of atorvastatin may be one reason for the observed heterogeneity in high HDL levels in the research. According to data from the PRESS-VI trial, there was an average 33% rise in HDL levels and an average 48% decrease in VLDL, or low-density lipoprotein, levels. Since statins were also given in addition to saroglitazar in both trials, we saw comparable outcomes in our analysis.[16]

Our investigation discovered that Saroglitazar caused a mean 28% drop in fasting blood sugar about the baseline value. In our study, the mean per cent reduction in HbA1c was discovered to be 13%. Our results on Saroglitazar's impact on glycemic management are consistent with the PRESS-VI research.[19] An observational investigation of its effects on glycemic and lipid markers has discovered that Saroglitazar causes a mean per cent drop in HbA1c of 6% and a decline in FBG level of 23%.[20] These glycemic control results are similar to those of our study. Saroglitazar 4 mg was found to be equivalent to pioglitazone 45 mg in the PRESS-V trial with regards to reducing HbA1c and FBG. Furthermore, after 24 weeks, saroglitazar appears to be safe and well-tolerated.[16]

No significant side effects were noted in our research and previously available studies involving saroglitazar. Considering the modest sample size in our investigation, no firm conclusions could be drawn. The doses of atorvastatin alongside other anti-diabetic drugs were unchanged during the trial.

This study's relatively small sample size is one of its limitations, which could affect how broadly the results can be applied. Furthermore, a 12-month research period might not be enough to evaluate the medicines' long-term safety and efficacy thoroughly. Moreover, the open-label design could introduce

bias in treatment administration and outcome assessment. More significant sample numbers, longer follow-up times, and double-blinded procedures would all help to confirm the effects that have been seen and offer more convincing proof for clinical choice-making in the future.

Conclusion

Saroglitazar may provide potential advantages in the management of diabetic dyslipidaemia and improvement of glycaemic control, compared to Fenofibrate, in a larger sample size. More investigation is required to validate these findings and evaluate long-term safety and efficacy.

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Authors Contribution

BF: Study designing, data analysis, results and interpretation
RRC: Idea conception, data collection
ZHQ: Study designing, data collection, manuscript writing, and proofreading
NY: Idea conception, data analysis, results and interpretation
EHS: Study designing, manuscript writing, and proofreading