Impact of Saroglitazar as an Add-On Therapy to Rosuvastatin in Patients with Diabetic Dyslipidemia – A prospective, single centre, observational study in Indian patients

Abstract:

Background: Diabetic dyslipidemia in type 2 diabetes mellitus is defined by elevated TG levels and decreased HDL-C levels, as well as elevated or normal LDL-C levels. In diabetic dyslipidemia, the addition of saroglitazar to statins may provide comprehensive control of lipid parameters as well as good glycemic control, particularly in patients with high TG levels that are not controlled by statins alone.

Objective: To evaluate the effectiveness and safety profile of saroglitazar as an add-on therapy in patients with diabetic dyslipidemia already receiving rosuvastatin therapy.

Methods: In this open-label, prospective, single-center, observational study, newly diagnosed DM patients were randomly assigned to one of two groups, Rosuvastatinonly (R) or Rosuvastatin plus Saroglitazar (RS). Both groups received rosuvastatin for 12 weeks, after which group R received the same treatment for another 12 weeks, and group RS received saroglitazar 4mg in addition to rosuvastatin for another 12 weeks. At the end of 24 weeks, the primary outcome measured were changes in baseline lipid parameters total cholesterol, serum TG, LDL, VLDL, HDL, and glycemic parameter HbA1c between and within Group R and Group RS. Secondary outcomes included changes in metabolic parameters such as blood urea, serum creatinine, SGOT, SGPT, and CPK, as well as reported adverse events. These assessments were made for both Group R and Group RS at both the 12-week and 24-week.

Result:

When compared to Group R, patients in Group RS improved significantly in lipid parameters such as total cholesterol, serum TG, LDL, VLDL, HDL, and glycemic parameter HbA1c at the end of 24 weeks. Secondary outcomes revealed that Group RS had no significant side effects when compared to Group R, as evidenced by low fluctuations in renal and hepatic markers such as B. urea, S. Creatinine, SGOT, SGPT, and CPK levels over 24 weeks. As a result, the safety profiles of the combination treatment and rosuvastatin alone were comparable.

Conclusion: Saroglitazar, when combined with rosuvastatin, was found to improve lipid and glycemic parameters in diabetic dyslipidemia patients who were already on rosuvastatin.

Keywords: Diabetic Dyslipidemia, Rosuvastatin, Saroglitazar, Hypertriglyceridemia, PPAR agonist

Introduction

Diabetes mellitus (DM) is a prevalent condition that has reached epidemic proportions. It is currently the most common endocrine ailment in the worldthat causes life-altering morbidity, high rates of mortality, and interacts with and exacerbates many other diseases, with estimates of more than 1·31 billionpeople being affected, by 2050 worldwide. (1) Most predominantly it causes microvascular problems including retinopathy, neuropathy, and nephropathy, as well as macrovascular complications like atherosclerotic cardiovascular disease (ASCVD) and coronary artery disease.(2)Diabetes-related cardiovascular disease, in particular, is the major cause of morbidity and mortality among diabetic patients, owing to diabetic dyslipidemia(DD), a group of lipoprotein abnormalities that are widespread in these patients.(3)Worldwide, the occurrence of dyslipidemia in individuals with diabetes is documented to be significantly elevated, with estimates ranging between 70% to 85%.(4)

In India, there is a remarkably high prevalence of dyslipidemia among individuals with diabetes, with recorded rates of 85.5% among males and 97.8% among females.(5)The complex interrelationship between diabetes and diabetes dyslipidaemia that leads to Atherosclerotic Cardiovascular Disease (ASCVD) encompasses a range of pathologies affecting the heart and vasculatures, most notably atherosclerosis, which has the potential to obstruct blood circulation to vital organs such as the heart and brain, culminating in events such as myocardial infarctions, cerebral infarctions, and aneurysm formations. (6) Atherogenic Dyslipidaemiain Diabetes (ADD) is characterized by high serum triglycerides, elevated small dense LDL levels, low HDL levels,in a person with type 2 diabetes. (20)Higher levels of non-HDL cholesterol (Triglycerides, LDL, and VLDL) were associated with a 60% greater risk of developing cardiovascular disease (CVD) in the general population, but this risk was 99% higher in people with type 2 diabetes mellitus.(7)

