International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Cross-Sectional Study on Non-Alcoholic Fatty Liver Disease Patients with Type 2 Diabetes Mellitus and the Association of Risk Factors with Liver Steatosis and Fibrosis Stages

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Abstract: ***Title: A Cross - sectional Study on Nonalcoholic Fatty Liver Disease Patients with Type 2 Diabetes Mellitus and the Association of Risk Factors with Liver Steatosis and Fibrosis Stages. Introduction: Nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes mellitus (T2DM) are associated with the worldwide diabetes pandemic, which speeds up the course of the illness and has negative health consequences. The intricate connection between metabolic diseases and liver health was brought to light at the 2023 European Association for the Study of the Liver Congress, when NAFLD was renamed to metabolic dysfunction - associated steatotic liver disease (MASLD). With this in mind, we set out to determine how common NAFLD is in the Indian community and what variables put people at risk for developing it at different stages. Methods and materials: 1, 521 individuals with type 2 diabetes mellitus were included in an observational cross - sectional research that took place at Saraswathi Medical College in Hapur. Quantitative measures were taken, including height, weight, age, gender, and anthropometric variables including BMI and waist circumference. By using FibroScan® vibration - controlled transient elastography (VCTE), the various phases of liver fibrosis and steatosis were discovered. Results: Out of 1, 521 diabetic cases, 75.1% had liver steatosis, with corresponding percentages of 25.9%, 15.1%, 24.4%, and 36.0%. In contrast, 28.0% had liver fibrosis, with corresponding percentages of 72.2%, 19. %, 5%, 1.5%, and 3.4%. Significant gender - related changes were seen in the S1 (p = 0.012), S3 (p = 0.001), F1 (p = 0.001), and F2 (p = 0.001) grades, indicating a positive relationship. In addition, there was a significant correlation between disease severity and waist circumference in both the steatosis and fibrosis phases of liver disease (p = 0.001), but a solitary correlation between steatosis degree and BMI (p = 0.001). With p - values of 0.149 for steatosis and 0.078 for fibrosis grades, respectively, the mean age differences between these groups did not achieve statistical significance. Conclusion: The research concludes that type 2 diabetics are at increased risk for advanced fibrosis due to the high frequency of non - alcoholic fatty liver disease (NAFLD) (steatosis and fibrosis). Appropriate screening and treatments are necessary for type 2 diabetic individuals who have risk factors such as a large waist and a high body mass index.***

Keywords: Diabetes, Fibroscan, MASLD, NAFLD, VCTE

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is highly prevalent among type 2 diabetes mellitus (T2DM) patients in India, with up to 70% affected.1–3 The synergy between T2DM and NAFLD accelerates disease progression and increases health risks. The alarming rise of T2DM in India contributes to the global diabetes epidemic, with NAFLD emerging as a parallel health challenge. The coexistence of these conditions poses management challenges and elevates the risk of adverse outcomes, 2–4 emphasizing the need for integrated approaches to prevention and treatment in the Indian healthcare system.

The well - established link between T2DM and NAFLD, in which people with T2DM have a higher prevalence of NAFLD, highlights the complex interplay between metabolic disorders and liver health.3, 5, 6 This observation prompted a significant paradigm shift at the 2023 European Association for the Study of the Liver (EASL) Congress, when the term "metabolic dysfunction - associated steatotic liver disease" (MASLD) was coined to replace "nonalcoholic fatty liver disease" (NAFLD). The EASL, La Asociación Latinoamericana para el Estudio del Hígado (ALEH), and the American Association for the Study of Liver Diseases (AASLD) announced the renaming of NAFLD to MASLD in June 2023. The rationale for this change was to offer a diagnosis for the most common chronic liver disease in the world while also establishing a supportive and nons tigmatizing nomenclature. O ver 30 % of p e ople worldwide are afflicted by this condition. Additionally, a wider range of liver conditions linked to metabolic dysfunction is covered by the new term, including nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL).7

Demographic and anthropometric analysis, a method focused on examining parameters related to body composition, dimensions, and structure, plays a pivotal role in comprehending the factors that contribute to the development and advancement of NAFLD within the subset of individuals who have T2DM. By assessing measurements such as body mass index (BMI), waist circumference (WC), and age, anthropometric analysis helps discern patterns that can shed light on the underlying mechanisms linking these two complex health conditions. Hence, in light of the existing knowledge gaps and the evident interconnection between T2DM and NAFLD, the cross - sectional study endeavors to address this dearth of information by investigating the

prevalence and risk factors associated with NAFLD specifically within the context of T2DM patients in India.

