ORIGINAL RESEARCH PAPER

Gastroenterology

# NON ALCOHOLIC FATTY LIVER DISEASE AMONG DIABETICS BY TRANSIENT ELASTOGRAPHY AND COMPARISON WITH OTHER NON INVASIVE METHODS IN HIMALYAN REGION

KEY WORDS:

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**ABSTRACT**

**INTRODUCTION:** The liver is an important organ in systemic metabolism and type 2 diabetes mellitus. T2DM patients develop NAFLD & NASH which further leads to cirrhosis and hepatocellular carcinoma. Role of imaging in the diagnosis and treatment of liver diseases has grown dramatically.

**METHODOLOGY:** We conducted this study for one year in a tertiary care centre at IGMC Shimla in department of Medicine and Gastroenterology. After serological tests and ultrasound abdomen, the CAP and liver stiffness measurement was performed on the right lobe of liver. Data collected was entered into excel sheet for further processing and statistical analysis.

**RESULTS:** NAFLD was found in 62 (42.2%) patients & 85(57.8%) patients did not have NAFLD. 42 (28.6%) patients had significant fibrosis and 105(71.4%) patients did not have significant fibrosis. Mean HbA1c levels were found to be 9.3% in patients with NAFLD and 8.5% in patients without NAFLD with a p value of 0.009.

## INTRODUCTION

The metabolic abnormalities associated with DM causes secondary pathophysiologic changes in various organs. [1] The liver is an important organ in systemic metabolism and contributing substantially to the development of insulin resistance and type 2 diabetes mellitus (T2DM). The mechanism involves hepatic fat accumulation, alterations of energy metabolism and inflammatory signals derived from various cell types. Patients with NAFLD are commonly insulin resistant and large no. of T2DM patients develop NAFLD with its inflammatory complication called Non alcoholic steatohepatitis (NASH) which further leads to cirrhosis and hepatocellular carcinoma. In 1980, Ludwig and colleagues from the Mayo clinic introduced the term NASH to describe a form of liver disease observed in middle aged patients with abnormal liver biochemical test results and histologic evidence of alcoholic hepatitis but no history of alcohol abuse. [2] Isolated NAFLD is characterized by steatosis in at least 5% of hepatocytes. [3] Not only NAFLD is prevalent in diabetics but also diabetes is a major risk factor for induction and progress towards fibrosis, cirrhosis and HCC. [4] Recent literature has estimated the global prevalence of NAFLD, as diagnosed by imaging in the absence of significant alcohol use, to be approximately 25%, with the highest prevalence in the Middle East and South America and the lowest in Africa. [5] NAFLD in Asian countries has higher prevalence rates in the urban areas. [6] The prevalence of NAFLD in Indian population ranges from 11-32% and about 4-5% have NASH while the prevalence of NAFLD in diabetics is 60-65% and 20-25% of these patients have NASH. [7] In the liver, insulin resistance is defined by impaired insulin mediated suppression of glucose production, resulting from increased gluconeogenesis and decreased hepatic glycogen synthesis. In patients who are obese and have T2DM, the presence of NAFLD associates with more severe hyperinsulinemia, dyslipidemia and insulin resistance in hepatic and adipose tissue than in patients without NAFLD. [8] Hyperinsulinemia and diets rich in fat and carbohydrate will contribute to elevated de novo lipogenesis in obesity and NAFLD. Finally the hepatocellular FFA pool can be further increased by impaired export of VLDL cholesterol in insulin resistant patients with NASH. The muscle insulin resistance shifts post prandial energy storage from muscle glycogen to hepatic lipid storage. Hepatic mitochondria transiently adapt to increased lipid availability by upreg ulating their oxidative capacity at the expense of decreased coupling efficiency. Eventually Loss of mitochondrial adaptation will favor lipid deposition and insulin resistance. [9] Finally, excessive lipid overloading will impair antioxidant capacity and accelerate oxidative stress with mitochondrial leakage, resulting in NASH and aggravated insulin resistance. Diabetes leads to a significantly increased prevalence and severity of NAFLD. [10,11] In a large study of a serial liver biopsies it was seen that patients with NASH rather than NAFLD, were more likely to be diabetic (56% vs 21%) and patients with advanced fibrosis and cirrhosis were more likely to be diabetic than those without advanced fibrosis (89% vs 47%). [12] A study by Targher et al of 250 patients with type 1 diabetes estimated the prevalence of NAFLD by ultrasound as 44.4%. Although studies in patients with type 2 diabetes examining the spectrum of pathology within NAFLD utilizing liver biopsy are limited by a small numbers, but they collectively estimate the prevalence of NASH at 63-87% and moderate to severe fibrosis at 22-60%. [13,14] In a study by Roulot d et al using fibroscan as a screening tool for significant liver disease involving 1190 patients over the age of 45 and presenting for a general medical checkup, elevated liver stiffness measurements (8kPa) were found in 7.5% patients. In a study by Huwart et al MRE performed better than Fibroscan and AST to platelet ratio index (APRI) in 141 patients with chronic liver disease of various etiologies. [15] Despite these encouraging results, the MRE technique has limitations like acquisition time of scanning, higher cost and requires expertise in analysis and standardized thresholds of measurement. So monitoring of the patients is important to look for NAFLD and liver fibrosis. Liver biopsy is the gold standard for evaluation of fibrosis but it has limitations. Therefore, non invasive methods for assessment of liver fibrosis including ultrasound elastographic methods have been an intense field of research. Over the last 25 years, the role of imaging in the diagnosis and treatment of liver diseases has grown dramatically. The rationale for elastography is that normal liver is viscous and favorable to wave propagation, whereas fibrosis increases the hardness of the tissue and favors more rapid propagation. The main drawback of elastography is that it cannot be performed in case of ascites, obesity and liver congestion. The TE device measures shear wave velocity that can then be converted into LSE which is expressed in kilo Pascal and level of steatosis is calculated with CAP value which estimates the fat. [16] Liver steatosis is graded as: S0 - <5% steatosis, S1 - 5-33% steatosis,

