Clinical Case Series on Assessmentof Therapeutic Efficacy of Saroglitazar in MASLD patients

Abstract:

Objective: This prospective case series aimed to evaluate the efficacy of saroglitazar 4 mg in improving clinical parameters in patients with type 2 diabetes mellitus (T2DM) with steatotic liver disease (SLD), focusing on glycemic control, lipid profile, liver enzymes, and transient elastography parameters (CAP and LSM scores).

Materials and Method: Eight T2DM patients having SLD; defined as Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD) were enrolled froma single-center,Dr. Dang's Clinic, Gaziabad, Uttar Pradesh India. Saroglitazar was administered daily, and various clinical parameters were monitored at baseline, 16 weeks, and 32 weeks. Statistical analysis was performed using paired t-tests to assess changes over time.

Results: Saroglitazar treatment significantly reduced HbA1c, Triglycerides (TG), Alanine aminotransferase (ALT), transient elastography parameters (CAP and LSM) along with other lipid and glycemic parameters from baseline to weeks 32. . These findings underscore potential role of saroglitazar in managing T2DM and associated SLD by improving metabolic parameters and liver health.

Conclusion: Saroglitazar showed significant improvements in glycemic control, lipid profile, liver enzymes, and liver fat and fibrosis in MASLD patients, indicating its potential as a therapeutic option for managing metabolic abnormalities and liver complications. Further research is needed to validate these findings.

Keywords: type 2 diabetes mellitus, saroglitazar, CAP, LSM, liver fibrosis, liver fat

Introduction:

Type 2 diabetes mellitus (T2DM) is commonly prevalent metabolic condition which is projected to reach 629 million by 2045.[1] Insulin resistance is a root cause factor for T2DM which can lead to further complications like cardiovascular disease (CVD), kidney disorders, steatotic liver disease (SLD) etc. SLD with T2DM is known as metabolic dysfunction associated steatotic liver disease

(MASLD); which is a revised nomenclature of NAFLD.[2]Almost 7 out of 10 T2DM patients are suffering from SLD and carry higher risk CV events. Managing T2DM may have impact on progression of SLD but no any anti-diabetic medications is approved for management of NAFLD/MASLD till date.[3]

Peroxisome proliferator-activated receptors (PPARα and PPARγ) are crucial for controlling insulin resistance, glucose metabolism, lipid metabolism and liver fat / fibrosis reduction. (4). Despite these setbacks, newer PPAR agonists continue to be pursued for their potential benefits and effects on glucose and lipid metabolism(5,6). These agonists can improve glycaemic control and address lipid abnormalities in T2DM patients(7). Saroglitazar, a new dual PPAR α/γ agonist was approved in 2013 for the management of diabetic dyslipidemia and hypertriglyceridemia and in 2020 , it received approval for Non Alcoholic Fatty Liver Disease (NAFLD) and non-cirrhotic non-alcoholic steatohepatitis (NASH) by DCGI in India.(8). Saroglitazar has shown positive benefits in glycemic control and lipid profile, along with reduction of liver fat, fibrosis and elevated liver enzymes in various studies including NAFLD patients.(9,10).

To assess the effect of saroglitazar 4 mg in MASLD (SLD with T2DM)patients in routine clinical practice, we performed this study, evaluating various clinical parameters over a 32-week treatment period. We also examined its impact on CAP (controlled attenuation parameter) and LSM (liver stiffness measurement) scores, which are crucial for assessing liver health and fibrosis in patients. The CAP score is vital for measuring liver fat accumulation, while LSM is linked to fibrosis, providing comprehensive insights into liver health.

Materials and Method:

Study design and participants:

This was a prospective case series conducted atDr. Dang's Diabetes Clinic, Ghaziabad, Uttar Pradesh, as a single-center study, for 32 weeks. The study was carried out in compliance with ICH-GCP ethical standards; before its commencement, participants were informed about the study and received their consent. Eight patients from the outpatient medical department were enrolled with the known case of T2DM with SLD.