In 2018, the American Heart Association and American College of Cardiology updated the Adult Treatment Panel (ATP) III guidelines of the National Cholesterol Education Program (NCEP) and recommended statins as the first-line treatment for lowering LDL levels in

diabetes dyslipidaemia. Bile acid sequestrants and ezetimibe should be added if statins are not successfully lowering cholesterol targets; however, fibrates or niacin may be used to treat high triglyceride levels. Numerous drugs have been shown to be effective in treating lipid markers connected to diabetic atherogenic dyslipidaemia, such as hypertriglyceridemia and low HDL-C; however, some research indicates that niacin may raise blood sugar levels.(8,9,11)

Rosuvastatin, one of the most potent statins, works by inhibiting HMG-CoA reductase, has been shown to be helpful in lowering LDL-C levels and lowering CVD risk in diabetic people. Despite maximal rosuvastatin therapy, a significant proportion of these individuals fail to attain target lipid values, particularly increased triglycerides and low HDL-C, as well as glycemic control in diabetic patients.(10)This treatment gap necessitated additional therapeutic strategies to comprehensively address the lipid abnormalities seen in diabetic dyslipidemia along with better control of glycemia.

The scarcity of such focused treatment interventions for diabetes dyslipidaemia resulted in the development of Saroglitazar, a dual peroxisome proliferator-activated receptor (PPAR)α/γ-agonist that improves lipid profile and glycemic management. PPAR-α and PPAR-γ receptor activation leads to increased lipoprotein lipase activity, decreased VLDL release, suppression of Apo CIII expression, and increased apolipoprotein synthesis. These effects reduce TG, LDL, VLDL, HDL cholesterol, and increase fatty acid uptake. (12,13)Thus, increasing the expression of these genes, Saroglitazar reduces the post-prandial fatty acid rise and metabolic load, and improves insulin-mediated glucose suppression.(21)According to a case study involving a male patient, age 26, Saroglitazar is the only drug for treating metabolic disorders that has a dual peroxisome proliferator-activated receptor (PPAR) α/γ action, which can lower high triglyceride levels, enhance insulin sensitivity, and possibly lessen the amount of liver fibrosis. (22)Amulticentric, prospective-randomized controlled trial also showed that theSaroglitazar 4 mg once daily, when combined with a statin, results in a significant reduction in TG (46.7%) and non-HDL-cholesterol (non-HDL-C; 32.5%), as well as a significant reduction in HbA1c (0.3%). Furthermore, Saroglitazar was discovered to be both safe and well-tolerated.(23)Several glitazars, including muraglitazar, ragaglitazar, tesaglitazar, naveglitazar, farglitazar, and aleglitazar, were developed but failed in preclinical or clinical development due to ineffectiveness or safety concerns.(12).

The present study was aimed to evaluate the effectiveness and safety profile of Saroglitazar as an add on therapy in patients of diabetic dyslipidaemia already receiving rosuvastatin therapy.

Methodology

Study Design: This study was a prospective, open-labelled, single-centre, observational study conducted on 100 patients with recently diagnosed Type 2 diabetes mellitus attending outdoor patient department or admitted in Guru Nanak Dev Hospital attached to Govt. Medical College Amritsar. The duration of the study was 6 months.

Studyparticipants:

Inclusion criteria:

All the patients recently diagnosed with Type 2 diabetes mellitusand were not undergoing any form of drug therapy were included in the study.

Exclusion criteria:

Participants who had been diagnosed with Type 1 Diabetes, less than 20 years of age, pregnant women, individuals with chronic kidney disease (CKD), hypothyroidism, primary hyperlipidaemia, and those who were already undergoing treatment with statins, other hypolipidemic medications, oral contraceptives, or oestrogen were excluded from the study.

Procedure:

Patients included in the study were randomly and equally divided into 2 groups, Group R received only Rosuvastatin for the entire study duration whereas Group RS received Rosuvastatin in the first 12 weeks and Saroglitazar in addition to Rosuvastatin for the duration of another 12 weeks . Both groups were put on rosuvastatin 10mg once daily OD for 12 weeks. Group R was continued with same treatment for further 12 weeks and group RS received Saroglitazar 4mg OD with Rosuvastatin 10 mg for further 12 weeks.