2. Materials and Methods

Study Design and Patients

This is a prospective, observational, crosssectional study conducted at Saraswathi medical college, Hapur among patients with T2DM attending the diabetes clinic. Patients over 18 years of age who provided written informed consent were included in the study. Furthermore, participants with secondary hepatic steatosis attributed to specific causes—namely, pregnancy, misuse of steatogenic drugs (including amiodarone, tamoxifen, methotrexate, corticosteroids, and estrogen), and severe malnutrition—were not included. The presence of a positive hepatitis B surface antigen or hepatitis C viral antibody also warranted exclusion. Other chronic liver diseases, encompassing autoimmune hepatitis, hemochromatosis, Wilson's disease, primary biliary cirrhosis, and drug - induced hepatitis, constituted additional grounds for exclusion. Lastly, instances of measurement failure or unreliable outcomes during vibration - controlled transient elastography (VCTE) evaluation, such as those stemming from ascites, cholestasis, acute exacerbation, or hepatitis flare with alanine aminotransferase (ALT) >5 times baseline, an interquartile range to median ratio (IQR/M) surpassing 30%, or a success rate falling below 60%, led to participant exclusion.

Data Collection

Demographic information, along with BMI and WC, were recorded. Using a FibroScan® device, VCTE was conducted under fasting conditions for over 4 hours, following the manufacturer's guidelines. A FibroScan® result was deemed reliable when it comprised 10 or more valid measurements and was expressed in kilopascals (kPa). Successful readings were characterized by a success rate exceeding 60% and an IQR/M of 0.3 or less among the 10 measurements. The controlled attenuation parameter (CAP) was used to determine the extent of hepatic steatosis, and the results were reported in decibels per meter (dB/m). CAP values for S0, no steatosis (16.0 for F4 (cirrhosis).9

Ethical Approval

In view of the nature of the study, all procedures were performed as part of routine care. Therefore, ethical approval was not applied for any Ethics Committee. Informed consent was obtained from all participants prior to their inclusion in the study. All data collected from the diabetes clinic OPD were kept confidential and were used only for research purposes.

Statistical Analysis

Results are expressed as mean ± standard deviation or number and percentage as appropriate for qualitative and quantitative variables. The statistical analysis was performed at 95% confidence intervals with p - value <0.05 considered to be significant. The statistical package SPSS, version 24.0, software was used to analyze the data.

3. Results

A total of 1, 521 patients were enrolled in this study. The prevalence of liver steatosis was 75.1% among the 1, 521 diabetes cases [S0 (24.9%), S1 (15.1%), S2 (24%), and S3 (36%)], whereas the prevalence of liver fibrosis was 28.0% [F0 (72%), F1 (19%), F2 (5%), F3 (1.5%), and F4 (3.4%)].

The overall mean age of the participants was 53.24 ± 11.33 years, height was 1.19 ± 0.72 m, weight was 71.78 ± 17.59 kg, WC measurement was 97.65 ± 30.36 cm, and BMI was 19.07 ± 13.60 kg/m2. There were 52.8% male participants in the study (Table 1). Among different grades of steatosis and fibrosis, S3 (36%) and F0 (74%) and F1 (19%) were found most common in this study population (Figs 1 and 2).

