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Original Research Article

Effect of saroglitazar in South Indian patients with diabetic dyslipidemia uncontrolled on a moderate-intensity statin and the association of PPAR α and γ gene polymorphisms with its response

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ABSTRACT

Background: Diabetic dyslipidemia is associated with atherosclerosis risk factors and cardiovascular disease. Saroglitazar is a dual PPAR α and γ agonist approved initially for diabetic dyslipidemia and later for managing non-alcoholic steatohepatitis and hyperglycemia in T2DM. This study was conducted to estimate the association of studied PPAR α and γ gene polymorphisms among patients with diabetic dyslipidemia at baseline and with triglyceride response to saroglitazar administration.
Methods: A total of 54 diabetic dyslipidemia patients who are not controlled i.e., triglycerides (TG)>200 mg/dl with moderate intensity of atorvastatin (≥10 mg) were recruited to the study. All the patients were given saroglitazar 4 mg once daily for 12 weeks. PPARα single nucleotide polymorphisms (SNPs) rs1800206, rs4253778, rs135542 and those of PPARγ gene rs3856806, rs10865710, rs1805192 were genotyped by real-time PCR.
Results: 54 patients (67% female) with a mean age of 48.01±6.73 years were given saroglitazar 4 mg once daily for 12 weeks. There was a significant decrease in TG (36.9%) from baseline of 292.33±83.81mg/dl (mean±SD) to 184.46±95.90 mg/dl (<0.001) and in HbA1c (0.66%) from baseline of 8.5% to 7.8% (<0.001). PPAR α and PPAR γ gene variants did not show any association with TG lowering response.
Conclusions: Saroglitazar 4mg once daily effectively decreases the TG, non-HDL-C levels, and HbA1c with no major adverse events, and TG lowering response is not associated with the studied polymorphisms.

Keywords: Diabetic dyslipidemia, PPARα/γ agonist, Single nucleotide polymorphisms, Saroglitazar

INTRODUCTION

Diabetic dyslipidemia is the most significant risk factor for cardiovascular diseases (CVD) in type 2 diabetes mellitus (T2DM) patients. CVD accounts for more than 80% of the mortality in patients with diabetes.[1,2] Patients with T2DM have an increased prevalence of dyslipidemia such as increased total cholesterol (TC), increased triglyceride (TG), high LDL-C, and reduced HDL-C resulting in macrovascular[coronary artery disease (CAD), stroke, and peripheral vascular disease] and microvascular (retinopathy, neuropathy, and nephropathy) complications.[3,4] The risk of having myocardial infarction or stroke is increased 2-3 fold, and the risk of death is 2-fold, independent of other known risk factors for disease. Early treatment to normalize the circulating lipids in

T2DM patients has been shown to reduce cardiovascular disease (CVD).[5] Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily, which form the primary treatment target for diabetes mellitus. Three receptor subtypes, PPAR α, PPAR β/δ, and PPAR γ, have been identified.[6] PPARα agonists like fibrates and PPAR γ agonists like glitazones are the most widely used pharmacological agents for regulating lipid metabolism and hyperglycemia in T2DM patients. Fibrates currently in use are weak PPAR α agonists with limited efficacy, and some of the glitazones, like pioglitazone, have been shown to have some cardiovascular complications.[7,8] Dual PPAR α/γ agonists are reportedly safe and could potentially benefit the patient with diabetes by controlling both hyperglycemia and dyslipidemia.[9] Saroglitazar is a novel PPAR α/γ dual agonist and the first glitazar to get approval for marketing in India. Although saroglitazar is a PPAR agonist, its structure differs from those of glitazones, fibrates, and other glitazars. It does not produce adverse reactions like other agents acting through PPAR.[10,11] There is inter-individual variability in the form of polymorphisms that also contributes significantly to the differential drug response in the population. Single nucleotide polymorphisms (SNPs) determine their corresponding proteins' expression level and activity. So the current study aims to study the association with response to saroglitazar with PPAR α/γ polymorphisms.