S2 - 34-66% steatosis, S3 - >66% steatosis. Results are measured using kPa and range from 2 to 75 kPa. The normal range for a TE is between 2 to 7 kPa with average of 5.3 kPa. [17] Scarring has 4 stages: F0 (<2 kPa) - no scarring, F1 (2 to 7 kPa) - mild fibrosis, F2 (7.5 to 10 kPa) - moderate fibrosis, F3 (10-14 kPa) - severe fibrosis, F4 (14 or higher kPa) - cirrhosis or advanced fibrosis. Non invasive liver tests (NILTs) have been developed as an alternative to liver biopsy. These can be biomarker based or based on routinely collected clinical and laboratory data such as NAFLD fibrosis score (NFS score), Fib-4, AST/ALT ratio, BARD (BMI, AST/ALT ratio, T2DM), APRI index (AST platelet ratio index). In our study, we have assessed the development of NAFLD in all diabetics through fibroscan and we have also correlated the findings of fibroscan with other non invasive markers i.e. NFS, APRI, AST/ALT ratio and ultrasound. This will help in finding high risk groups for recommendations of the use of fibroscan for screening NAFLD in diabetics. Also for places where fibroscan will not be available, we have assessed the efficacy of non invasive markers and USG to detect NAFLD.

## METHODOLOGY

We conducted this study for one year from 1st June 2017 to 30th May 2018 in a tertiary care centre at IGMC Shimla in department of Medicine and Gastroenterology. The study population included diabetic patients attending the diabetic clinic, medicine OPD or admitted in medicine ward during this period. Patients of >18 years of age, diagnosed with type 1 or 2 diabetes who had negative viral markers and were consuming less than 20gms of alcohol per day were included in the study. After informed written consent, the anthropometric data was noted and a questionnaire was given to all the participants to investigate family history of diabetes mellitus, frequency and amount of alcohol consumption and smoking status. Serological tests for HBsAg, anti-HCV, AST, ALT, total bilirubin, hemogram, lipid profile and ultrasound abdomen was done. After that the CAP and liver stiffness measurement was performed on the right lobe of liver. A CAP value of 230 Db/m was selected as the cutoff for presence of steatosis, a CAP value of 231-260 db/m for moderate and 261-290 db/m for severe steatosis was selected respectively. NAFLD was diagnosed on the basis of ultrasound and TE findings, after excluding the other etiologic factors known to be related to chronic liver disease (alcohol intake >20gm/day, autpimmune hepatitis, hepatitis B and hepatitis C). Based on CAP values steatosis was graded as S0, S1,S2,S3 and fibrosis was graded as f0,f1,f2, f3 and cirrhosis. Findings of fibroscan were interpreted as: S0 – no fatty liver, S1 (mild) - ≥ 11% of hepatocytes with fat, S2 (moderate) - ≥ 34% hepatocytes with fat, S3 (severe) - ≥ 67% of hepatocytes with fat. F0-F1 (LSM - 2.5-7.5) = No to mild fibrosis, F2 (LSM score - 7.5- 10) = moderate fibrosis, F3 (LSM score - 10-14) = sever fibrosis, F4 (LSM - >14) = cirrhosis. Fibroscan machine used for the study was "Fibro scan 502 touch" with probe M7 71701; all 147 scans were done by the supervisors themselves. At least 20 minimum attempts were made and 10 valid measurements were taken. Scan quality, IQR, mean liver stiffness and equivalent shear wave speed were evaluated. Data collected was entered into excel sheet for further processing and statistical analysis. Continuous variables were expressed as mean values & standard deviation while categorical variables were presented as proportions, percentages and 95% CI. To find out the association between different variables appropriate parametric and non parametric test of significance were applied depending upon type and normality of data. For association P value less than 0.05 was considered statistically significant. According to the guidelines set up by ICMR (1994) and Helsinki declaration (modified 2000) patients involved in the study were informed and written informed consent was obtained. Each patient was adequately informed of the aims, methods, the anticipated benefits and potential risks of the study. Every precaution was taken to respect the privacy of the patients. The patients were given the right to abstain from participation in the study or to withdraw consent to participate at any time of the study without reprisal. Due care and caution was taken at all stages of the study to ensure that the patient is put to minimum risk, suffer from no irreversible adverse effects.

