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Impact of Saroglitazar in patients with Diabetic Dyslipidemia

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Abstract

Introduction: Diabetic dyslipidemia is characterized by higher fasting and postprandial triglycerides, low level of HDL-cholesterol, elevated levels of LDL-cholesterol and there is predominance of small dense LDL particles. This lipid level alteration represents linkage between diabetes mellitus and the increased cardiovascular risk which is predominant in patients with higher lipemic levels especially in diabetic patients.

Aim: To evaluate the efficacy of Saroglitazar in patients with Diabetes dyslipidemia.

Method and Material: This study is an observational study; the patients who were selected for the study were already having anti diabetic medication and were prescribed Saroglitazar 4 mg OD for a period of 16 weeks, in continuation to Statins. Patients who are established T2DM with presence of fatty liver disease using ultra sonography were only considered for this study.40 patients fulfilled the inclusion criteria and data was collected and analyzed.

Results and Discussion: The data obtained was analyzed using spss 20.0 software; paired t test was done to assess the change in biochemical parameters. It was observed that the mean age of the study population was 45.17±10.62 yrs. 64 % were males and 26 % were females, Mean BMI in the study group was 27.8 Kg/m^2, Mean duration of Diabetes was 4.6 yrs. In our study it was observed that Mean FBS, PPBS, Hba1c was significantly lower 16 weeks after initiation of Saroglitazar $p < 0.05$. Mean difference in the FBS was observed to be 16.9 mg/dl, PPBS was 43.3 mg/dl, and hba1c was 0.3%.

Conclusion: Saroglitazar leads to significant improvement in glycemic control and lipid parameters in patients with Diabetes dyslipidemia.

Keywords: Diabetes dyslipidemia, Glycemic control, NASH, Lipid parameters, Saroglitazar

INTRODUCTION

Diabetic dyslipidemia is characterized by higher fasting and postprandial triglycerides, low level of HDL-cholesterol, elevated levels of LDL-cholesterol and there is predominance of small dense LDL particles. This lipid level alteration represents linkage between diabetes mellitus and the increased cardiovascular risk which is predominant in patients with higher lipemic levels especially in diabetic patients. The underlying pathophysiology is not clearly understood, only a partially pathophysiology is understood. It is postulated that there is alteration in the pathway of insulin sensitivity apart from that it also known that there is a higher or increased concentrations of free fatty acids and it is also noted that there is a low grade inflammation also seen which can eventually lead to overproduction of triglyceride rich lipoproteins and decreased catabolism of triglyceride rich lipoproteins of intestinal and hepatic origin. The observed changes in HDL and LDL are mostly sequence to this.

Modification of Lifestyle and good control of glucose may improve the glycemic control apart from that it can also have an impact on lipid profile also but as many patient require the statin therapy in view of multiple risk factors, it is known that statin mediation in patient with diabetes dyslipidemia is the biggest benefit with respect to cardiovascular risk reduction.[1-3]Currently used therapies for the management of diabetes and dyslipidemia are only selected medication such as thiazolidinedione's, it is PPAR-g agonist and it is usually used in cases with insulin resistance cases apart from glycemic control and fibrates are very commonly used (PPAR-a agonist; for hypertriglyceridemia) have many limitations and side effects. Saroglitazar, dual PPAR-a/g agonists, is a newer therapeutic option with provides dual benefit on glycemic and lipid parameters.

It is well known that Asian Indians are having a unique pattern of dyslipidemia with predominantly increased TG levels, lower HDL-C levels and higher proportion of small dense LDL cholesterol (sd LDLC).

PPARs are nuclear lipid-activated transcription factors that regulate the gene expression which is involved in control of lipid and lipoprotein metabolism, glucose homeostasis and inflammatory processes. Their wide range of potential therapeutic actions make them attractive targets for the development of oral agents targeting risk factors associated with the metabolic syndrome, T2DM and CVDs .