METHODS

The prospective cohort study was conducted in the department of Endocrinology of a tertiary care institute in South India, JIPMER, Puducherry. The study period was from July 2017 to September 2021. Written informed consent was obtained from all the participants before the initiation of the study. A total of 54 diabetic dyslipidemia patients who are not controlled (i.e., TG>200 mg/dl) with moderate intensity of atorvastatin (≥10 mg) were recruited. Saroglitazar, 4 mg tablet, was prescribed daily before breakfast. All the T2DM patients recruited into the study were continued on their regular diabetic medications without dose changes during the three months of saroglitazar intervention. The exclusion criteria were other types of diabetes and other endocrine disorders. Those with HbA1C >10% were excluded from the study. The duration of drug intervention was 12 weeks. Patients' anthropometric data, glycemic, lipid parameters, and adverse events, if any, were recorded at baseline and three months post-intervention visit. Subjects were asked to come with overnight fasting. From each patient, 5 ml of fasting venous blood sample was collected for genotyping, measurement of biochemical parameters, and glycated hemoglobin (HbA1c). The lipid profile was measured using a fully automated chemistry analyzer system (AU680, Beckman Coulter), while HbA1c was measured by an HbA1c analyzer (Bio-Rad D 10). Apo A1 and Apo B levels were measured using the ELISA method (Fine test kits) and free fatty acid by spectrophotometric methods (Solarbio life science) according to the manufacturer's protocol. Six SNPs were selected for genotyping in this study, 3 in PPAR α, rs1800206 C>G (*Leu162Val*), 4253778 7G>C and rs135542 T>C and 3 in PPAR γ, rs3856806 C161T, rs10865710 C681G, and rs1805192 C>G (*Pro12Ala*) genes respectively as shown in (Table 1). We selected these SNPs based on the following criteria: 1. Previous association with diabetes and lipid abnormalities, combined or in isolation. Minor allele frequency (MAF) >0.05%. Genomic DNA was extracted from WBCs by the phenol-chloroform manual method. The DNA was analyzed quantitatively and qualitatively using Infinite 200 Pro Microplate Reader (Tecan, Austria). Further, the quantified DNA sample was diluted at a concentration of 50ng/µl and incubated at 37°C for 12 hrs before real-time PCR analysis. The selected SNPs were genotyped using Real-time PCR (AB 7300, USA: Applied Biosystems). The final volume of 10 µl reaction per well was prepared to contain 5 µl of TaqMan master mix (2x), 0.25 µl TaqMan assay kits (40x), 2.5 µl of DNA, and 2.25 µl of milli-Q water. The TaqMan SNP genotyping assay kits from Applied Biosystems were used as per the manufacturer's protocol. Change in TG levels was used to determine the effect of saroglitazar response in diabetic dyslipidemia patients. Therefore, patients were categorized according to the change in TG level following three months of saroglitazar and were classified into responders and non-responders. Responders were arbitrarily defined as those with a minimum absolute TG reduction of 50mg/dl from the baseline after treating with saroglitazar 4mg for three months. Non-responders were those with an absolute reduction of TG less than 50 mg/dl. The characteristics of patients were summarized using descriptive statistics. Changes in anthropometric, serum lipid profile and glycemic parameters after 12 weeks of saroglitazar 4mg treatment from baseline were analyzed using the paired t-test. Categorical data were described as percentages, whereas mean ±SD was used for continuous data. The Chi-square test was used to investigate deviation from Hardy-Weinberg Equilibrium (HWE). The dominant model was amended to account for less number of homozygous mutants. Odds ratios (OR) were calculated for the association between polymorphisms of the PPAR gene and response, with confidence intervals (CI) at 95%. A p value <0.05 was considered statistically significant. SNPs analysis was performed using the SNPStats web tool (https://www.snpstats.net/start.htm). The data were analyzed by Statistical Package for Social Sciences SPSS 19.0.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 54 diabetic dyslipidemia patients uncontrolled with moderate intensity of atorvastatin (≥10 mg) were recruited in this study. The baseline characteristic of the patients is mentioned in (Table 2). The average duration of the patients with T2DM was 6.5 (±3.54) years. The mean age of patients was 48 (±5.73) years, and 66.7% were female. Out of 54 patients, 31.5% of patients were reported to have hypertension, and 53.7% of the patients were obese.