Baseline parameters were investigated for Fasting Lipid Profile including Total cholesterol, Triglyceride, LDL, VLDL, HDL, C – Reactive Protein, Liver Function Tests, Renal Function Tests, CPK, Fasting Blood Sugar, Post Prandial Blood Sugar, HbA1c. The same parameters were investigated at 12 weeks and 24 weeks again at the end of study.

Primary Outcome

The primary outcome was measured any difference in lipid parameters including Total cholesterol, Triglyceride, LDL, VLDL, HDL, and glycaemic parameter HbA1c between R and RS groups at 24 weeks and within Group R and Group RS at 12 and 24 weeks.

Secondary Outcome:

The secondary outcome assessed safety profile by measuring changes in metabolic parameters like B. urea, S. creatinine, SGOT, SGPT, and CPK between Groups R and RS at the end of 24-weeks.

Statistical analysis:

The Statistical package SPSS, version 26, [SPSS Inc., Chicago, Ill., USA] software was used to analyse the data. The outcome was expressed as mean ± standard deviation. Student t test and chi- square was performed with 95% confidence intervals with p-value <0.05 considered to be statistically significant.

Results

The study involved 100 patients in all, who were randomly split into two groups of 50 individuals each and received appropriate anti-diabetic medications as per requirement (Table 1).

The clinical characteristics of the Rosuvastatin group (Group R) were examined individually at the beginning of the study, at 12 weeks, and at 24 weeks and compared for any significant difference. The mean triglyceride level was significantly reduced from 245.70 mg/dL at baseline to 214.86 mg/dL after 12 weeks and 197.94 mg/dL after 24 weeks of treatment, and the mean total cholesterol level was reduced significantly as well, from 241.14 mg/dL at baseline to 171.08 mg/dL after 24 weeks of treatment. The mean LDL and VLDL values reduced significantly from 154.76 mg/dL and 49.10 mg/dL at baseline to 88.96 mg/dL and 39.52 mg/dL at 24 weeks of treatment, respectively. Additionally, the mean value of HDL increased significantly from 37 mg/dL at baseline to 43.04 mg/dL at 24 weeks, indicating a lipid profile improvement. The mean of HbA1c decreased significantly from 8.04% at baseline to 7.70% at 12 weeks and 7.38% at 24 weeks, showing better glycemic management. On the other hand, the study showed no significant difference in B. urea, S. creatinine, SGOT, SGPT, and CPK levels, indicating no major changes in renal or hepatic function.(Table 2)

In the Rosuvastatin and Saroglitazar Group (Group RS), when the clinical characteristics were compared, the mean of triglyceride decreased significantly from 231.68 mg/dL at baseline to 176.38 mg/dL at 12 weeks and 152.8 mg/dL at 24 weeks. The mean of total cholesterol also decreased significantly from 238.38 mg/dL at baseline to 195.8 mg/dL at 12 weeks and to 162.32 mg/dL at 24 weeks. The mean of LDL and VLDL also decreased significantly from 156.7 mg/dL and 46.26 mg/dL at baseline to 82.76 mg/dL and 35.34 mg/dL after 24 weeks of treatment, respectively. The mean HDL values increased considerably from 35.54 mg/dL at baseline to 37.68 mg/dL at 12 weeks and 43.7 mg/dL at 24 weeks. This decrease in lipid markers was especially significant because increased total cholesterol is a well-known risk factor for CVD. The mean of HbA1c fell considerably from 8.06% at baseline to 7.74% at 12 weeks and 7.28% at 24 weeks, and this gradual decrease indicates better glycemic control at the end of the study. In contrast to this, the means of B. urea, S. creatinine, SGOT, SGPT, and CPK in Group RS remained rather steady throughout the study.(Table 2)

At the beginning of this experiment, both groups, R and RS, were compared for several clinical features and showed no statistical difference between the groups, indicating both groups were comparable.