Table 1: Demographic details of study participants (*N= 1, 521*)

Variables	Mean ± SD
Age (year)	53.24 ± 11.33
Height (m)	1.19 ± 0.72
Weight (kg)	71.78 ± 17.59
WC (cm)	97.65 ± 30.36
BMI (kg/ m^2)	19.07 ± 13.60
Gender	
Male, *n* (%)	804 (52.8%)
Female, *n* (%)	719 (47.2%)

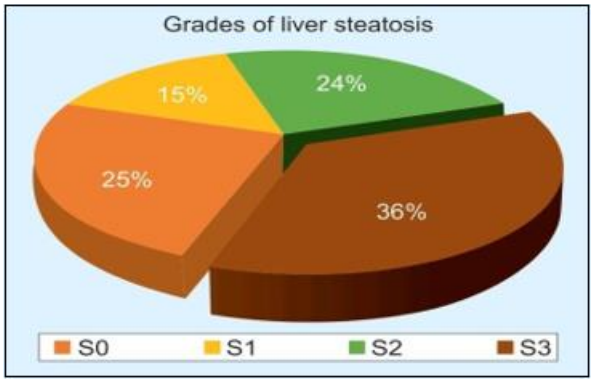

Figure 1: Grade-wise distribution of liver Steatosis in the study population

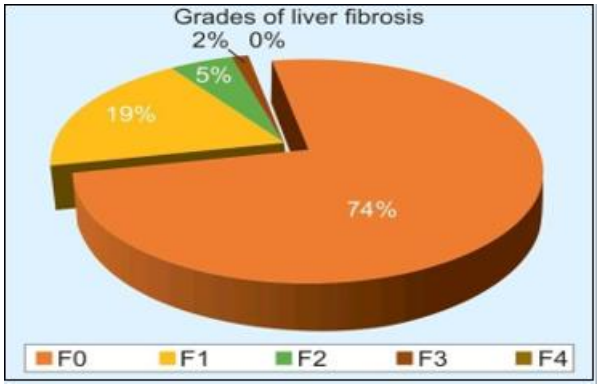

Figure 2: Grade-wise distribution of liver Fibrosis in the study population

There was no significant difference in mean age between the different grades of liver steatosis (p - value = 0.149) and fibrosis (p - value = 0.078), implying that age may not be a significant differentiator between these grades. Steatosis

analysis shows that grades S1 and S2 have higher mean ages, implying an age - related aspect in disease progression. Similarly, cirrhosis analysis shows that advanced fibrosis stages (F3 and F4) have higher mean ages, implying an age - related trend (Table 2).

Table 2: Association of age with different grades of liver Steatosis and liver Fibrosis

Grades	No. of cases	Age (yr)(mean ± SD)	*p*- Value*
Steatosis (N= 1,521)			
S0	278	52.90 ± 12.91	0.149
S1	231	54.25 ± 10.79	
S2	365	53.92 ± 10.24	
S3	547	52.58 ± 11.08	
Fibrosis (N= 1,516)			
F0	1,092	52.86 ± 11.51	0.078
F1	274	54.34 ± 10.68	
F2	76	52.68 ± 10.58	
F3	23	56.00 ± 10.18	
F4	51	56.00 ± 11.57	

The study reveals possible gender differences in the distribution of liver steatosis and fibrosis grades. Grade S0 has a nearly equal gender distribution, with males accounting for 52.1% of cases and females accounting for 47.9% (p = 0.244). In contrast, there is a significant gender disparity in grade S1. Females have a significantly higher proportion of cases (55.8%) than males (44.2%) (p - value = 0.012). Cases in grade S2 are almost evenly divided between genders, with 50.7% males and 49.3% females (p = 0.711). Surprisingly, there is a significant gender disparity in grade S3. Males account for a significantly higher percentage of cases (58.1%) than females (41.9%) (p - value = 0.001) (Table 3, Fig.3). Further investigation reveals distinct gender patterns within different fibrosis grades. Notably, gender disparities exist in grades F1 and F2, emphasizing gender's potential role in influencing fibrosis progression in those stages. Gender appears to play a lesser role in the distribution of fibrosis in grades F0, F3, and F4 (Table 3, Fig.4).

