Role of Saroglitazar in Type 2 Diabetes Mellitus Patients with Moderate to Severe Hypertriglyceridemia: A Single-center, Open-Label, Single-Arm Study

ABSTRACT:

Background: Saroglitazar is dual peroxisome proliferator-activated receptor (PPAR) α/γ agonist and approved for elevated triglyceride (TG) reduction in type 2 diabetes mellitus (T2DM) and Non-alcoholic fatty liver disease in India. This study was conducted to evaluate the effect of Saroglitazar in T2DM patients with moderate to severe hypertriglyceridemia to contribute to nationwide existing data of real time clinical practice. **Methods:** It is a retrospective, observational study conducted from April 2023-2024, among T2DM participants with either moderate hypertriglyceridemia (200-499 mg/dl) or severe hypertriglyceridemia (≥500 mg/dl) who were prescribed Saroglitazar 4 mg once daily and followed up for 6 months with laboratory parameters (blood sugar and lipid profile). **Results:** A total of 53 patient's data on demographic and clinical profile was collected and analysed. Saroglitazar, in addition with oral antidiabetic and lipid lowering medication showed statically significant improvement in total cholesterol, triglyceride and HbA1c at 6 months follow-up without any serious adverse events. **Conclusion:** In T2DM with moderate to severe hypertriglyceridemia, saroglitazar as an add on to statins is an effective and safe therapeutic option to reduce elevated TG and other lipid and glycemic parameters.

Key words: Type 2 Diabetes mellitus, Hypertriglyceridemia, Metabolic dysfunction, PPAR α/γ agonist

INTRODUCTION:

Diabetes mellitus comprises of a group of heterogeneous disorders, which have an increase in blood glucose concentrations in common.[1] According to the American Diabetes Association (ADA), various genetic and environmental factors can result in the progressive loss of β-cell mass and/or function that manifests clinically as hyperglycemia, frequently on the background of insulin resistance[2]. This in turn, results in decreased metabolism and thereby accumulation of carbohydrates and lipids and increase in free fatty acids within the circulation.

Dyslipidemia is a commonly observed feature of diabetes.[3] Despite the contribution of dyslipidemia to the high and rising burden of arteriosclerotic cardiovascular disease (ASCVD) in the world; the condition is under-diagnosed, under-treated, and under-described.[4] India ranks second, after China, in terms of the maximum number of patients having diabetes mellitus.[5] In India, there are estimated 77 million people above the age of 18 years, suffering from type 2 diabetes mellitus (T2DM) and nearly 25 million are prediabetics (at a higher risk of developing diabetes in the near future. [6]

Diabetic Dyslipidemia is characterized by elevated fasting and postprandial triglycerides (TG), low high density lipoprotein cholesterol (HDLc), elevated low density lipoprotein cholesterol (LDLc) and the predominance of small dense LDL particles. These lipid changes represent the major link between diabetes and the increased cardiovascular risk of diabetic patients.[7] As per the Cardiology Society of India (CSI) 2023 guidelines, lipid management

based on LDLc and non-HDLc target is crucial to reduce the incidence of coronary artery disease (CAD). [8] Prevalence of diabetes and other metabolic non communicable diseases (NCDs) in India is considerably higher than previously estimated. [9] Approximately 57% of these individuals remain undiagnosed. T2DM, which accounts for majority of the cases, can lead to multiorgan complications, broadly divided into microvascular and macrovascular complications. These complications are a significant cause for increased premature morbidity and mortality among individuals with diabetes, leading to reduced life expectancy and financial and other costs of diabetes leading to profound economic burden on the Indian health care system. [10]

Insulin resistance (IR) is the pathogenesis of a battery of interlinked diseases like metabolic syndrome, hypertriglyceridemia, metabolic dysfunction associated steatotic liver disease (MASLD), atherosclerosis, and T2DM. Thus, drugs targeting multiple organ systems simultaneously are now preferred as it decreases drug interactions and adverse events. This improves patient compliance as well as adherence in the long run.[11] Saroglitazar, a dual peroxisome proliferator activated receptor (PPAR) α/γ agonist has proven to be effective in diabetic dyslipidemia in various published studies. It acts as PPAR-α agonist to improve lipid profile by increasing fatty acid uptake and oxidation. Through its moderate action on PPAR-γ receptors, it increases insulin sensitivity [12,13] Thus this drug has double benefits in reducing lipid levels of TG, LDLc, total cholesterol (TC) and non-HDLc along with reduction of insulin resistance. This study was conducted as a retrospective observational analysis aimed to evaluate the effect of saroglitazar for the treatment of T2DM patients with moderate to severe hypertriglyceridemia at a single centre.