At the end of 24 weeks, the lipid-lowering impact and the glycaemic control of Group R and Group RS were assessed by comparing their S. triglyceride, total cholesterol, HDL, LDL, VLDL, and HbA1c levels. The mean of triglyceride was significantly lower in Group RS (152.8 mg/dL vs. 197.94 mg/dL) than in Group RS ($p<0.001$), and the mean of total cholesterol level was also lower in Group RS (162.32 mg/dl vs. 171.08 mg/dl) than in Group RS ($p<0.001$). Furthermore, Group RS had a lower mean of LDL 82.76 mg/dL vs. 154.76 mg/dL ($p<0.001$) and VLDL 35.34 mg/dL vs. 49.10 mg/dL ($p<0.001$) compared to Group R, respectively. On the other hand, Group RS showed a higher mean of HDL 43.7 mg/dL vs. 37 mg/dL ($p<0.001$). At the end of 24 weeks, the mean of HbA1c was reduced in Group RS (7.28% vs. 7.38%) compared to Group R ($p<0.001$). (Table 3, Figure 1)

Secondary outcomes revealed that Group RS had no major side effects as compared to Group R, as evidenced by the low fluctuations in renal and hepatic markers such as B. urea, S. creatinine, SGOT, SGPT, and CPK levels across the 24-week period. As a result, both the combination treatment and rosuvastatin alone had comparable safety profiles.

Table- 1: Base line demographic characteristics of participants of both the groups N=100)

Demographic Characteristics	**Group R (n=50)**	**Group RS (n=50)**	**P-value**
Gender			
Male	23 (46%)	32 (64%)	0.11
Female	27 (54%)	18 (36%)	
Age group			
35-50 years	20 (40%)	31 (62%)	0.19
51-65 years	25 (50%)	12 (24%)	
66-75 years	5 (10%)	7 (14%)	

*R= Rosuvastatin; RS= Rosuvastatin with Saroglitazar)

Table 2: Comparison of Clinical characteristics for Group Rosuvastatin R) and Rosuvastatin and Saroglitazar RS) each at baseline, 12 weeks, and 24 weeks. N=100)

	Rosuvastatin (R-Group)				**Rosuvastatin and Saroglitazar(RS-Group)**			
Clinical Characteristics	**0 weeks**	**12 weeks**	**24 weeks**		**0 weeks**	**12 weeks**	**24 weeks**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**p-value**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**p-value**
Triglycerides, mg/dL	245.70 ± 46.04	214.86 ± 39.93	197.94 ±36.18	**< 0.001**	231.68 ± 39.82	176.38 ± 34.58	152.8 ± 28.67	**<0.001**
Total Cholesterol, mg/dL	241.14 ± 35.24	196.90 ± 26.22	171.08 ± 22.88	**< 0.001**	238.38 ± 30.27	195.8 ± 22.43	162.32 ± 17.54	**<0.001**
HDL, mg/dL	37.00 ± 6.04	39.70 ± 5.77	43.04 ± 6.09	**< 0.001**	35.54 ± 5.24	37.68 ± 5.40	43.7 ± 5.48	**<0.001**
LDL, mg/dL	154.76 ± 36.69	114.06 ± 27.58	88.96 ± 23.68	**< 0.001**	156.7 ± 33.35	117.2 ± 24.77	82.76 ± 20.11	**<0.001**
VLDL, mg/dL	49.10 ± 9.24	43.70 ± 8.70	39.52 ± 7.21	**< 0.001**	46.26 ± 8.00	40.84 ± 6.89	35.34 ± 5.77	**<0.001**
HbA1c, %	8.04 ± 0.73	7.70 ± 0.63	7.38 ± 0.57	**< 0.001**	8.06 ± 0.61	7.74 ± 0.57	7.28 ± 0.57	**<0.001**
B. urea, mg/dL	23.88 ± 4.21	25.84 ± 4.67	23.98 ± 3.66	**0.034**	23.98 ± 3.59	26.8 ± 4.2	24.28 ± 3.85	**0.001**
S. Creatinine, mg/dL	0.94 ± 0.12	0.93 ± 0.11	0.94 ± 0.11	0.860	0.95 ± 0.11	0.92 ± 0.11	0.93 ± 0.10	0.347
SGOT, U/L	30.96 ± 4.47	30.94 ± 5.04	30.10 ± 4.87	0.803	29.48 ± 4.25	31.1 ± 4.10	28.5 ± 4.37	**0.011**
SGPT, U/L	32.92 ± 4.90	32.36 ± 4.88	31.70 ± 4.87	0.800	31.70 ± 4.63	31.14 ± 4.45	31.66 ± 4.33	0.788
CPK, U/L	155.90 ± 10.01	157.52 ± 10.57	156.98 ± 9.96	0.721	157.00 ± 10.74	154.9 ± 8.23	155.7 ± 8.36	0.536