Table 1: Description of the 6 SNPs in peroxisome proliferator-activated receptor genes.

SNP ID	SNP	Chromosome	Base substitution	Amino acid substitution	Position
PPAR α					
rs1800206	Leu162Val	22	C>G	p.Leu162Val	46218377
rs4253778	7G>C	22	G>C	NA	46234737
rs135542	Intron T>C	22	T>C	NA	46160138
PPAR γ					
rs3856806	C161T	3	C>T	p.His477His	12434058
rs10865710	C681G	3	C>G	NA	12311699
rs1805192	Pro12Ala	3	C>G	p.Pro12Ala	12379739

Table 2: Characteristics of the study participants at baseline.

Total patients (n=54)	Mean±SD
Age (years)	48.01±5.73
Duration of diabetes (years)	6.50±3.54
Male, N (%)	18 (33.3)
Height (cm)	154.73±7.74
Weight (kg)	64.90±10.80
BMI kg/m2	27.13±4.10
Obesity, N (%)	29 (53.7)
Systolic BP (mmHg)	136.35±21.87
Diastolic BP (mmHg)	84.06±11.96
Hypertension, N (%)	17 (31.5)
Pattern of antidiabetic drugs	
Metformin	51 (94.4)
Sulphonylureas	34 (62.9)
Insulin	9 (16.7)
Gliptin	5 (9.3)

Table 3: Change in parameters after 12 weeks treatment with saroglitazar 4 mg once daily (n=54).

Parameters	Baseline Mean±SD	Post-saroglitazar Mean±SD	Absolute change (±SD)	Percentage change (%) ±SD	P value
Total Cholesterol (mg/dl)	198.77±46.46	166.14±53.90	-32.62±44.12	-14.19±19.29	<0.001
Triglyceride (mg/dl)	292.33±80.86	184.46±91.09	-107.87±98.14	-36.90±22.84	<0.001
LDL-C (mg/dl)	126.90±32.31	106.77±34.09	-20.12±30.65	-13.33±20.53	<0.001
HDL-C (mg/dl) Male	38.58±7.73	38.0±10.28	-0.58±9.69	-1.58±25.07	0.8
HDL-C (mg/dl) Female	45.58±7.51	42.19±14.34	-3.38±11.20	-7.4±17.87	0.078
Non-HDL-C (mg/dl)	155.44±27.05	125.30 ±28.76	-30.12±23.61	-15.83 ±21.67	<0.001
Apo A1 (ng/ml)	12.93±1.83	12.32±2.20	-0.61±2.80	-4.71±17.72	0.109
Apo B (ng/ml)	3652.92±997.23	3254.73±954.97	-398.19±1034.56	-10.90±19.40	0.026
Oxidized -LDL (ng/ml)	105.30±59.71	77.14±57.06	-28.16±79.26	-10.61±58.86	0.012
Free fatty acid (µmol/l)	374.5±273.49	337.94±246.47	-36.64±185.24	-9.78±36.07	0.144
HbA1C (%)	8.54±0.57(%)	7.88±0.53(%)	-0.66 ± 0.37(%)	-	<0.001

*p value <0.05 and **p value <0.001 were considered statistically significant

The mean body mass index (BMI) was 27.13 kg/cm2. The pattern of antidiabetic drugs is shown in (Table 2). All the baseline characteristics, including the anthropometric, lipid, and glycemic parameters, were not significantly different between responders and non-responders. The treatment of saroglitazar 4mg once daily for three months showed significant improvement in lipid and glycemic parameters (Table 3). There was a reduction of 36.9% in TG from a baseline of 292.33±80.86 mg/dl to 184.46±91.09 mg/dl (p<0.001). Saroglitazar 4 mg treatment also resulted in a significant mean% of change from baseline reduction in total cholesterol (TC) of 14.2%, non-HDL-C of 15.8%, LDL-C of 13.33%, oxidized LDL of 10.6% and Apo B of 10.9% respectively.

