ORIGINAL ARTICLE

Study of **S**aroglitazar in **T**reatment **O**f **P**re-diabetes with **D**yslipidemia: STOP-D

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Abstract

Objectives: Patients with prediabetes are not only at increased risk of progression to type 2 diabetes, but they are also at high risk of developing cardiovascular risk compared to normoglycemic people. Further, prediabetes is also often associated with abnormal lipid levels (dyslipidemia). We therefore aimed to evaluate the effect of Saroglitazar in patients with prediabetes and dyslipidemia.

Methods: This was a prospective, single centre, single arm study involving patients with pre-diabetes and dyslipidemia. Subjects with baseline HbA1c 5.7-6.4% and dyslipidemia (Total cholesterol > 200mg/dl, LDL-C > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl) were enrolled in this study. Subjects with on-going medications affecting blood glucose or lipids were excluded from the study. Saroglitazar 4mg once daily was administered for a period of 24 weeks. The primary outcome was change in serum triglycerides and secondary outcome parameters included changes in other lipid parameters and HbA1c levels at 24 weeks follow-up.

Results: Forty patients with prediabetes and dyslipidemia were enrolled in the study. At 24 weeks follow-up, serum triglycerides was significantly reduced from 348 ± 86.98 mg/dl to 216.4 ± 72.34 mg/dl (P <0.0001). HbA1c was significantly reduced from 6.3 ± 0.16 % to 5.5 ± 0.30 % after 24 weeks of Saroglitazar therapy (P<0.0001). There were significant improvements observed in other lipid parameters at 24 weeks follow-up period. Saroglitazar was found to be safe and well tolerated, no serious adverse event reported during entire study period.

Conclusion: Saroglitazar is safe and effective in prediabetes with dyslipidemia by exerting its dual lipid lowering and glycemic actions.

Trial Registration: ctri.nic.in CTRI/2016/03/006778.

Introduction

Type 2 Diabetes Mellitus (T2DM) is on the rise with its many complications and high cost to the society, and its prevention is of primordial concern. According to International Diabetes Federation 2015 Diabetes Atlas (7th edition), in addition to the 415 million adults who are estimated to currently have diabetes, there are 318 million adults with impaired glucose tolerance (IGT), which puts them at high risk of developing the disease in the future. India is the second largest contributor of diabetes in the World with 69.2 million and 2040 projection estimates of 123.5 million, second only to China. India is already the largest contributor of IGT in the world with 36.5 million population affected with IGT in 2015.[1]

Prediabetes is the precursor stage to T2DM which is defined by American Diabetes Association (ADA) as impaired fasting glucose (IFG) of 100–125 mg/dl (5.6–6.9 mmol/l) or IGT of 140–199 mg/dl (7.8–11.0 mmol/l) after two hours postprandial. ADA also recommends glycosylated hemoglobin (HbA1c) prediabetic range of 5.7–6.4%.[2] Prediabetes is not only associated with increased risk of progression to T2DM but also with increased cardiovascular disease (CVD) risk.[3]

Current consensus definition of metabolic syndrome incorporates hyperglycemia, obesity, hypertension, hypertriglyceridemia and reduced high density lipoprotein cholesterol (HDL-C).[4] However, many researchers believe that insulin resistance is the core pathophysiology which mediates metabolic syndrome.[5] Hence, there is an overlap between prediabetes and metabolic syndrome and prediabetes is often associated with dyslipidemia. The risk of diabetes is 5–7 fold higher in patients with IFG or IGT as compared to normoglycemic patients and for the patients with metabolic syndrome, the risk of developing diabetes is 5 fold more as compared to the patients who are not having metabolic syndrome.[6] However, when prediabetes combines with metabolic syndrome, the risk is increased even more.

Saroglitazar, a dual peroxisome proliferator activated receptor (PPAR) α/γ agonist is approved in India for the treatment of diabetic dyslipidemia which is not controlled with statin alone. Pivotal phase III studies have shown triglyceride reduction by 45–46.7%, Non HDL-C reduction by 32.5%, Apo B reduction by 32% and HbA1c reduction by 0.3% from baseline at 12-24 week follow-up with Saroglitazar 4 mg once daily treatment.[7,8] The safety and efficacy of Saroglitazar in prediabetes population with dyslipidemia had not been studied till date. Hence, we strived to evaluate the safety and efficacy of Saroglitazar in patients with dyslipidemia and meeting the criteria of prediabetes.