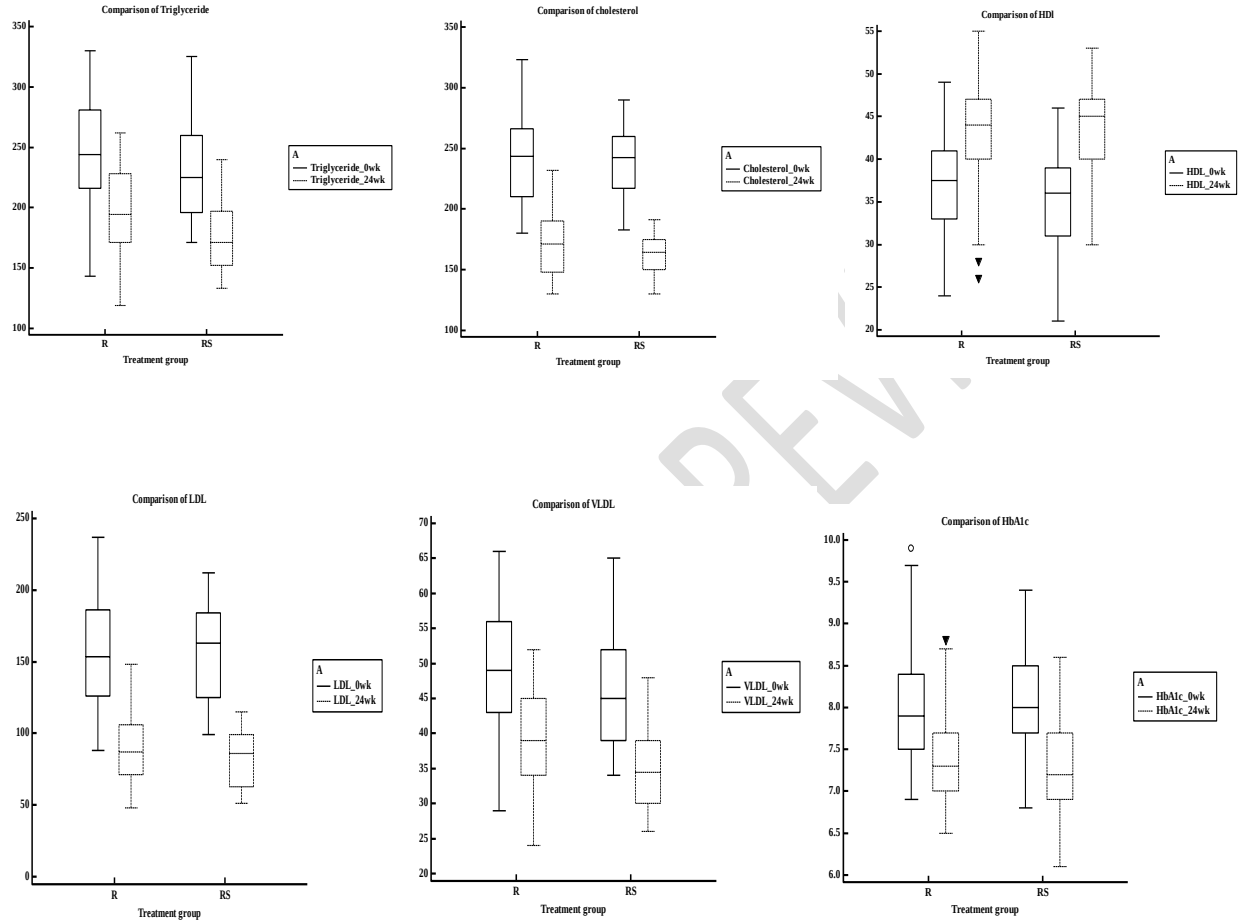
(HDL, high-density lipoprotein; LDL, low density lipoprotein; VLDL, very low-density lipoprotein;HbA1c, glycated haemoglobin; B. urea, blood urea; S. creatinine, serum creatinine; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CPK, creatine phosphokinase.)