Table 4: Response to saroglitazar according to PPAR α and γ gene polymorphisms.

Gene	Genotype and Allele	Responder Frequency (%) (N=42)	Non responder Frequency (%) (N=12)	OR (95% CI)	P value
PPAR α					
rs1800206 C>G					
(Leu162Val)	CC	40 (95)	12 (100)	1	0.9
	CG+GG	2 (5)	0	0.77 (0.63 - 0.89)	
	Allele				
	C	82 (98)	24 (100)	1	0.9
	G	2 (2)	0	0 (0-7.60)	
rs4253778 G>C					
-	GG	39 (93)	11 (91.7)	1	0.89
	GC+CC	3 (7)	1 (8.3)	1.18 (0.11-12.1)	
	Allele				
	G	80 (95)	23 (96)	1	0.99
	C	4 (5)	1 (4)	0.86 (0.06-5.74)	
rs135542 T>C					
-	TT	31 (74)	11 (91.7)	1	0.189
	TC+CC	11 (26)	1 (8.3)	3.90 (0.45-33.83)	
	Allele				
	T	71 (85)	23 (96)	1	0.19
	C	13 (15)	1 (4)	0.23 (0.02-1.45)	
PPAR γ					
rs3856806 C>T					
-	CC	32 (76.2)	10 (83.3)	1	0.41
	CT+TT	10 (23.8)	2 (16.7)	0.64 (0.12- 3.42)	
	Allele				
	C	73 (87)	22 (93)	1	0.72
	T	11 (13)	2 (8)	0.60 (0.12-2.4)	
rs10865710 C>G					
-	CC	35 (83)	11 (91.7)	1	0.47
	CG+GG	7 (17)	1 (8.3)	0.45 (0.05- 4.11)	
	Allele				
	C	75 (89)	23 (96)	1	0.37
	G	9 (11)	1 (4)	0.36 (0.03-2.53)	
rs1805192 C>G					
(Pro12Ala)	CC	42 (100)	12 (100)	--	--
	CG	0	0		
	GG	0	0		
	Allele				
	C	84 (100)	24 (100)	--	
	G	0	0		

P value <0.05 was considered statistically significant

However, there was a non-significant mean reduction of 9.8% in free fatty acid and 4.7% in Apo A1. Analysis of glycemic parameters showed a significant reduction of 0.66% in HbA1c from a baseline of 8.5% to 7.8% following 12-week saroglitazar therapy. The genotype and minor allele frequencies distribution of PPAR α (rs1800206, rs4253778, rs135542) and PPAR γ gene (rs3856806, rs10865710, rs1805192) variants are presented in (Table 4). All the PPAR α and PPAR γ gene variants were in Hardy-Weinberg equilibrium (p>0.05). The overall minor allele frequencies (MAF) for PPARα rs1800206 C>G (Leu162Val), 4253778 7G>C, rs135542 T>C were 1.9% (G allele), 4.6% (C allele), 13% (C allele) and PPAR γ gene (rs3856806 C161T, rs10865710 C681G) were 12% (T allele), 9.3% (G allele) respectively the total number of responders were 42 (77.7%). No polymorphism was reported from rs1805192 Pro12Ala. The studied PPAR α and PPAR γ gene variants did not correlate with the response (responder and non-responder), as shown in (Table 4). The most common adverse events that occurred are shown in (Table 5). No severe adverse reactions were reported in this study. Adverse drug reaction was scored based on the Naranjo scale; the score was probable in 3 (5.6%) subjects and possible in 5 (9.2%) subjects, as

shown in (Table 5). There was no significant change in body weight, BMI, BP, and creatinine from baseline to the 3-months drug intervention follow-up.

Table 5: Adverse events with saroglitazar.