Material and Methods

This is an interventional, prospective, single center, single arm trial conducted in patients with pre-diabetes and

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Table 1: Baseline demographic profile of participants

Total patients (n)	40
Mean Age, years	48.15±7.53
Participants, male: n (%)	28 (70)
Mean Weight (kg)	74.02±3.66
Mean BMI (kg/m^2)	26.93±2.26

dyslipidemia to evaluate the safety and efficacy of Saroglitazar. The subjects were recruited at Deogiri Diabetes Centre, Aurangabad, Maharashtra, India. Subjects with baseline HbA1c 5.7–6.4% and dyslipidemia [Total cholesterol > 200mg/dl, low-density lipoproteins cholesterol (LDL-C) > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl] as per National cholesterol education programme-adult treatment panel III (NCEP ATP III) criteria (borderline high and above) were enrolled in this study[9] Institutional ethical committee approval was sought and granted by the MGM-ECRHS (Mahatma Gandhi Mission's Ethics Committee for Research on Human Subjects) based at MGM Medical College, Aurangabad, India and the trial was in accordance with the revised Helsinki Declaration of 2000. Patient's informed consent was taken prior to each patient enrollment after proper explanation of the study details and interventions to the patient in their own regional language. The trial was registered in Clinical Trials Registry- India (CTRI) with CTRI number CTRI/2016/03/006778.

The inclusion criteria of the study were patients of either sex with age group of 20-60 years, patients with prediabetes (HbA1c 5.7–6.4%) and deranged lipids as per NCEP ATP III criteria.

Participants with borderline high and above range of dyslipidemia i.e total cholesterol > 200mg/dl, LDL-C > 130 mg/dl, triglycerides > 150 mg/dl and HDL< 40 mg/dl were included in the study. Patients with Type I DM, Type II DM, secondary hypertension, bronchial asthma, chronic obstructive pulmonary disease or any other respiratory disorders and any hepatic or renal diseases were excluded from the study. Also, subjects with on-going medications affecting blood glucose or lipids were excluded from the study.

After fulfillment of inclusion criteria and informed written consent, subjects were enrolled into study and Saroglitazar 4mg once daily was administered for a period of 24 weeks. Saroglitazar is available in only 4 mg strength in the market. The primary outcome was change in serum triglycerides and secondary outcome parameters included changes in HbA1c, serum total cholesterol, serum LDL-C, serum HDL-C and Non HDL-C at 24 weeks follow-up. Serum urea and creatinine as Kidney function test (KFT), Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) as Liver function test (LFT) and electrocardiography (ECG) were also assessed at baseline and at 24 weeks follow-up to evaluate the safety of Saroglitazar.

The results were analyzed by using paired student "t-test" with SPSS (statistical package for the social science) software (version 22). P value < 0.05% was considered as significant.

Results

A total of 40 participants were enrolled in the study. The mean age was 48.15 years with 28 male participants out of the total 40.The baseline demographic profile is tabulated in Table 1.

The mean baseline HbA1c and triglycerides were 6.3 ± 0.16 % and 348 ± 86.98 mg/dl respectively (Table 2). All subjects were given Saroglitazar 4mg once daily for 24 weeks. There was no loss to follow-up as all 40 enrolled subjects completed the study. All participants who got enrolled in the study were hypertensive and they were on anti-hypertensive drug therapy. Hence, they were advised to continue the same. The participants were also provided routine dietary advice at enrollment.

The change in lipid parameters, HbA1c, liver enzymes, and kidney functions were evaluated at 24 weeks by using paired t-test.

At 24 weeks, there were significant improvements in lipid parameters and HbA1c level (Table 2).