Table 3: Comparison of Clinical characteristics between Group Rosuvastatin (R) and Rosuvastatin and Saroglitazar (RS) at baseline and 24 weeks. (N=100)

Characteristics, units	**At the time of initiation of treatment**			**After 24 weeks of treatment**		
	Group R	**Group RS**	***p*-value**	**Group R**	**Group RS**	***p*-value**
	Mean ± SD	**Mean ± SD**		**Mean ± SD)**	**Mean ± SD)**	
Triglycerides, mg/dL	245.7 ±46.05	231.68 ±40.23	0.1082	197.94 ±36.18	152.8± 28.67	**<0.001**
Cholesterol, mg/dL	241.14 ±35.24	238.38 ±30.58	0.6767	171.08 ± 22.88	162.32 ± 17.54	**<0.001**
HDL, mg/dL	37 ±6.1	35.54 ±5.3	0.2021	43.04 ± 6.09	43.7 ± 5.48	**<0.001**
LDL, mg/dL	154.76 ±36.69	156.7 ±33.69	0.7836	88.96 ± 23.68	82.76 ± 20.11	**<0.001**
VLDL, mg/dL	49.1 ±9.24	46.26 ±8.08	0.1051	39.52 ± 7.21	35.34 ± 5.77	**<0.001**
HbA1c, %	8.04 ±0.72	8.06 ±0.62	0.8711	7.38 ± 0.57	7.28 ± 0.57	**<0.001**
B. urea, mg/dL	23.88 ±4.21	23.98 ±3.63	0.8990	23.98 ± 3.66	24.28 ± 3.85	0.98
S. Creatinine, mg/dL	0.94 ±0.12	0.96 ±0.11	0.3413	0.94 ± 0.11	0.93 ± 0.10	0.42
SGOT, U/L	30.96 ±4.47	29.48 ±4.29	0.0947	30.10 ± 4.87	28.5 ± 4.37	0.86
SGPT, U/L	32.92 ±4.9	31.7 ±4.68	0.2058	31.70 ± 4.87	31.66 ± 4.33	0.36
CPK, U/L	155.9 ±10.01	157 ±10.86	0.5997	156.98 ± 9.96	155.7 ± 8.36	0.21

(HDL, high-density lipoprotein; LDL, low density lipoprotein; VLDL, very low-density lipoprotein; HbA1c, glycated haemoglobin; B. urea, blood urea; S. creatinine, serum creatinine; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; CPK, creatine phosphokinase.)

Figure 1: Comparison of Triglyceride, Cholesterol, HDL, LDL, VLDL and HbA1c between Group Rosuvastatin (R) and Rosuvastatin and Saroglitazar (RS) at baseline and 24 weeks after treatment initiation. (N=100)



(HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low density lipoprotein; VLDL, very low-density lipoprotein)

Discussion

Diabetic Dyslipidemia is a metabolic abnormality affecting mostly the diabetic patients, increasing tremendously the CV risk in them. Rosuvastatin, a potent statin, helps lower LDL-C and CVD risk in diabetic patients but many fail to achieve target lipid values, leading to a treatment gap. Saroglitazar, a novel drug with dual peroxisome proliferator-activated receptor (PPAR) α/γ-agonist, enables better reduction in the lipid parameters while improving glycemic control in patients with type 2DM and NAFLD. This study was conducted to evaluate the effectiveness and safety profile of Saroglitazar as an add on therapy in patients of diabetic dyslipidaemia already receiving rosuvastatin therapy.