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METHODOLOGY:

It is a retrospective, observational, single arm, single centre and post marketing study, conducted at Karkhanis Superspeciality Hospital, Manpada, Thane (West), Maharashtra. Data of patients, who were prescribed Saroglitazar 4 mg once daily and followed up for 6 months during April 2023 to April 2024 were collected. Total 53 patients' data was recorded by convenient sampling, who were having T2DM with either moderate (200-499 mg/dl) or severe (≥500 mg/dl) hypertriglyceridemia and prescribed Saroglitazar 4 mg, as an add on to ongoing statin therapy. Saroglitazar was prescribed at the discretion of the treating physician, as per prescribing information only. ***INCLUSION CRITERIA –*** Clinical data of patients with age ≥ 18 years, Type 2 Diabetes Mellitus with moderate (250-499 mg/dl) to severe (≥500 mg/dl) hypertriglyceridemia, who were on anti-diabetic medication and statin, were recorded. ***EXCLUSION CRITERIA –*** a. Patient with eGFR <30 ml/min/m^2, b. Severe hepatic failure, c. New York Heart Association (NYHA) class III or IV heart failure, d. Malignancy, e. patients with history of hypersensitivity to Saroglitazar or any of the excipients used in the formulation, f. Pregnant or Lactating women, g. Lost to follow-up.

Data regarding demographic details (age, gender, height, body weight), clinical profile (duration of T2DM in years, existing treatment) and laboratory measurements (lipid and glycaemic parameters at baseline and 6 months) were recorded. Data of only those patients who had both baseline and 6 months follow up parameters were considered for analysis. The SAS® system for Windows was used for statistical analysis. Significant differences in the

Mean ± SD from baseline and 6 months were assessed by using paired t-tests. A p-value of <0.05 was considered to be statistically significant.

ETHICAL CONSIDERATION- The study was undertaken in accordance with the Declaration of Helsinki. This being an observational, retrospective study; the Institutional Ethics Committee approval was not taken.

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CONFLICT OF INTERESTS: Authors have declared that no conflict of interests exist.

RESULTS:

A total of 53 type 2 diabetic dyslipidaemia patient's data on demographic and clinical profile was collected and analysed (Table 1). All patients were on mild to moderate statin therapy [Atorvastatin (56%) and Rosuvastatin (44%)] with optimal anti-diabetic therapy (Figure 1).

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Table 1: Baseline demographic details

Demographic parameters	N	%
Male	42	79.25
Female	11	20.75
	Mean ± SD	
Age (years)	54.05 ± 11.81	
Weight (kg)	77.2 ± 16.03	
Height (cm)	168.64 ± 7.66	
Duration of T2DM (years)	7.05 ± 5.29	

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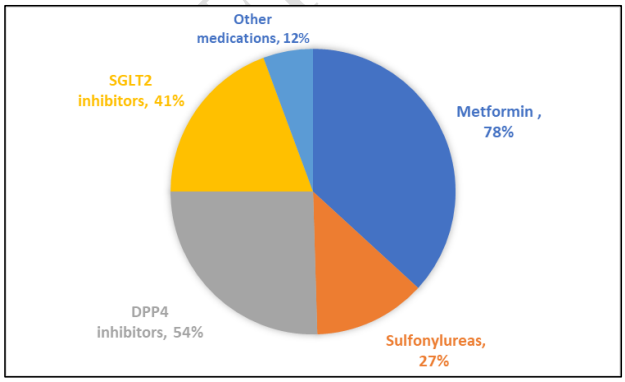
Figure 1: Anti-diabetic medications prescribed to patients



[AGI – Alpha Glucosidase Inhibitor, DPP4 – Dipeptidyl Peptidase 4, SGLT2 – Sodium Glucose Co-Transporter 2]

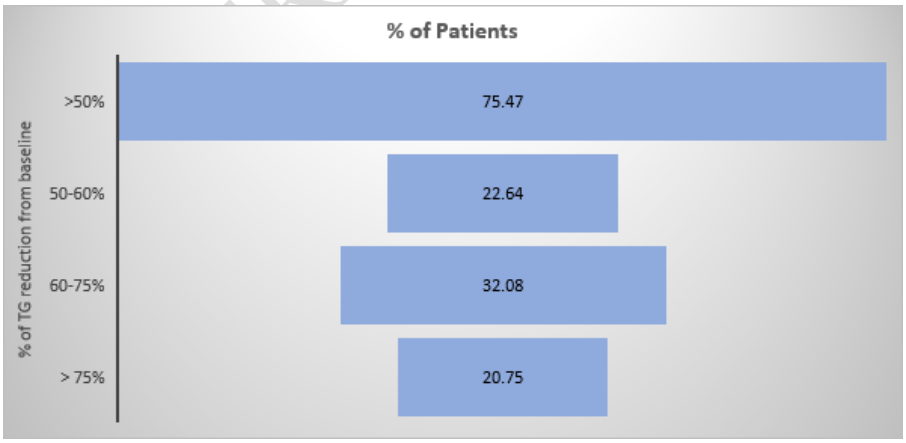
Saroglitazar, in addition with oral antidiabetic and lipid lowering medication showed statically significant reducing effect in lipid parameters, especially TG, TC; with non-significant improvement in HDLc and LDLc levels after 6 months of therapy. At 6 months of treatment, drug also reduced HbA1c significantly in study participants. (Table 2)