## RESULTS

A total of 147 patients were included in the study. Out of them 72 (49%) were males and 75(51%) were females. There were no patients in the age group of 18-30 years, 19 (12%) patients in the age group of 31-40 years, 40(27.2%) patients in the age group of 41-50 years, 42(28.6%) patients in the age group of 51-60 years, 27(18.4%) patients in the age group of 61-70 years and 19(12.9%) in >70 years of age group. The study population consisted of 118(80.3%) patients from rural and 29(19.7%) patients from urban background. Significant liver steatosis, suggestive of NAFLD was found in 62 (42.2%) patients and 85(57.8%) patients did not have significant steatosis suggestive of NAFLD. Those with significant steatosis suggestive of NAFLD were graded as mild steatosis (S1) in 13(8.8%), moderate steatosis (S2) in 25(17%) and severe steatosis in 24(16.4%) patients. Out of these, 33 were male and 29 were female patients. Fibrosis was calculated on the basis of LSM score and it was found that 42 (28.6%) patients had significant fibrosis (cut off value for fibrosis was taken as >7.5) and 105(71.4%) patients did not have significant fibrosis. Fibrosis was graded as F0-F1, F2, F3 and cirrhosis. Out of 147 patients, 105(71.4%) had no to insignificant fibrosis (F0-F1), 15(10.2%) had moderate fibrosis, 12(8.2%) had severe fibrosis and 15(10.2%) patients had cirrhosis on fibroscan (TE). Out of the patients with fibrosis, 24 were female and 18 were male patients. We compared the variables in patients of DM with NAFLD and without NAFLD and it was found that mean age of patients with NAFLD was found to be 55.5 years and in non –NAFLD was 54.3 with a significant p value of 0.002 suggesting a significant association between age and NAFLD with DM. Mean BMI was found to be 27.5 in patients with NAFLD and 24.9 in patients with non-NAFLD, with a significant p value of 0.0017. Mean total bilirubin was found to be 0.85 mg/dl in patients with NAFLD and 0.81 mg/dl in patients with non-NAFLD patients. Similarly mean conjugated bilirubin was found to be 0.25 mg/dl in NAFLD patients and 0.21 mg/dl in non-NAFLD patients with insignificant p value of 0.289 and 0.308 respectively. Mean ALT was found to be 44.7 in patients of NAFLD and 34.1 in patients with non-NAFLD, with a significant p value of 0.009. Mean AST was found to be 41.4 in patients of NAFLD and 33.7 in patients with non-NAFLD group with a insignificant p value of 0.050. Mean ALP was found to be 104.2 in patients with NAFLD and 103.8 in patients of non-NAFLD, with a insignificant p value of 0.731. Mean triglyceride was 161.6 in patients of NAFLD and 142.6 in patients of non-NAFLD, with a significant p-value of <0.001. Mean HDL was 37.26in patients of NAFLD and 40.03 in patients of non-NAFLD, with a insignificant p-value 0.216. Mean LDL was found to be 107.04 in patients of NAFLD, and 101.96 in patients of non-NAFLD, with a significant p value of 0.014. Total cholesterol levels were found to be 172.46 in the patients of NAFLD and 167.51 in patients of non-NAFLD with a significant p value of 0.016. Mean HbA1c levels were found to be 9.3% in patients with NAFLD and 8.5% in patients without NAFLD with a significant p value of 0.009. Mean fibrosis (LSM value) in patients with NAFLD was 11.2 and in patients without NAFLD were 4.11 with a significant p value of 0.001. Mean steatosis (CAP value) in patients with NAFLD was 267.2 and in patients without NAFLD were 148.9 with a significant p value of 0.002. Out of total 147 diabetic patients, 78 patients were found to have NAFLD through fibroscan and only 6 out of those patients had significant APRI score value with a sensitivity of 7.69% and specificity of 98.5% with a p value of 0.076 (table 1). Out of total of 147 diabetic patients, 78 patients were found to have NAFLD through fibroscan and only 30 out of those patients had significant NFS score value with sensiticity of 38.46% and specificity of 91.3% with significant p value of 0.000 (table 2). Out of total 147 diabetic patients, 78 patients were found to