Saroglitazar 4 mg (n=8/54)	
Adverse drug reactions	**N (%)**
Chest discomfort	2 (3.7)
Gastritis	2 (3.7)
Abdominal pain	1 (1.9)
Salty taste	1 (1.9)
Reddish stool	1 (1.9)
Dizziness	1 (1.9)
Naranjo score	
Definite (≥9)	-
Probable (5-8)	3 (37.5)
Possible (1-4)	5 (62.5)
Doubtful (≤0)	-

DISCUSSION

This prospective cohort study evaluated the effect of saroglitazar 4 mg once daily over 12 weeks in 54 diabetic dyslipidemia patients with uncontrolled TG (>200 mg/dl) on the moderate intensity of atorvastatin ≥10 mg and its association with response to saroglitazar. We observed a significant reduction in TG, TC, non-HDL-C, LDL-C, oxidized LDL, and apo B from baseline. There was a non-significant mean reduction in free fatty acid and apo-A1 levels. Glycemic parameters such as HbA1c were significantly reduced from baseline to post-12-week saroglitazar. Moreover, saroglitazar 4 mg was safe throughout the intervention without significant adverse events or changes in body weight, BMI, BP, and serum creatinine. Our study showed a mean reduction in TG of 36.9% and an HbA1c of 0.66%. Bhattarchaya et al. similarly showed a reduction of TG by 33.7% and of HbA1c by 0.76% following the treatment of diabetic dyslipidemia patients with a combination of saroglitazar 4 mg and atorvastatin 10mg for 12 weeks.[12] Another study with saroglitazar reported a reduction in TG of 32.1% and HbA1c of 0.9% from the baseline.[13] Furthermore, Kaul et al found a decrease of 35.6% in TG and 0.9% in HbA1c from baseline over 24 weeks in 104 subjects.[14]

Shetty et al conducted an observational, post-marketing study of 2804 diabetic dyslipidemia patients and reported a significant reduction of all the lipid and glycemic parameters at a 12-weeks follow-up.[15] The baseline mean TG was 312.3±122.7 mg/dl, decreasing to 188.7±61.4 mg/dl, a reduction of 35.8%. The baseline mean non-HDL-C was 201.8±64.1mg/dl, which decreased to 149.4±41 mg/dl, a reduction of 23.4%. A significant decrease from the mean baseline was also observed in TC (19%), LDL-C (16.4%), and VLDL-C (31.5%), while a significant increase of 7.3% was documented in HDL-C level. HbA1c significantly decreased from a mean baseline of 8.3±1.3 (%) to 7.4±0.9(%) at the 12-week follow-up. A phase 3, multicentre, randomized, double-blinded study (PRESS V) was conducted by Pai et al.[16] The efficacy and the safety of saroglitazar 2 mg and 4 mg were evaluated and compared to that of pioglitazone 45mg in 122 patients with diabetic dyslipidemia following 24 weeks of therapy. The primary endpoint was a change in TG level after six months. Saroglitazar 4mg decreased TG level by 45% (baseline mean of 257.0±52.39 mg/dl and absolute change ±SD of 115.4 ±68.11 mg/dl). There was also a significant reduction in TC (7.7%), VLDL-C (45.5%), LDL-C (5%), HbA1c (0.3%) and Apo B (10.9%). Jani et al evaluated the efficacy and tolerability of saroglitazar 2 mg and 4 mg compared to placebo in 302 T2DM subjects with hypertriglyceridemia uncontrolled with 10 mg atorvastatin once daily in a randomized, multicentre, prospective, double-blind study (PRESS VI) for 12 weeks.[17] Saroglitazar 4 mg decreased serum TG levels by 46.7% (baseline mean of 287.3±85.94 mg/dl and absolute change of -139.5±8.29 mg/dl), non-HDL-C by 32.5%, LDL-C by 31.3%, TC by 26.1% and VLDL-C by 46%, Apo B by 32% and HbA1c by 0.3% along with an increase in HDL-C. These reductions in lipid (TG, non-HDL-C, LDL-C, VLDL-C, TC) and glycemic(HbA1c) parameters were statistically significant ($p<0.05$) as compared to baseline and placebo. Both the American diabetes association and American heart association guidelines recommend statins as the primary drug therapy for the management of dyslipidemia in T2DM subjects. Statin therapy does not eliminate the risk of CVD associated with high TG levels.[18-20] Also, many patients on statins develop rhabdomyolysis, myositis, myopathy.[21] Fibrates are used for the treatment of hypertriglyceridemia. FIELD and ACCORD trials showed that fibrates do not significantly reduce cardiovascular risk events. Moreover, long-term use of fibrates is associated with an increase in creatinine, an increase in plasma homocysteine, and other side effects like cholelithiasis.[22-24] PPAR γ agonists such as pioglitazone are used for the treatment of T2DM. PROactive trial study in T2DM patients showed a non-significantly reduced risk for coronary and peripheral vascular events. However, the study also reported the association between an increased risk of heart failure and bladder cancer.[25,26] Glitazar (PPARα and γ dual agonist) such as aleglitazar was studied and later discontinued due to adverse events of renal function and heart failure. Another PPARα and γ dual agonist, muraglitazar, was discontinued due to adverse events such as myocardial infarction and heart failure.[27] Saroglitazar is the only dual PPARα and γ agonist approved for the treatment of diabetic dyslipidemia by the drug controller general of India (DCGI). The use of saroglitazar treatment was found to be safe and well tolerated by patients, and no increase in body weight.[28] In this study, the overall MAFs for PPAR α C>G(Leu162Val), 7G>C, and T>C were 1.9%, 4.6%, and 13%, respectively. A similar frequency of L162V (1%) SNP was reported in the South Indian population by Lacquemant et al, Purushothaman et al showed 7G>C SNP (9%) in the South Indian population, which is comparable to the frequency documented in our study.[29,30] Halder et al showed T>C SNP (26.7%) among the USA population, which is higher than our study population.[31] Further,