Table 2: Effect of Saroglitazar after 6 months of therapy in Diabetic Dyslipidemia patients

Parameters	Baseline (Mean ± SD)	After 6 months (Mean ± SD)	Absolute change from baseline at 6 months	Mean % change from baseline at 6 months	p value
TC (mg/dl)	233.57 ± 62.12	178.13 ± 32.27	- 55.44	- 23.74	< 0.001
TG (mg/dl)	615.3 ± 203.62	239.38 ± 121.78	- 375.92	- 61.10	< 0.001
HDLc (mg/dl)	36.38 ± 10.5	36.43 ±7.82	0.05	0.14	NS
LDLc (mg/dl)	107.11 ± 33.9	101.94 ± 29.86	- 5.17	- 4.83	NS
HbA1c (%)	8.52 ± 1.9	7.75 ± 1.31	- 0.77	NA	< 0.001

Out of 53 patients, 75.47% patients had > 50% of TG reduction from baseline after 6 months of therapy, while in 32.08% and 20.75% patients had 60-75% and > 75% TG reduction from baseline. At end of 6 months, 51% patients had achieved < 200 mg/dl of target TG with Saroglitazar therapy. (Figure 2)

Figure 2: Study population (%) with TG reduction (%) from baseline after 6 months of therapy



DISCUSSION:

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia. Increased hepatic glucose output predominantly accounts for increased fasting sugar level, whereas decreased peripheral glucose utilization results in postprandial hyperglycemia. The increased production of free fatty acids and some adipokines may cause insulin resistance in skeletal muscle and liver leading to impaired glucose utilization, increased glucose production by the liver, and impairment of beta cell function. This, in turn, leads to a spectrum of disorders, like *metabolic syndrome*, the *insulin resistance syndrome*, and *syndrome X* that include insulin resistance, hypertension, dyslipidemia (decreased HDL and elevated triglycerides), central or visceral obesity, T2DM and accelerated cardiovascular disease. [14]

India is currently the global capital for T2DM due to higher prevalence of insulin resistance. Higher prevalence of T2DM and insulin resistance is also one of the key factors for elevated triglyceride levels.[9] Currently, there are many medications are available to control glycemic parameters and elevated triglyceride level individually. But, Saroglitazar is the only medication which is dual PPAR α/γ agonist and approved for treatment of hypertriglyceridemia in T2DM patients as it reduces insulin resistance as well.[12] In Diabetic dyslipidemia, controlling both glucose and lipid levels appeared to be challenging, and a single pill that addresses not only insulin resistance but reduced elevated TG level also may beneficial for better patients.[15,16]

Randomized, controlled, phase 3 clinical trials (PRESS V & VI) have shown that Saroglitazar 4 mg once daily leads to a significant decrease in TG (45.0% to 46.7%) along with non-HDLc and HbA1c. [17,18] As per Singh H et al[19], when compared to patients only on statins, the patients who were on statin + Saroglitazar combination, showed significant improvement in lipid parameters such as total cholesterol, serum TG, LDL, VLDL, HDL, and glycemic parameter HbA1c at the end of 24 weeks. In a review of 18 studies evaluated by Kaul et al[20], there was a consistent mean reduction in TG levels (~ 45% to 62%), TC levels (~ 17% to 26%), non-HDLc levels (~ 21% to 36%), LDLc levels (~ 11% to 27%), and HbA1c (~ 0.7% to 1.6%) with an increase in mean HDLc levels (up to 9%) from baseline to end of the study. In this study, baseline mean TG was > 500 mg/dl and significant TG reduction (61.1%) was observed at end of 6 months of therapy. Along with that significant reduction in TC (23.74%) and numerical improvement in HDLc and LDLc were observed in present study.

In the study by Roy et al[15] , it was stated that Saroglitazar, a dual PPAR α/γ agonist, has a reducing effect on elevated TG and a positive effect on insulin sensitivity. It also reduces HbA1c levels. Jain et al[16] concluded that in euglycemic clamp study, saroglitazar treatment resulted in significant reduction in triglycerides, HbA1c along with improvement in Insulin sensitivity index and glucose metabolism. Similar HbA1c reduction by 0.77% has been observed in this study. In this study, during follow up for 6 months, no serious adverse events were observed with saroglitazar therapy.

Our present study showed significant reduction of triglyceride and HbA1c; which in accordance with the phase III clinical trials (PRESS V and PRESS VI) and various observational studies. Though saroglitazar is TG reducing agent, but lifestyle modification and reduction of HbA1c may have beneficial effect on TG reduction. Small sample size, short duration and single centre were major limitations of this study.

CONCLUSION:

In T2DM patients with moderate to severe hypertriglyceridemia, the use of saroglitazar 4 mg once daily for 6 month is associated with significant improvement of TG, TC and HbA1c.

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