Inclusion criteria:

The participants included in the study with the age between 18-70 years and known case of type 2 diabetes mellitus as per American Diabetes Association criteria(1), with≥ grade I fatty liver confirmed by ultrasonography along with signed informed consent.

Exclusion criteria:

Patients were excluded from the study if they had history of liver injury due to chemicals or drugs during the 9 months of assessment. Additionally, use of GLP1 analogues, SGLT2 inhibitors, or

pioglitazone during the assessment period or within 3 months prior to assessment was prohibited. Positive status for Hepatitis B or Hepatitis C also led to exclusion. Further, any conditions or factors that could interfere with the study outcomes or patient safety not mentioned in the inclusion criteria.

Baseline Examination and Laboratory Investigation:

Initially, a comprehensive medical history was obtained from the patients, along with tests for liver function, including aspartate transaminase (AST) and alanine transaminase (ALT), lipid profile (low-density lipoprotein, triglycerides, total cholesterol, and high-density lipoprotein), kidney function, with a specific focus on serum creatinine level. Additionally, postprandial blood glucose (PPBG), fasting blood glucose (FBG), and glycosylated hemoglobin (HbA1c) levels were assessed. Systolic and diastolic blood pressures were measured at each appointment. Basic anthropometric measurements such as waist-to-hip ratio and body mass index (BMI) were also recorded and documented in the case report form.

A dietician recommended diet and lifestyle changes, including exercise, to help people lose weight, and antidiabetic drugs were kept constant during the course of the study. Patients received 4 mg of saroglitazar daily and were monitored for 32 weeks.

Non-Invasive Test:

The patients were underwent ultrasonography to evaluate the liver size and to screen any liver disease. Following that, the patients had FibroScan®, recording LSM, and CAP.

Statistical analysis:

The GraphPad Insta Online Version® (https://www.graphpad.com/quickcalcs/ttest2/) was employed for the statistical analysis, and the paired t test was conducted to analyse the findings. P values of <0.05 were considered statistically significant.

Results:

Baseline characteristics

Basic demographic details of a total 8 patients, whose mean age was 56.9 years (male: female, 5:3) are mentioned in table 1.

Table 1: Baseline Findings

Parameter	Patient No.							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Age (Years)	62	50	67	58	66	64	44	44
Gender	M	F	M	M	F	F	M	M
BMI (kg/m2)	30.1	34	33.5	32.3	30.5	33.8	29.7	30.8
SBP (mmHg)	150	135	122	110	125	130	119	160
DBP (mmHg)	90	88	81	68	90	80	76	100
ALT (U/L)	63	37	14	48.5	52	40	60	14
AST (U/L)	45	62	18	35	40	41	46	21
S. Creatinine (mg/dl)	0.49	0.5	0.6	0.8	0.9	0.53	0.99	0.8
HbA1c (%)	6.4	7.2	7.8	6.8	8.2	8.5	9.2	6.4
FBG (mg/dl)	115	112	95	122	110	84	158	86
PPBG (mg/dl)	142	125	110	125	118	135	158	105
TC (mg/dl)	206	145	110	184	172	212	152	159.3
HDL (mg/dL)	28	36	26	38	52	48	32	75.4
LDL (mg/dl)	94	54	79	64	95	45	81	55.3
TG (mg/dl)	210	184	119	134	145	162	195	142.8
CAP (db/m)	314	339	296	350	321	300	312	295
LSM (kPa)	12	16	15	17	19.16	15	18	19
USG findings	GRADE 3	GRADE 3	GRADE 3	GRADE 3	GRADE 3	GRADE 2	GRADE 3	GRADE 3

[Abbreviations: ALT-Alanine transaminase, AST-Aspartate transaminase, BMI-Body Mass Index, CAP-Controlled Attenuation Parameter, DBP-Diastolic Blood pressure,db/m – decibel per meter, FBG - Fasting Blood Glucose,HbA1c - Glycated Hemoglobin, HDL - High Density Lipoprotein, kPa- Kilopascal, LDL- Low Density Lipoprotein, LSM-Liver Stiffness Measurement, PPBG- Post Prandial Blood Glucose, SBP-Systolic Blood Pressure, TC- Total Cholesterol, TG-Triglyceride, USG- Ultrasonography]

