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Original Research Article

PROSPECTIVE OBSERVATIONAL STUDY OF SAROGLITAZAR IN NON-DIABETIC NAFLD USING SERIAL FIBROSCAN FOLLOW UP

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ABSTRACT

Background: Non-alcoholic fatty liver disease is common in our setting. Non-diabetic patients also show raised transaminases and FibroScan abnormalities. Local prospective data with 12-month follow up are still limited.

Materials and Methods: This prospective observational study was done in Department of General Medicine, Hind Institute of Medical Sciences, Mau Atariya Sitapur. Adults 18–65 years with fatty liver on ultrasound or FibroScan and non-diabetic profile were enrolled after consent. Total sample was 170. AST ALT BMI and FibroScan markers (LSM, CAP) were assessed at baseline, saroglitazar 4 mg OD, 6 months and 12 month. Paired comparisons were done across time points.

Results: Mean AST reduced from 53.56 ± 8.32 U/L at baseline to 43.97 ± 8.76 at 6 month and 44.36 ± 8.79 at 12 month. Mean ALT reduced from 63.28 ± 8.77 to 50.84 ± 9.27 and 50.58 ± 9.27. LSM reduced from 9.00 ± 1.77 kPa to 7.78 ± 1.83 and 7.69 ± 1.76. CAP reduced from 310.31 ± 19.65 dB/m to 276.04 ± 21.51 and 275.66 ± 22.32. BMI reduced from 29.5 ± 2.8 to 28.3 ± 2.7 and 27.4 ± 1.5. Baseline to 6 month and baseline to 12 month changes were significant for all parameters ($p<0.01$). From 6 to 12 month AST ALT and CAP were not significantly different, while LSM showed small further fall ($p=0.047$) and BMI continued to reduce ($p<0.01$).

Conclusions: Saroglitazar therapy in non-diabetic NAFLD was associated with sustained improvement in transaminases and FibroScan markers over 12 months, with maximum change by 6 months.

Keywords: Non-alcoholic fatty liver disease; Saroglitazar; Transaminases; FibroScan; Liver stiffness measurement; Controlled attenuation parameter.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is now one of the most common chronic liver disease worldwide. Pooled global data suggests around one-fourth adults have NAFLD so the clinical load is huge in routine practice.[1] NAFLD can stay silent for years but a subgroup progress to steatohepatitis and fibrosis. Fibrosis stage is the main driver for long term mortality and liver related events so fibrosis assessment is important even when enzymes are only mildly raised.[2]

Lifestyle and weight loss remain first line but long term adherence is poor in many patients. Current guidelines support risk stratification using non-invasive tools and follow up based on fibrosis risk.[3] Transient elastography (FibroScan) gives liver stiffness measurement (LSM) for fibrosis and controlled attenuation parameter (CAP) for steatosis. CAP was developed as an immediate steatosis estimate during FibroScan and has been validated in large prospective cohorts.[4] Reviews and meta-analyses show CAP and LSM have good diagnostic performance in NAFLD though cut-offs vary with BMI and probe type.[5,6]

Because of limited approved drug options there is ongoing interest in metabolic pathway drugs. Saroglitazar is a dual PPAR-α/γ agonist with favourable effects on lipid and insulin resistance pathways which are central in NAFLD biology.[7] In

a multicentre phase 2 RCT in NAFLD saroglitazar showed benefit on liver fat and aminotransferases with acceptable safety profile.[8] Indian real world and trial data also report improvement in transaminases with reduction in FibroScan markers like CAP and LSM after saroglitazar therapy.[9, 10,11] Still long term prospective data focusing on non-diabetic NAFLD with serial FibroScan follow up are limited from routine clinical settings. To evaluate this gap we assessed 12-month changes in transaminases and FibroScan parameters in non-diabetic NAFLD patients treated with saroglitazar in a prospective observational design.