have NAFLD through fibroscan and only 50 out of those patients had significant AAR score value with sensitivity of 64.1% and specificity of 66.67% with a significant p value of 0.000 (table 3). Out of 147 diabetic patients, 78 patients were found to have NAFLD through Fibroscan and only 43 out of those patients had fatty liver detected on ultrasound with a sensitivity of 55.13% and specificity of 84.06% with a significant p value of 0.000 (table 4). Out of the 35 patients who had NAFLD according to fibroscan but missed in ultrasound, more than half of the patients were in initial stages of steatosis (no steatosis and S1 – 20 patients) and fibrosis (F0-F1 and F2 – 27 patients). In our study, out of 147 patients ultrasound was normal in 93 (63.3%) patients, 36 (24.5%) patients had grade 1 fatty liver, 14 (9.5%) patients had grade 2 fatty liver and 4 (2.7%) patients had grade 3 fatty liver.

## DISCUSSION

In our study of 147 patients of diabetes, NAFLD was found in 78 (53.3%) patients. It was comparable to some Indian studies. The overall prevalence of NAFLD in Asian countries varies from 9 – 40% and in western countries from 15 – 40%. In india, the prevalence of NAFLD is around 9 – 32% in the general population, but it is 12.5 – 87.5% in patients with type 2 diabetes mellitus as reported in various studies. [18] Sprint study by Sanjay Kalra et al had almost similar prevalence of NAFLD in diabetes i.e. 56.5%. [19] Other studies in India showed different values as mentioned in the table 1. In our study, patients with NAFLD had mean age of 55.5 years and without NAFLD had mean age of 54.3 years. Gender distribution was fairly even, with slight female preponderance. Our study revealed a mean higher BMI in patients with NAFLD which was comparable to other studies. In the study by Kartikayan et al the average BMI of the patients with NAFLD was 26.60, comparable to our study. [20] Our patients had a higher total cholesterol and triglyceride levels, in patients with NAFLD than in patients without NAFLD, comparable to other studies. Patients with NAFLD had almost similar values of total & conjugated bilirubin, ALT, AST and ALP as compared to non NAFLD group. Our results were not in accordance with the study by Sanyal D et al in which patients with NAFLD had significantly higher ALT, AST, GGT and AST: ALT ratio. [21] Previous studies based on liver enzymes screening, normal levels of liver enzymes have been demonstrated in subjects with the entire spectrum of NAFLD and therefore ALT, AST, GGT have not been very useful in predicting NAFLD. [22] In our study we found that fibrosis was present in higher no. of patients with NAFLD. So we can say that fibrosis present in diabetes with NAFLD is severe compared to diabetes without NAFLD. In our study, fibroscan detected 78 cases of NAFLD and only 43 patients had fatty liver on ultrasound. So ultrasound cannot be relied for the diagnosis NAFLD accurately. Only 6 had significant APRI score values, 30 patients had significant NFS score value and 50 patients had significant AAR score value. In an Indian study by Parikh Pathik et al. [23] efficacy of fibroscan versus non invasive markers were determined i.e. NFS and AAR. It was found that fibroscan was superior to these non invasive methods. In our study also fibroscan was better in detecting NAFLD than other non invasive methods. So we can conclude that there is high prevalence of NAFLD in patients of DM as compared to general population. Most of the patients of DM with NAFLD are having moderate to severe steatosis than mild. Most of the patients of DM with NAFLD are having mild degree of fibrosis (F2) than (F3, 4). Patients of DM with NAFLD are having a higher mean BMI, TG, steatosis and fibrosis levels than non NAFLD group. TE is more sensitive and better modality for diagnosing NAFLD and fibrosis as compared to USG and other non invasive methods like APRI, AAR and NFS score. In areas where fibroscan is not available, other non invasive markers can be used. Limitation of our study is that the gold standard modality to diagnose NAFLD and fibrosis is liver biopsy and it was not used in our study. TE machine is not readily available and is costly. In patients with high grades of steatosis, TE can overestimate the level of associated fibrosis.