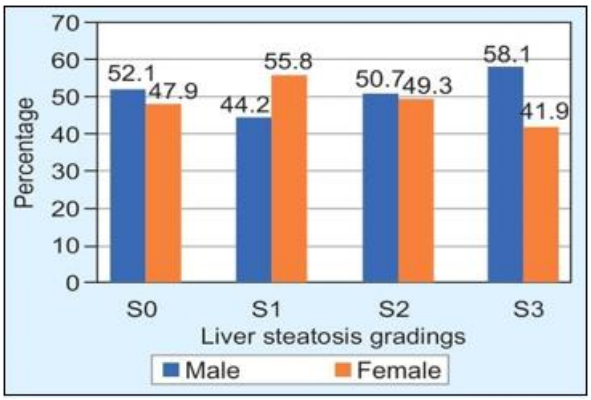

Figure 3: Gender- wise distribution of study participants among different grades of liver steatosis

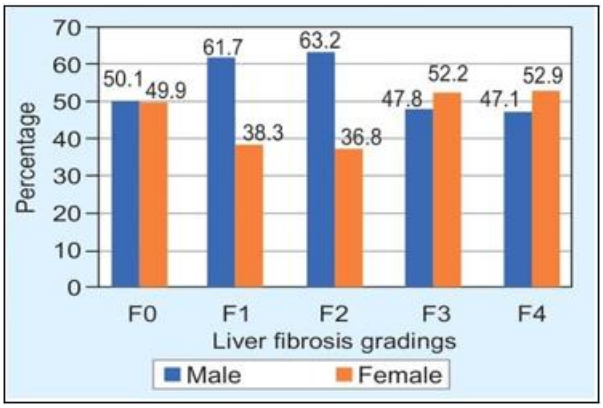

Figure 4: Gender- wise distribution of study participants among different grades of liver fibrosis

A consistent pattern emerges in both steatosis and fibrosis, as disease severity increases, mean WC tends to increase. This pattern emphasizes the potential role of abdominal adiposity in the progression of liver diseases. Notably, the results of this study also support the relationship between WC and disease severity grade in both liver steatosis (p - value = 0.001) and liver fibrosis (p - value = 0.001). This relationship is consistent with our understanding of the impact of central obesity on liver health (Table 4).

In both steatosis and fibrosis evaluations, a consistent trend emerges in which increased disease grades are associated with elevated mean BMI. The high p - value (p = 0.001) in the steatosis analysis suggests that BMI could be an accurate predictor of disease severity in the context of steatosis. The absence of significance (p > 0.05) in the fibrosis analysis, on the other hand, suggests a more intricate interplay between BMI and fibrosis, indicating a nuanced relationship that goes beyond a simple association (Table 5).

Table 2: Association of gender with different grades of liver steatosis and liver fibrosis

Grades	Steatosis (N= 1,521)				*p*- Value
	Male (*n*= 802)		Female (*n*= 719)		
	No. of cases	%	No. of cases	%	
S0	197	52.1	181	47.9	0.244
S1	102	44.2	129	55.8	0.012
S2	185	50.7	180	49.3	0.711
S3	318	58.1	229	41.9	0.001
	Fibrosis (N= 1,516)				
	Male (*n*= 799)		Female (*n*= 717)		
	No. of cases	%	No. of cases	%	
F0	547	50.1	545	49.9	0.932
F1	169	61.7	105	38.3	0.001
F2	48	63.2	28	36.8	0.001
F3	11	47.8	12	52.2	0.768
F4	24	47.1	27	52.9	0.552

*p- Value <0.05 is considered to be statistically significant

Table 3: Association between WC with different grades of liver steatosis and liver fibrosis

Grades	No. of cases	WC (cm)(mean ± SD)	*p*- Value
Steatosis (N= 1,521)			
S0	272	25.62 ± 4.66	0.001
S1	147	27.40 ± 4.10	0.001
S2	246	28.42 ± 4.51	0.001
S3	374	29.48 ± 5.93	0.001
Fibrosis (N= 1,037)			
F0	746	95.14 ± 10.56	0.001
F1	186	99.36 ± 11.59	0.001
F2	55	103.13 ± 12.36	0.001
F3	17	99.71 ± 13.27	0.001
F4	33	104.55 ± 11.81	0.001

*p- Value <0.05 is considered to be statistically significant

Table 5: Association between mean BMI and liver steatosis and fibrosis severity

Grades	No. of cases	WC (cm)(mean ± SD)	*p*- Value
Steatosis (N= 1,032)			
S0	263	25.62 ± 4.66	0.001
S1	150	27.40 ± 4.10	0.001
S2	249	28.42 ± 4.51	0.001
S3	370	29.48 ± 5.93	0.001
Fibrosis (N= 1,030)			
F0	736	27.45 ± 5.31	>0.05
F1	188	28.69 ± 5.03	>0.05
F2	54	29.96 ± 4.99	>0.05
F3	16	28.89 ± 5.65	>0.05
F4	36	29.96 ± 4.55	>0.05