Serum triglycerides was significantly reduced from 348 ± 86.98 mg/dl to 216.4 ± 72.34 mg/dl (P <0.0001) with 38.7 ± 10.72 % change from baseline. Other lipid parameters like total cholesterol, LDL-C and non HDL-C were also reduced significantly (P <0.0001) by 17.1 ± 2.48 %, 15.7 ± 8.47 % and 19.9 ± 10.35 % respectively and HDL-C was increased by 9.6 ± 5.54 % (P<0.0001). In addition to significant changes in lipid parameters, there was significant improvement observed in glycemic parameter as well. Mean HbA1c reduced from 6.3 ± 0.16 % at baseline to 5.5 ± 0.30 % after 24 weeks of Saroglitazar therapy (P <0.0001). These results signify the dual role of Saroglitazar in reducing both lipid and glycemic parameters.

Apart from the above parameters, lipid and kidney function were also assessed in the study. The results are depicted in Table 3. After 24 weeks of Saroglitazar therapy, ALT significantly reduced by 6.7% ± 23.14 (P =0.024) and serum urea reduced by 2.5% ± 26.17 though, not statistically significant. (P =0.2217)

There was no serious adverse event reported with Saroglitazar during the entire study period. The ECG reports of all subjects were within normal limits with no QT prolongation. One patient reported with an episode of diarrhea which was resolved with antimicrobials without interrupting study medication. There was no adverse effect on liver enzymes or kidney function at week 24. There was no weight gain or edema reported. Mean baseline weight of 74.02±3.66 kg was reduced to 73.9±3.92 kg. (P=0.3468) (Table 3).

Discussion

The incidence and prevalence of T2DM has been progressing rapidly worldwide over the last few decades posing as a major public health problem. Moreover, the disease manifestations start at an earlier stage, even before it gets established as a full blown condition, the pre-stage to T2DM called prediabetes.

South East Asia has 42.2 million people with IGT and is at increased risk of developing T2DM in the future and projected 2040 estimates are 73.9 million people. India constitutes over 86% of adults amongst South East Asia population.[1]

Much of the socioeconomic burden of diabetes is due to the complications of this disease, notably from CVD. This increased risk for cardiovascular morbidity and mortality is mostly an indirect manifestation of cardio-metabolic abnormalities, including lipid abnormalities. In general, people with diabetes tend to have elevated concentrations of triglycerides and Apo-lipoprotein B, low concentrations

Table 2: Change in lipids and HbA1c after 24 weeks treatment with Saroglitazar

Laboratory parameters	Baseline (n=40)	24 weeks follow-up (n=40)	Absolute change from baseline	% change from baseline	P-value
Total cholesterol (mg/dl)	324.7 ± 43.39	270.1 ± 43.61	-54.6 ± 2.38	-17.1 ± 2.48	<.0001
Triglycerides (mg/dl)	348.0 ± 86.98	216.4 ± 72.34	-131.5 ± 48.64	-38.7 ± 10.72	<0.0001
LDL-C (mg/dl)	209.8 ± 47.67	177.9 ± 47.56	-31.9 ± 14.22	-15.7 ± 8.47	<0.0001
HDL-C (mg/dl)	44.8 ± 5.71	49.0 ± 6.13	4.2 ± 2.39	9.6 ± 5.54	<0.0001
Non HDL-C (mg/dl)	278.6 ± 42.38	224.1 ± 47.15	-54.5 ± 25.11	-19.9 ± 10.35	<0.0001
HbA1c (%)	6.3 ± 0.16	5.5 ± 0.30	-0.7 ± 0.25	-	<0.0001

All values are in Mean ± SD

Table 3: Change in kidney, liver function and weight after 24 weeks treatment with saroglitazar

Laboratory parameters	Baseline (n=40)	24 weeks follow-up (n=40)	Absolute change from baseline	% change from baseline	P-value
Serum urea (mg/dl)	22.0 ± 4.21	20.9 ± 4.74	-1.1 ± 5.73	-2.5 ± 26.17	0.2217
Serum creatinine (mg/dl)	1.0 ± 0.17	1.0 ± 0.14	0.0 ± 0.18	6.1 ± 19.46	0.21
Alanine aminotransferase (U/L)	26.9 ± 6.16	24.6 ± 6.61	-2.3 ± 6.12	-6.7 ± 23.14	0.024
Aspartate aminotransferase (U/L)	25.2 ± 6.11	26.5 ± 6.39	1.4 ± 8.33	11.3 ± 38.81	0.311
Weight (kg)	74.02 ± 3.66	73.9 ± 3.92	-0.125 ± 0.26	-0.182	0.3468

All values are in Mean ± SD

of HDL-C and an elevated number of small dense LDL-C particles.[10] Findings from the National Health and Nutrition Examination Survey 1988–1991 to 2005–2008 reveal that participants with prediabetes had worse lipid profiles than those with diagnosed diabetes.[11] Hence, prediabetes and dyslipidemia might be needed to be addressed and interventions sought in order to prevent their progression to frank diabetes and its chronic complications.