MATERIALS AND METHODS

This was a prospective observational study conducted in the Department of General Medicine, Hind Institute of Medical Sciences, Mau, Atariya, Sitapur. The study period was 12 months and it started from 24/07/2024. Total sample size was 170 patients. Sample size was calculated using Cochrane formula with prevalence (P) taken as 30% as per reference, 99% confidence interval (Z = 2.576) and margin of error (d) 10%. Nonresponse was taken as 20% of sample size. Using $n = Z^2 \times p \times (1 - p) / d^2$, n came as 139.35 and after adding 20% nonresponse final sample size was fixed at 170.[3]

Adults of either sex aged 18–65 years were included. Fatty liver had to be confirmed on imaging either FibroScan or ultrasound. Patients had to be non-diabetic with normal fasting blood sugar and HbA1c. Participants with high blood pressure (SBP >139 or DBP >89) and metabolic syndrome were also allowed. Patients not giving consent were excluded. Patients with prior diabetes mellitus type 1 or type 2 or fasting blood glucose consistently >100 mg/dL or HbA1c >5.7% were excluded. Patients with other significant liver diseases like viral hepatitis, autoimmune hepatitis, primary biliary cholangitis or primary sclerosing cholangitis were excluded. History of pancreatitis, excessive alcohol intake or chronic alcoholism (more than 21 units/week for males and more than 14 units/week for females) was excluded. Patients with baseline LFT within normal limits (SGOT and SGPT <40) were also excluded.

After recruitment and informed consent, baseline assessments were done including demographic details, medical history, anthropometric measurements and laboratory tests. USG and FibroScan were performed to assess baseline liver fat content and fibrosis. Participants received saroglitazar 4 mg once daily (OD) and were followed at baseline, 6 month and 12 month to evaluate change in liver function and related outcomes. The main follow up variables analysed in this manuscript were AST, ALT, FibroScan parameters liver stiffness measurement (LSM) and controlled attenuation parameter (CAP), along with BMI. Data were summarised using descriptive statistics. Paired comparisons were used to assess change across time points baseline to 6 months, baseline to 12 months and 6 months to 12 months. One-way ANOVA was used for baseline comparison across age categories where applicable.

RESULTS

Table 1: Baseline profile of study group

Variable	Value
Age (years) mean ± SD	48.52 ± 10.87
Age (years) median (min–max)	50 (30–64)
Male n (%)	81 (47.6)
Female n (%)	89 (52.4)
BMI (kg/m²) mean ± SD	29.45 ± 2.80
FBS (mg/dL) mean ± SD	96.23 ± 7.23
HbA1c (%) mean ± SD	5.56 ± 0.23
Platelet count (×10⁹/L) mean ± SD	200.41 ± 29.90
FIB-4 index mean ± SD	1.45 ± 0.36
APRI mean ± SD	0.49 ± 0.11

Total 170 cases were analysed. Mean age was 48.52 ± 10.87 years with median 50 years. Sex distribution was near equal. Baseline BMI was 29.45 ± 2.80 kg/m². FBS and HbA1c stayed in non-diabetic range. Platelet count was 200.41 ± 29.90 ×10⁹/L. Baseline FIB-4 and APRI were 1.45 ± 0.36 and 0.49 ± 0.11.

Table 2: Mean trend of liver enzymes and FibroScan markers at baseline 6 month 12 month

Parameter	Baseline mean ± SD	6 month mean ± SD	12 month mean ± SD
AST (U/L)	53.56 ± 8.32	43.97 ± 8.76	44.36 ± 8.79
ALT (U/L)	63.28 ± 8.77	50.84 ± 9.27	50.58 ± 9.27
LSM (kPa)	9.00 ± 1.77	7.78 ± 1.83	7.69 ± 1.76
CAP (dB/m)	310.31 ± 19.65	276.04 ± 21.51	275.66 ± 22.32
BMI (kg/m²)	29.5 ± 2.8	28.3 ± 2.7	27.4 ± 1.5

AST, ALT, LSM and CAP reduced at 6 month and remained near similar at 12 month. BMI also showed steady fall from baseline to 6 month and further at 12 month.

Table 3: Baseline to 6 month change with percent drop

Parameter	Baseline mean	6 month mean	Absolute drop	% drop	p value
AST (U/L)	53.56	43.97	9.59	17.91	<0.01
ALT (U/L)	63.28	50.84	12.44	19.66	<0.01
LSM (kPa)	9.00	7.78	1.22	13.56	<0.01
CAP (dB/m)	310.31	276.04	34.27	11.04	<0.01
BMI (kg/m²)	29.5	28.3	1.20	4.07	<0.01

At 6 month AST reduced by 9.59 U/L (17.91%) and ALT reduced by 12.44 U/L (19.66%). LSM reduced by 1.22 kPa (13.56%) and CAP reduced by 34.27 dB/m (11.04%). BMI reduced by 1.20 kg/m² (4.07%). All baseline to 6 month changes were statistically significant with p<0.01.