MAFs of PPAR γ gene C161T and C681G) were 12% and 9.3%, respectively. The MAF of 14.2% observed for PPAR γ gene SNP C161T was in accordance with Haseeb et al.[32] However, a higher MAF of 32.2% for SNP C161T was reported in the Chinese population by Hai et al.[33] The PPAR γ gene C>G (Pro12Ala) polymorphism was not found in our study. Similar findings were documented by Sarkar et al. in the northeast Indian population.[34] Fan et al showed that MAFs of PPAR γ gene C>G(Pro12Ala) was 26.5% in the Chinese Han population.[35] Our study did not find any association of PPAR α and γ gene polymorphism with TG response to saroglitazar. Yohan Bosse et al. studied the C>G (Leu162Val) variant of PPARα for association with TG response to gemfibrozil 600mg over 24 weeks in 63 obese men. However, no association was found for TG lowering response of gemfibrozil with C>G (Leu162Val) variant.[36] Foucher et al conducted the DIAS study in 207 diabetes patients with lipid abnormalities being treated with fenofibrate 200mg/day for three years. The TG level and PPARα 7G>C variant were associated with response to fenofibrate (p=0.012; OR=3.0; 95% 1.28-7.52), whereas no association between the TG response and PPARα C>G(Leu162Val) variant was seen in the DIAS subjects with T2DM.[37] Further, Brisson et al. showed no association of the PPARα gene C>G (Leu162Val) and PPAR γ gene C>G(Pro12Ala) between TG response to fibrates among 292 hypertriglyceridemic subjects for 12 weeks.[38] This study has unique features. This is the first study to evaluate the association of PPARα and γ gene polymorphisms with a response to saroglitazar 4mg od in South Indian patients with diabetic dyslipidemia uncontrolled on a statin. Additional evaluation of Apo A1, Apo B, and FFA levels is one of the study's strengths. The study has a few limitations. It is not a randomized, controlled clinical trial, and the saroglitazar exposure was only 12 weeks long.

CONCLUSION

In conclusion, saroglitazar 4mg was effective, significantly improving lipids and glycemic parameters. There is a significant decrease in triglyceride and HbA1c levels from the mean baseline following 12 weeks of saroglitazar. Other biochemical parameters such as total cholesterol, LDL-C, VLDL-C, non-HDL-C, oxidized LDL, and apo B were also significantly decreased. There was no association between the studied SNPs and diabetes dyslipidemia. The significant improvement in metabolic parameters was also not associated with studied SNPs.

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