Asian Indians have a phenotype which is generally a combination of characteristics that predisposes more to the development of insulin resistance, T2DM and CVD.[12] A study by the ICMR–INDIAB (Indian Council of Medical Research-INdiaDIABetes) Collaborative Study Group showed that the onset of T2DM is earlier and at lower levels of BMI in Asian Indians compared with Caucasians.[13] In spite of a relatively lower rate of obesity as defined by BMI cut points, Asian Indians tend to have larger waist measurements and waist-to-hip ratios, indicating a greater degree of central body obesity.[14] This is associated with a characteristic metabolic profile with a greater degree of insulin resistance, a premature loss of beta cell function, metabolic syndrome or prediabetes.

Diabetic dyslipidemia (DD) is condition where in there is increased triglycerides, low HDL-C and increased proportion of small dense LDL-C.[15] Hypertriglyceridemia has been reported as an important risk factor for CVD.[16] Hypertriglyceridemia may be as prevalent as 50% in T2DM and is often unresponsive to statin treatment.[17] In an article by Anders Berg Jorgensen et al, using data from 75,725 participants in two general-population studies, it was ascertained that participants with non-fasting TG <90 mg/dl had 60% lesser risk of CV events compared to participants with non-fasting TG >350 mg/dl.[18] Hence, triglyceride management becomes important along with reduction of other lipid parameters not only in diabetes but in prediabetes as well.

Phase III trials of Saroglitazar have shown significant reductions in triglycerides and other lipid parameters along with effective reductions in glycemic parameters in diabetes patients suffering from dyslipidemia.[9,10] Similar efficacy and safety results were further reiterated in a post marketing study where at 3 months follow-up, use of Saroglitazar 4 mg in patients with diabetic dyslipidemia led to significant reduction in triglycerides (35.8%), LDL-C (16.4%), total cholesterol (19%) and non-HDL-C (23.4%). Addition of Saroglitazar to baseline antidiabetic medications showed a significant 0.9% absolute reduction in HbA1c with significant improvement in fasting and post prandial plasma glucose.[19]

All studies till date on Saroglitazar has been on diabetes patients with dyslipidemia. This is the first study which was solely conducted on subjects with prediabetes and dyslipidemia. The results are encouraging and in lines with the previous studies on Saroglitazar with significant reduction in triglycerides (38.7 ± 10.72 %), LDL-C (15.7 ± 8.47 %), total cholesterol (17.1 ± 2.48 %) and non-HDL-C (19.9 ± 10.35 %) as well as 0.7 ± 0.25 % reduction in HbA1c levels.

In a recent study data on pioglitazone, a PPAR γ agonist, it was found to almost half the progression to Type 2 DM in people with insulin resistance and CVD.[20] It was hypothesized that its metabolic actions mediated through PPAR- γ in adipocytes, skeletal muscle, and the liver might have led to such impressive results. In this study, Saroglitazar having agonistic action on PPAR γ, following a similar trend might have resulted in 0.7 ± 0.25 % reduction in HbA1C levels from baseline 6.3 ± 0.16 % to 5.5 ± 0.30 % thus halting the progression of diabetes. However, to establish the efficacy of Saroglitazar in the prevention of diabetes, evidences based on larger randomized controlled trials are warranted.

In addition to above, there were no major adverse events reported. The one reported adverse event of diarrhea was also unrelated to the drug and easily managed with medication. Liver, kidney parameters and ECG were within normal limits and not adversely affected by Saroglitazar.

Strength and limitations: This is the first study to examine the effect of first approved dual PPAR α/γ agonist, Saroglitazar in patients with prediabetes and dyslipidemia. The study was however limited by its sample size and other limitations such as single centre study and absence of comparator group. Also, blood glucose levels were not included as part of trial which could have added more dimension over and above HbA1c. A more robust study with a larger sample size is required to further establish the results of this study.