**Table 1: Diagnostic accuracy of APRI in comparison to TE to detect NAFLD**

| | | | NAFLD | | TOTAL |
|---|---|---|---|---|---|
| | | | NO | YES | |
| APRI | <1.5 | n (%) | 68 (48.6%) | 72 (51.4%) | 140 |
| | >1.5 | n (%) | 1 (14.3%) | 6 (85.7%) | 7 |
| Total | | n (%) | 69 (46.9%) | 78 (53.1%) | 147 |

| Statistics | Value | 95% CI |
|---|---|---|
| Sensitivity | 7.69% | 2.88 to 15.99 |
| Specificity | 98.55% | 92.19 to 99.96 |
| Positive Predictive Value | 85.71% | 42.55 to 97.98 |
| Negative Predictive Value | 48.57% | 46.82 to 50.33 |
| Accuracy | 50.34% | 41.98 to 58.68 |
| P Value | 0.076 | |

**Table 2: Diagnostic accuracy of NFS in comparison to TE**

| | | | NAFLD | | TOTAL |
|---|---|---|---|---|---|
| | | | NO | YES | |
| NFS Score | <0.67 | N (%) | 63 (56.8%) | 48 (43.2%) | 111 |
| | >0.67 | N (%) | 6 (16.7%) | 30 (83.3%) | 36 |
| Total | | N (%) | 69 (46.9%) | 78 (53.1%) | 147 |

| Statistics | Value | 95% CI |
|---|---|---|
| Sensitivity | 38.46% | 27.66 to 50.17 |
| Specificity | 91.30% | 82.03 to 96.74 |
| Positive Predictive Value | 83.33% | 68.89 to 91.86 |
| Negative Predictive Value | 56.76% | 52.05 to 61.35 |
| Accuracy | 63.27% | 54.93 to 71.06 |
| P Value | 0.000 | |

**Table 3: Diagnostic accuracy of AAR in comparison to TE to detect NAFLD**

| | | | NAFLD | | TOTAL |
|---|---|---|---|---|---|
| | | | NO | YES | |
| AAR | >1 | N (%) | 46 (62.2%) | 28 (37.8%) | 74 |
| | <1 | N (%) | 23 (31.5%) | 50 (68.5%) | 73 |
| Total | | N (%) | 69 (46.9%) | 78 (53.1%) | 147 |

| Statistics | Value | 95% CI |
|---|---|---|
| Sensitivity | 64.10% | 52.44 to 74.66 |
| Specificity | 66.67% | 54.29 to 77.56 |
| Positive Predictive Value | 68.49% | 59.96 to 75.94 |
| Negative Predictive Value | 62.16% | 53.90 to 69.78 |
| Accuracy | 65.31% | 57.02 to 72.96 |
| P Value | 0.000 | |

**Table 4: Diagnostic accuracy of USG in comparison to TE to detect NAFLD**

| | | | NAFLD | | TOTAL |
|---|---|---|---|---|---|
| | | | NO | YES | |
| Fatty liver on USG | NO | N (%) | 58 (62.4%) | 35 (37.6%) | 93 (100%) |
| | YES | N (%) | 11 (20.4%) | 43 (79.6%) | 54 (100%) |
| Total | | N (%) | 69 (46.9%) | 78 (53.1%) | 147 (100%) |

| Statistics | Value | 95% CI |
|---|---|---|
| Sensitivity | 55.13% | 43.44 to 66.41 |
| Specificity | 84.06% | 73.26 to 91.76 |
| Positive Predictive Value | 79.63% | 68.69 to 87.45 |
| Negative Predictive Value | 62.37% | 55.93 to 68.39 |
| Accuracy | 68.71% | 60.55 to 76.09 |
| P Value | 0.000 | |

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