Table 4: Baseline to 12 month change with percent drop

Parameter	Baseline mean	12 month mean	Absolute drop	% drop	p value
AST (U/L)	53.56	44.36	9.20	17.18	<0.01
ALT (U/L)	63.28	50.58	12.70	20.07	<0.01
LSM (kPa)	9.00	7.69	1.31	14.56	<0.01
CAP (dB/m)	310.31	275.66	34.65	11.17	<0.01
BMI (kg/m²)	29.5	27.4	2.10	7.12	<0.01

At 12 month AST remained lower by 9.20 U/L (17.18%) and ALT lower by 12.70 U/L (20.07%). LSM reduced by 1.31 kPa (14.56%) and CAP reduced by 34.65 dB/m (11.17%). BMI reduced by 2.10 kg/m² (7.12%). All baseline to 12 month comparisons were statistically significant with p<0.01. Main improvement was seen by 6 month then values mostly plateau till 12 month. Enzymes and CAP stayed stable, while LSM showed small continued fall and BMI continued to decrease.

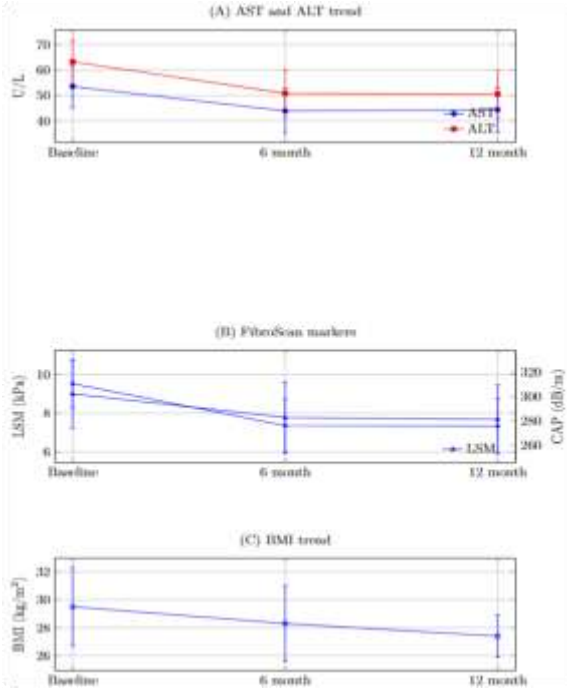

Figure 1: Twelve-month trend in transaminases and FibroScan markers in non-diabetic NAFLD patients on saroglitazar

DISCUSSION

In this 12-month prospective observational follow-up of non-diabetic NAFLD patients treated with saroglitazar 4 mg, the main signal was early fall in transaminases and improvement in FibroScan parameters. The drop happened mainly by 6 months and then it stayed stable till 12 months. This pattern suggests quick metabolic and inflammatory improvement first. Later it plateaus, so it may not be ongoing fibrosis reversal every month.

When we compare with controlled trial data, the direction matches but the magnitude is usually smaller in real-world single arm cohorts like ours. In the phase 2 randomized placebo-controlled trial by Gawrieh et al., saroglitazar 4 mg showed a much larger ALT fall at week 16 (least-squares mean percent change about −45.8% vs placebo +3.4%). It also improved liver fat content and showed favourable trend in non-invasive fibrosis readouts over short term.[6] In our cohort, the 12-month ALT reduction is more modest but it is sustained. This is typical when there is no placebo group and lifestyle changes are not tightly controlled.

Real-world Indian data also supports improvement in LSM and CAP with saroglitazar over 52 weeks. Chaudhuri et al. (tertiary care centre experience) reported significant LSM improvement from 11.03 ± 7.19 kPa at baseline to 8.59 ± 6.35 kPa at 52 weeks, along with reductions in CAP and transaminases. They also noted no significant weight change, which is important because it suggests benefit can happen even without major weight loss in some patients.[3] Your LSM and CAP trend is in the same direction and clinically plausible, especially because baseline stiffness in your group is not very high, so large absolute fall should not be expected.