On evaluating the outcomes related to the triglyceride levels at the end of 24 weeks, the mean triglyceride levels showed a significant improvement from 245.7 mg/dL to 197.94 mg/dL in Group R and from 231.68 mg/dL to 152.8 mg/dL in Group RS throwing light on the increased effectiveness of the combination regimen. A similar improvement was also seen in a study by Baidya A et al., 2022, where lower triglyceride levels were associated with improved lipid metabolism and a reduced risk of cardiovascular diseases (14). In the present study, the patients' HDL levels displayed an increasing trend in both groups, with slightly higher surge in group RS (*p*-value <0.001) rising from 37 mg/dL to 43.04 mg/dL in Group R and from 35.54 mg/dL to 43.7 mg/dL in Group RS at the end of the study. The results were supported in a study done byby Mehta A, et al., where furthermore higher HDL levels were considered beneficial as they help remove excess cholesterol from the bloodstream, reducing the CV risk(16). The observed increase suggests a considerable impact on the participants' lipid profile and could be possibly attributed to the combination therapy of rosuvastatin and saroglitazar.

A randomized controlled trial conducted by Chhabra M, et al.,2022, evaluated the efficacy of saroglitazar in patients with DD. The study showed significant reductions in triglyceride levels, LDL-C, and total cholesterol, along with an increase in HDL-C levels. Additionally, saroglitazar was found to improve glycemic control and reduce insulin resistance (17). A substantial decline was reported in both the LDL and VLDL levels in the study population at the end of 24 weeks, where LDL was reduced from 154.76 mg/dL to 88.96 mg/dL in Group R and in Group RS it was reduced from 156.7 mg/dL to 82.76 mg/dL (18). It is evident from the results that, LDL levels in Group RS are markedly lesser than in Group R (*p*-value <0.001). LDL cholesterol is associated with an increased risk of atherosclerotic diseases, and this

higher reduction in LDL levels indicates a potential decrease in CVD risk among Group RS patients. In Group R, the VLDL levels decreased from 49.10 mg/dL at baseline to 39.52 mg/dL at the end of study. Similarly in Group RS, the VLDL levels decreased from 46.26 mg/dL to 35.34 mg/dL. Corresponding to the current study, total cholesterol level results exhibited a significant difference from 241.14 mg/dL to 171.08 mg/dL in Group R and from 238.38 mg/dL to 162.32 mg/dL in Group RS at 24 weeks, parallel to HbA1c; total cholesterol levels show higher reduction rates in Group RS than in Group R (*p*-value <0.001). This reduction suggests an important impact on cardiovascular health as high total cholesterol levels are a risk factor for heart diseases, and the observed decrease indicates a potential reduction of CVD in both groups (15).

When comparing the glycaemic control at the end of 24 weeks, Group R and Group RS showed a statistically significant difference (*p*-value<0.001) in their mean HbA1c levels. Group R had a mean HbA1c of 7.38% at the end of study compared to 8.04 ± 0.72 at baseline, while Group RS had a mean HbA1c of 7.28% as compared to 8.06 ± 0.62 at the baselineindicating better improvement in glucose control among the Group RS patients.Similar results have been reportedin theobservational study by Shetty, Sadanand R., et al.,2015 evaluating Saroglitazar in Indian populationwhere HbA1c levels declined from 8.3 ± 1.28% to 7.4 ± 0.89%(13).

The safety of Saroglitazar have also been evaluated in Indian patients with DD where no adverse reactions were reported during the period of 12 weeks(19).Results of this study add to the growing body of evidence supporting the safety profile of combination therapy of saroglitazar and rosuvastatin treatment inDDpatients. The renal parametersB. urea, S. Creatinine, hepatic parameters SGOT, SGPT and CPK levels, indicated minimal variations over the 24-week period in group RS compared to the group R suggesting that the combination therapy of saroglitazar and rosuvastatin is safe and well-tolerated in patients with DD.It is important to note that the sample size and demographics of the participants may not accurately represent the general population. This could limit the generalizability of the study findings.

Conclusion

According to the results of this study, Saroglitazar, when administered in combination with Rosuvastatin, lowered triglyceride, total cholesterol, LDL, and VLDL levels, improved HDL levels, and improved glycemic index in type 2 diabetes patients without causing any

significant negative effects. So, Saroglitazar as an add on therapy to Rosuvastatin, was safer and more effective than the Rosuvastatin therapy alone.

Consent

A written informed consent was taken from all the patients or the surrogate informer of the patients prior to including them in the study.

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