Three different receptor subtypes, PPAR-a, PPAR-g and PPAR-b/d have been identified. PPAR-a is found in the liver, kidney, heart and muscle, and is implicated in the uptake and oxidation of fatty acids and lipoprotein metabolism. PPAR-b/d is expressed in most cell types and plays an important role in lipid metabolism and cell differentiation and growth. PPAR-g is mainly expressed in adipose tissue with lower expression detected in a wide range of differing tissues like spleen, intestine, pancreas, colon, kidney, skeletal muscle and macrophages.[4-7]

The most recent agent for the management of diabetic dyslipidemia and hypertriglyceridemia in T2DM patients not controlled with statin is saroglitazar. Saroglitazar is a dual PPAR-a/g agonist. It has strong PPAR-a action with moderate PPAR-g action. Two Phase III, prospective, randomized, controlled, multicenter clinical trials (prospective, randomized efficacy and safety of saroglitazar [PRESS] V and PRESS VI) lead to approval of saroglitazar by Drug Controller General of India (DCGI) on February 25, 2013. Saroglitazar is now also an option for the treatment of hypertriglyceridemia and dyslipidemia associated with diabetes in India.

The chemical name for saroglitazar is benzenepropanoic acid, a-ethoxy-4-[2-[2-methyl-5-[4-(methylthio)phenyl]-1H- pyrrol- 1-yl]ethoxy]-, magnesium salt (2:1), (aS) -- with the structural formula. Structure--activity relationship studies have indicated that most PPAR agonists have a lipophilic heterocyclic tail and acidic side chain with aromatic center in-between. Saroglitazar has a-alkoxy carboxylic group at acidic side chain and pyrrole as core heterocycle with Phenyl ring as aromatic center. The a-ethoxy carboxylic acid group forms the H-bond with various amino acids of PPAR-a and PPAR-g receptors and activates these receptors with higher potency for PPAR-a.

Dual agonists simultaneously stimulate PPAR-a and PPAR-g receptors with varying potencies at each site for treatment of T2DM, insulin resistance and dyslipidemia. Glitazar is a class of agents having dual PPAR-a and PPAR-g agonistic activity. Several dual PPAR-a and PPAR-g agonists have been clinically developed; however, none have progressed beyond Phase III development due to various reasons like lack of efficacy or safety and compound specific. Saroglitazar is a strong PPAR-a with moderate PPAR-g action. Currently, saroglitazar is the only approved glitazar, available in India for the treatment of diabetic dyslipidemia.[6-8]

Material and Methods:

This study is an observational study; EDSC retrospective data was collected for the set duration of two years and those patients who were started on molecule Saroglitazar were only taken under consideration. Patients who are established T2DM with presence of fatty liver disease using ultra sonography were only considered for this study. Patients who were classified with grade 1 or more fatty liver disease were selected for the study.

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The patients who were selected for the study were already having anti diabetic medication and were prescribed Saroglitazar 4 mg OD for a period of 16 weeks. Patients were continued on Statins.

Inclusion Criteria:

1. T2DM with Fatty liver disease confirmed on Ultrasound
2. Age group between 30 – 70 yrs
3. Established Type 2 Diabetes mellitus with dyslipidaemia despite on Statins

Exclusion Criteria:

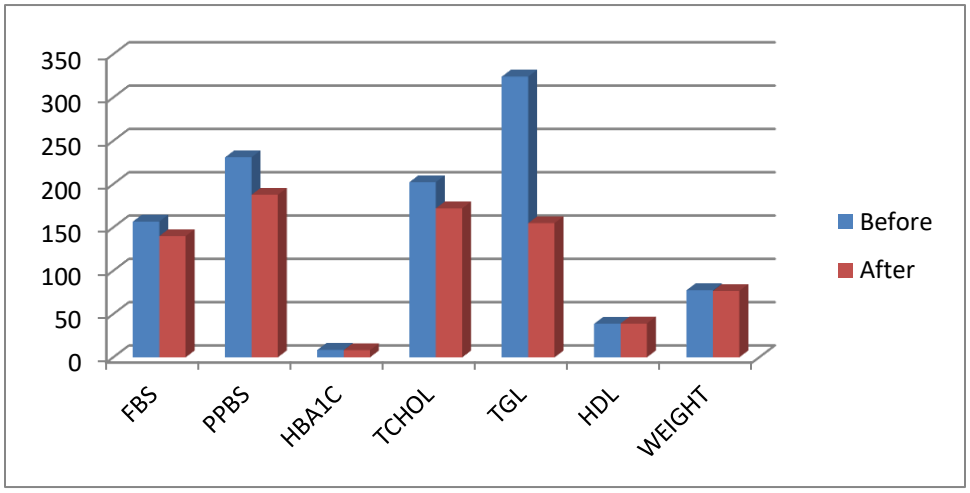
1. End organ involvement
2. Pre-existing liver disease
3. Pre-existing Renal disease
4. Pre-existing CNS disorders
5. Alcohol and smoker
6. Patient who does not give consent

100 patients were selected; only 40 patients fulfilled the inclusion criteria were selected randomly among both the genders. Base line laboratory parameters such as FBS, PPBS, HbA1c, and Lipids levels were measured in patients who showed fatty liver on ultra sonography. Subsequently 16 weeks after initiation of Saroglitazar 4 mg patients were re-evaluated for the biochemical parameters.

Results and Discussion:

The data obtained was analyzed using spss 20.0 software; paired t test was done to assess the change in biochemical parameters. Probability value (p value) was used to determine the level of significance p value < 0.05 was considered as significant, p value < 0.01 was considered as highly significant.

	Before		After			
	Mean	SD	Mean	SD	t value	p value
FBS	156.85	18.47	139.95	11.97	15.437	<0.001
PPBS	230.95	42.06	187.65	23.25	13.250	<0.001
HBA1C	8.55	0.69	8.25	0.57	12.631	<0.001
TCHOL	202.30	31.67	171.93	32.22	25.184	<0.001
TGL	324.05	74.41	154.93	24.94	19.321	<0.001
HDL	38.73	6.71	39.15	6.10	2.070	0.055
WEIGHT	77.45	8.57	76.65	8.07	3.323	0.002



It was observed that the mean age of the study population was 45.17±10.62 yrs. 64 % were males and 26 % were females, Mean BMI in the study group was 27.8 Kg/m^2, Mean duration of Diabetes was 4.6 yrs.

In our study it was observed that Mean FBS, PPBS, Hba1c was significantly lower 16 weeks after initiation of Saroglitazar p <0.05. Mean difference in the FBS was observed to be 16.9 mg/dl, PPBS was 43.3 mg/dl, and hba1c was 0.3%.

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Considering the dual benefits of saroglitazar, it seems to be a potential therapeutic option for the management of diabetic dyslipidemia. It is not associated with conventional side effects of fibrates and pioglitazone. Also, being an insulin sensitizer, saroglitazar may not have the potential to result in hypoglycemia[7-9]

A cross-sectional survey from India (ICMR INDIAB study) involving general adult population aged 20 years and above (age range: 20 -- 90 years) in three states and one union territory, indicated that 13.9% study population had hypercholesterolemia, 29.5% had hypertriglyceridemia, 72.3% had low HDL-C, 11.8% had high LDL-C levels and 79% had abnormalities in one of the lipid parameters. Dyslipidemia is highly prevalent in population with type 2 diabetes mellitus (T2DM; insulin resistance).[10]

There was a statistically significant decrease in the total cholesterol, triglycerides p <0.05. The mean difference was observed to be 30.4 mg/dl for total cholesterol and 160.9 mg/dl for triglycerides.

There was a significant decrease in weight with a mean difference of 0.8 kg. There was no statistically significant difference in the mean HDL. P >0.05

Conclusion:

Saroglitazar leads to significant improvement in glycemic control and lipid parameters in patients with Diabetes dyslipdemia.

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