Follow up data:

Table 2 represents various clinical parameters of patients at baseline, 16 weeks, and 32 weeks, along with changes from baseline at each time point and corresponding p-values indicating the statistical significance of these changes. At end of 32 weeks, saroglitazar has shown significant reduction of PPBG, HbA1c in glycemic parameters; TC and TG in lipid parameters and ALT in Liver enzymes. Transient elastography parameters; CAP and LSM value had been consistently reduces at 16 and 32 weeks with $P<0.05$. (Table 2)

Table 2: Effect of Saroglitazar in various parameters at weeks 16 and 32

Parameter	Baseline	16 weeks	Change from baseline to weeks 16	p-value	32 weeks	Change from baseline to weeks 32	p-value
FBG (mg/dl)	110.25 ± 23.77	107.88 ± 17.68	- 2.38	0.40	113.00 22.97	2.75	0.74
PPBG (mg/dl)	127.25 ± 17.37	116 ± 17.43	- 11.25	0.01*	113.13 16.39	- 14.13	0.008*
HbA1c (%)	7.56 ± 1.03	6.76 ± 0.66	- 0.8	0.03*	6.11 0.94	- 1.4	0.005*
TC (mg/dl)	167.53 ± 33.54	137.5 ± 18.33	- 30.08	0.04*	134.13 22.56	- 33.41	0.03*
HDL (mg/dl)	41.92 ± 16.28	39.02 ± 10.71	- 2.9	0.48	41.39 12.12	- 0.54	0.90
LDL (mg/dl)	70.91 ± 19	58.01 ± 16.05	- 12.9	0.0002*	64.55 29.34	- 6.36	0.40
TG (mg/dl)	161.48 ± 31.99	127.91 ± 19.30	- 33.56	0.01*	122 20.08	- 39.48	0.01*
ALT (U/L)	41.06 ± 18.89	32.41 ± 14.31	- 8.65	0.04*	26.50± 6.90	- 14.56	0.02*
AST (U/L)	38.50 ±14.13	37.83 ± 11.41	- 0.66	0.68	28.86 ± 8.70	- 9.63	0.10
CAP (db/m)	315.88 ± 20.10	265.75 ± 13.71	- 50.13	0.0001*	238.75 ± 5.68	- 77.13	0.0001*
LSM (kPa)	16.40 ± 2.41	11.81±1.13	- 4.58	0.0001*	7. 16 0.44	- 9.23	0.0001*
S. Creatinine (mg/dl)	0.70 ± 0.19	0.62 ± 0.26	- 0.08	0.47	0.64 0.26	- 0.07	0.57

[P value at weeks 16 and 32, is compared with baseline. *p value<0.05, denotes significant data]

Saroglitazar is predominantly TG lowering drug, which can be observed in **Figure 1(A)** with significant TG reduction in all eight patients. ALT levels decreased significantly from 41.06 ± 18.89 U/L at baseline to 32.41 ± 14.31 U/L at 16 weeks (p = 0.04) and further to 26.50 ± 6.90 U/L at 32 weeks (p = 0.02). AST levels did not show significant changes. CAP scores showed significant reductions from 315.88 ± 20.10 dB/m at baseline to 265.75 ± 13.71 dB/m at 16 weeks (p = 0.0001) and

to 238.75 ± 5.68 dB/m at 32 weeks (p = 0.0001), indicating decreased liver fat content is depicted in **Table 2, Figure 1B.**LSM values also decreased significantly from 16.40 ± 2.41 kPa at baseline to 11.81 ± 1.13 kPa at 16 weeks (p = 0.0001) and to 7.16 ± 0.44 kPa at 32 weeks (p = 0.0001) shown **in Table 2, Figure 1C**, suggesting reduced liver fibrosis. Serum creatinine levels remained stable, with no significant changes observed.