A pooled view also exists now. A 2023 meta-analysis reported that saroglitazar was associated with reductions in ALT and AST (mean difference roughly −26 U/L for ALT and −16 U/L for AST across included studies).[2] Our enzyme reduction is consistent with this overall direction, but again slightly smaller, which can happen due to baseline levels, adherence variation, and inclusion criteria differences.

Now the important opposing note. Not every controlled dataset shows significant CAP or LSM improvement vs a control arm in short duration. In

the SVIN randomized four-arm study (saroglitazar, vitamin E, combination, control), saroglitazar significantly reduced ALT compared with control, but CAP and LSM changes with saroglitazar alone did not reach statistical significance versus control at 24 weeks. Combination therapy showed significant LSM reduction vs control.[13] This is a key caution for our work. Our observed LSM fall is encouraging, but we donot not overclaim "fibrosis reversal". It can be a mix of reduced hepatic inflammation, reduced steatosis, and measurement variability, apart from true collagen remodeling.

Fibrosis stage is the strongest prognostic driver in NAFLD, and higher fibrosis is linked with higher liver-related and overall mortality. Angulo et al. showed fibrosis stage was independently associated with mortality and liver outcomes (reported hazard ratio around 1.88 per stage for overall mortality in NAFLD cohorts).[1] Long follow-up cohort data also supports fibrosis stage as the strongest predictor of disease-specific mortality.[14] So any improvement in stiffness is relevant clinically. But FibroScan is still a surrogate. It can move with inflammation, hepatic congestion, meal timing, operator factors, and BMI. Current guidance keeps lifestyle change and metabolic risk control as the base of management, with pharmacotherapy considered selectively and endpoints ideally supported by validated non-invasive tests and longer follow up.[15] EASL 2024 guidance also emphasizes risk stratification with non-invasive tests and careful interpretation of changes over time.[16]

In that frame our data adds a practical Indian prospective signal in non-diabetics showing sustained improvement in enzymes with parallel non-invasive improvement in steatosis and stiffness over 12 months. Safety discussion also needs a line even if our dataset did not actively capture adverse events in detail. Published real-world data reported pruritus needing discontinuation in one patient and mild loose motions in another, overall tolerability was acceptable.[4] Our work should clearly state what safety monitoring you actually did, and what we could not capture.

This was a single-centre prospective observational study with no control arm. So causality cannot be claimed. Regression to mean and lifestyle change during follow up can contribute. Diet and exercise adherence was not objectively quantified, so confounding remains. FibroScan (LSM and CAP) are non-invasive surrogates. They are not equal to liver biopsy and they can change with inflammation and technical factors, so stiffness reduction should be interpreted as "suggestive" not definitive fibrosis regression. Follow-up was 12 months only. That is good for biochemical trend, but still short for hard outcomes like cirrhosis events. Also this cohort is non-diabetic NAFLD, so generalisability to diabetic MASLD or advanced fibrosis groups is limited. Nomenclature also is evolving (MASLD framework), so wording should be kept aligned with current consensus and guidance.[17]

A controlled design is the next step. A pragmatic randomized trial or matched control cohort in Indian settings will clarify the drug effect beyond lifestyle. Longer follow up (18–24 months or more) is needed to see whether LSM change translates into lower progression to advanced fibrosis. Stratified analysis by baseline fibrosis stage, CAP severity, and metabolic syndrome features will help identify who benefits most. Adding MRI-PDFF for liver fat and validated serum fibrosis panels in parallel with FibroScan will make interpretation stronger. If feasible, a subset with histology endpoints will answer the key journal question on true fibrosis and MASH activity change. Combination strategies also deserve study because some controlled evidence suggests combination therapy may give more consistent LSM improvement than saroglitazar alone in short term.[10] Finally, safety monitoring should be structured with active adverse event capture, and cardiometabolic outcomes (lipids, insulin resistance markers, CV events) should be tracked because NAFLD is a multisystem metabolic disease.

CONCLUSION

Saroglitazar use in non-diabetic NAFLD showed clear fall in AST and ALT over 12 months. Most improvement happened by 6 months then values stayed stable. FibroScan CAP and LSM also improved from baseline and the benefit persisted at 12 months. The stiffness fall continued mildly even after 6 months but the change was small. BMI reduced across follow up which can also support metabolic improvement. This is an observational study so association is shown not causation. Longer controlled studies are still needed to confirm fibrosis level benefit and hard clinical outcomes.

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