Conclusion

This study concluded that Saroglitazar is safe and effective in prediabetes with dyslipidemia by exerting its dual lipid and glycemic lowering benefits.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas, 7 ed.* Brussels, Belgium: International Diabetes Federation, 2015.
2. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003; 26:3160–3167.
3. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 2010; 55:1310–1317.
4. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/ National Heart, Lung, and Blood Institute Scientific Statement (erratum in: Circulation 2005;112:e297–8). *Circulation* 2005; 112:2735–2752.
5. Reaven GM. Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. *Panminerva Med* 2005; 47:201–210.
6. Lorenzo C, Williams K, Hunt KJ, Haffner SM. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007; 30:8–3.
7. Pai V, Paneerselvam A, Mukhopadhyay S, Bhansali A, Kamath D, Shankar V et al. A Multicenter, Prospective, Randomized, Double-blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4 mg Compared to Pioglitazone 45 mg in Diabetic Dyslipidemia (PRESS V). *Journal of Diabetes Science and Technology* 2014; 8:132-141.
8. Jani R, Pai V, Jha P, Jariwala G, Mukhopadhyay S, Bhansali A, et al. A Multicenter, Prospective, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Saroglitazar 2 and 4 mg Compared with Placebo in Type 2 Diabetes Mellitus Patients Having Hypertriglyceridemia Not Controlled with Atorvastatin Therapy (PRESS VI). *Diabetes Technology & Therapeutics* 2014; 16:63-71.
9. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106:3143–3421.
10. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di AE et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; 375:2215–2222.
11. Earl S Ford, Chaoyang Li , Sniderman A : Temporal changes in concentrations of lipids and apolipoprotein B among adults with diagnosed and undiagnosed diabetes, prediabetes, and normoglycemia: findings from the National Health and Nutrition Examination Survey 1988–1991 to 2005–2008. *Cardiovascular Diabetology* 2013; 12:26
12. Unnikrishnan R, Anjana RM., and Mohan V. Diabetes in South Asians: Is the Phenotype Different? *Diabetes* 2014; 63:53–55.
13. Anjana RM, Pradeepa R, Deepa M, Datta M, Sudha V, Unnikrishnan R.et al. ICMR–INDIAB Collaborative Study Group. Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-INdia DIABetes (ICMR-INDIAB) study. *Diabetologia* 2011; 54:3022–3027
14. Ramachandran A, Snehalatha C, Viswanathan V, Viswanathan M, Haffner SM. Risk of noninsulin dependent diabetes mellitus conferred by obesity and central adiposity in different ethnic groups: a comparative analysis between Asian Indians, Mexican Americans and Whites. *Diabetes Res Clin Pract* 1997; 36:121–125.
15. Mooradian AD. Dyslipidemia in type 2 diabetes mellitus. *Nat Clin Pract Endocrinol Metab* 2009; 5:150-159.
16. Murad MH, Hazem A, Coto-Yglesias F, Dzyubak S, Gupta S, Bancos I et al. The association of hypertriglyceridemia with cardiovascular events and pancreatitis: a systematic review and meta-analysis. *BMC Endocr Disord* 2012; 12:2
17. Feher M, Greener M, Munro N. Persistent hypertriglyceridemia in statin treated patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes* 2013; 6:11-15.
18. Berg Jørgensen A, Frikke-Schmidt R, Børge G. Nordestgaard, and Tybjærg-Hansen A. Loss-of-Function Mutations in *APOC3* and Risk of Ischemic Vascular Disease. *N Engl J Med* 2014; 371:32-41.
19. Shetty SR , Kumar S , Mathur RP , Sharma KH , Jaiswal AD.Observational study to evaluate the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients. *Indian Heart J* 2015; 67:23-26.
20. Inzucchi SE, Viscoli CM, Young LH, Furie KL, Gorman M, Lovejoy AM. Pioglitazone Prevents Diabetes in Insulin-Resistant Patients With Cerebrovascular Disease. *Diabetes Care* 2016; 39:1684-1692.