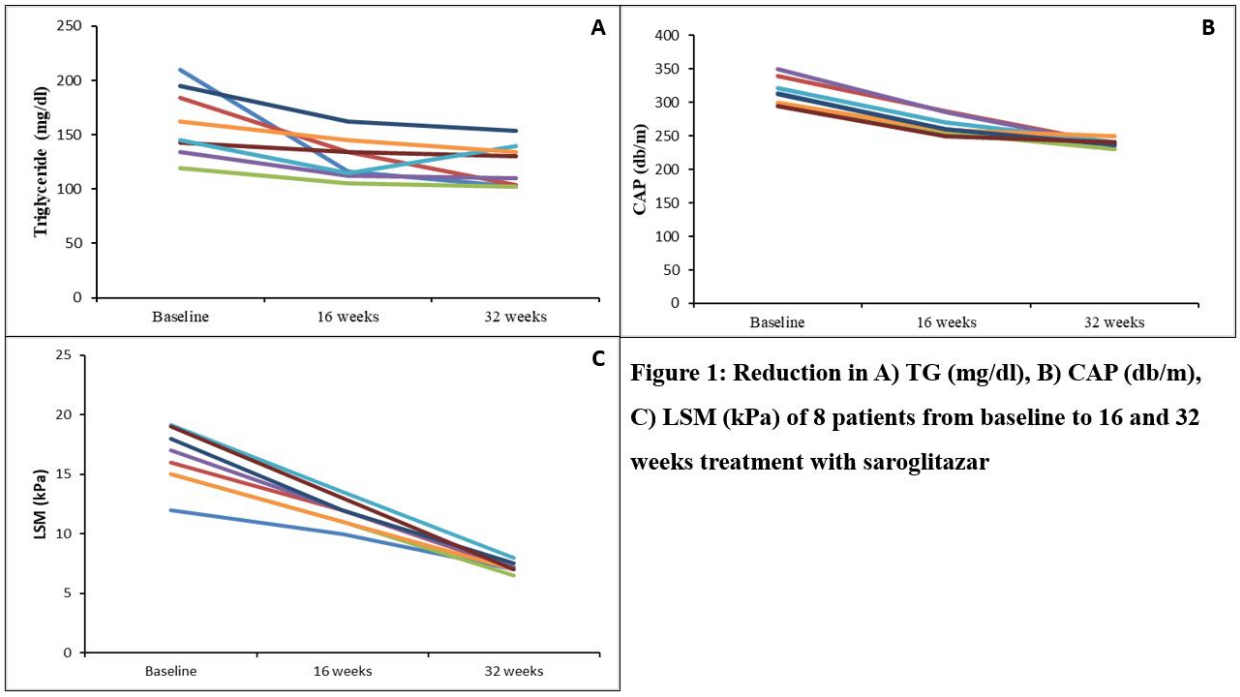

Figure 1: Reduction in A) TG (mg/dl), B) CAP (db/m), C) LSM (kPa) of 8 patients from baseline to 16 and 32 weeks treatment with saroglitazar

Overall, these findings indicate that the treatment was effective in improving glycemic control, lipid profile, liver enzyme levels, and reducing liver fat and fibrosis in patients over the study period.

Discussion

Thiscase series explores the potential of saroglitazar inT2DM patients, focusing on its effects on glycemic control, lipid profile, liver enzymes, and transient elastography parameters like CAP and LSM scores. Given the increasing prevalence of T2DM and its association with increased risk of cardiovascular disease, this research provides valuable insights. The findings indicate that the majority of the patient's exhibit Grade 3 fatty liver which is most severe form MASLD (11,12).