*p- Value <0.05 is considered to be statistically significant

4. Discussion

The findings presented in this study shed light on the intricate relationship between liver steatosis, fibrosis severity, and associated factors among diabetes patients. The study included 1, 521 individuals, of which 75.1% exhibited liver steatosis and 28.0% showed signs of fibrosis. The analysis provides valuable insights into disease progression, age - related variations, gender - related patterns, and the role of anthropometric measures such as WC and BMI. Notably, the analysis of mean ages across steatosis and fibrosis grades underscores a consistent trend, although statistical assessments reveal that the differences in mean age among these grades are not significant. N ever theless, subtle trends b e come apparent, indicating potential age - related factors in the advancement of the disease. These findings echo recent studies that have similarly explored age - related trends in liver disease progression, underscoring the intricate interplay between age and disease severity. A study involving 380 diabetes patients, for instance, documented that 72.6% of the participants exhibited liver steatosis, accompanied by a mean age of 55.22 ± 10.88 years and a mean BMI of 29 kg/m2. Notably, this study focused on exploring the association between type 2 diabetes status and the prevalence of liver steatosis and fibrosis among individuals aged ≥40 years.10 While the study did not specifically mention the prevalence of liver fibrosis, it is worthwhile to note that other independent studies have identified age as a pivotal factor that can influence the development of liver fibrosis in diabetes patients.6, 11

The study's exploration of gender related variations within liver steatosis and fibrosis grades in diabetes patients reveals intriguing patterns. While the distribution in certain grades does not display statistical significance, such as in grade S0 and F0 (as they denote the absence of disease), other grades exhibit significant gender disparities. In particular, grades S1 and S3 and fibrosis grades F1 and F2 show substantial gender - related differences. There is limited information on the association of gender - related variations within liver steatosis and fibrosis grades in diabetes patients. However, some studies have found that gender differences are prominent in NAFLD, and different factors are associated with liver status in males as compared to females.

The investigation into anthropometric measures, namely WC and BMI, unveils significant associations with liver disease severity. The significant p - value (p = 0.001) observed in the steatosis analysis provides valuable insights into the potential role of BMI as an indicator of disease severity within the context of steatosis. This significance suggests that higher BMI values are associated with more severe steatosis grades, possibly reflecting the contribution of excess adiposity to lipid accumulation in the liver. The observation is in line with a study that identified a correlation between increasing BMI and higher NAFLD prevalence, along with elevated steatosis levels among individuals with overweight and diabetes compared to those without diabetes.13 Another study found that hepatic steatosis in patients with T2DM is associated with more significant BMI.

As per the present study, WC is associated with liver steatosis in T2DM patients. The observation is in alignment with a study, in which waist - to - calf circumference ratio (WCR) is an independent predictor of hepatic steatosis and fibrosis in patients with type 2 diabetes.15 Another study found that increased central obesity, measured by WC, was the strongest factor associated with steatosis.16 The accumulation of visceral fat is believed to contribute to insulin resistance and inflammation, both of which play crucial roles in the development and progression of liver steatosis.

The present study's comprehensive analysis emphasizes the interplay between liver steatosis, liver fibrosis severity, and various contributing f ac tor s among diabetes patients. The findings underscore the importance of understanding these complex dynamics for effective disease management. H owever, as with any study, limitations must be acknowledged, including potential selection bias and the need for further longitudinal investigations to establish causal relationships. Nonetheless, this study contributes to the evolving understanding of liver health in the context of diabetes and its associated factors.

5. Conclusion

In conclusion, the study shows the high incidence of hepatic steatosis (75.1%) and fibrosis (28.0%) in patients with type 2 diabetes. Further, age, gender, WC, and BMI are all associated with the severity of liver steatosis and fibrosis in T2DM patients. While age and gender play minor roles, WC and BMI emerge as significant predictors of disease severity. Given the multifaceted nature of these associations, these

findings highlight the need for a comprehensive approach to assessing and managing liver health in T2DM patients.

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