Further, results demonstrate a significant improvement in glycemic control among patients treated with saroglitazar. The reduction in HbA1c levels from 7.56% at baseline to 6.11% at 32 weeks is noteworthy, indicating better overall blood glucose management compared toprevious study showed the mean HbA1c reduction of 0.3% with saroglitazar treatment(9).Additionally, PPBG levels showed a significant decrease over the study period, whereas FBG levels, although improved, did not reach

statistical significance. In recent comparative study of saroglitazar (2 mg and 4 mg) and pioglitazone treatment groups showed statistically significant reduction in FPG and 2 h PPG at week 12, week 24 and week 56(7,13). These findings align with previous studies that suggest PPAR agonists, including saroglitazar, can enhance insulin sensitivity and glycemic control in patients with diabetes(5,9,13,14). Significant improvements were observed in the lipid profiles of the patients. Total cholesterol and triglyceride levels both showed substantial reductions by the 32-week mark. In comparison with pioglitazone after 24 weeks, saroglitazar 4mg showed significant reduction in TG by 45% from baseline, LDL-C by 5%, VLDL by 45.5%, TC by 7.7% respectively, hence it is best therapeutic option for the hypertriglyceredimia patients with T2DM(13). Meanwhile, at week 12, saroglitazar 4 mg tablets significantly reduced mean plasma triglyceride levels by −46.7 ± 3.02%(14). Regarding MASLD, Saroglitazar is the only approved drug in India for NAFLD with co-morbidities and pre-cirrhotic NASH. Gawrieh et al. recordedthat in MRI-PDFF driven study, mean percent change from baseline in ALT at week 16 was -45.8% with saroglitazar 4 mg, with additional improvement in liver fat content (LFC), insulin resistance, and atherogenic dyslipidemia in participants with NAFLD/NASH.[15] According to the multiple clinical trials, giving individuals with NAFLD or NASH, 4 mg of saroglitazar improved their lipid profile and blood glucose levels, as well as their liver enzymes and liver stiffness(8). As per Goyal et al, after 24 week of follow, ALT score improved from baseline 94 U/L to 39 U/L , and AST from baseline 89 U/L to 37 U/L, it indicates that saroglitazar is effective on liver enzymes levels(5).

Saroglitazar has demonstrated efficacy in reducing inflammation and fibrosis, resulting in improved LSM scores, suggesting a decrease in fibrosis and improved liver health(19). In this study, findings showed the reduction in CAP and LSM scores, indicating decreased liver fat and fibrosis, respectively. The CAP score reduction from 315.88 dB/m to 238.75 dB/m over 32 weeks is consistent with other studies where CAP score reduced from 335 dB/m to 256 dB/m after 24 weeks, demonstrating saroglitazareffectiveness in reducing hepatic steatosis. Similarly, the LSM score reduction from 16.40 kPa to 7.16 kPa align with the findings of the previous research where LSM score decreased from 8.4 kPa to 7.4 kPa, suggesting a marked decrease in liver stiffness, correlating with reduced fibrosis(5).

These improvements are critical, as liver fibrosis is a key determinant of morbidity and mortality in NAFLD patients. While the use of CAP and LSM became more popular, results began to diverge, particularly regarding differences in diagnostic accuracy and cut-off values between different BMI populations and between different probes. Earlier, several meta-analyses had discussed the accuracy of

CAP or LSM alone in NAFLD patients, but few studies were included, with only nine studies, which might lead to relatively limited conclusions(8,19).

Overall, the baseline characteristics of the patients, including elevated liver enzymes (ALT and AST), significant liver fat accumulation (indicated by CAP scores), and varying degrees of liver fibrosis (indicated by LSM values), suggest the presence of NAFLD. This finding indicated that these 8 T2DM patients were having MASLD, and the substantial improvements in a number of clinical indices highlightedsaroglitazar's potential as a multimodal treatment agent for MASLD.

This case-series study represents promising results, but challenges are involved such as single-centre approach, limited sample size, and limited follow-up duration. The interaction between the antidiabetic drugs and saroglitazar along with its combined effectson the overall parameters were not discussed. To validate these findings and assess the long-term effects of saroglitazar on type 2 diabetes mellitus patient’s and steatotic liver disease, further research with larger, varied cohorts and longer follow-up durations is needed, ensuring broad applicability and long-term safety and efficacy evaluation.

Conclusion

Saroglitazar considerably reduces liver enzyme levels, glycemicparameter, lipid parameters and the amount of liver fat and fibrosis in MASLDpatients. These results demonstrate the drug's potential as a beneficial choice for managing with steatotic liver disease, especially when other metabolic disorders are involved.

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