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Original Research Article

Assessment of liver involvement in type 2 diabetes mellitus using fibroscan® and correlation with risk factors

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver injury. The most important predictor of mortality in NAFLD is the extent of liver fibrosis. Advanced liver fibrosis is associated with overall and liver related mortality. The upcoming non-invasive imaging modality for the evaluation of liver fibrosis is transient elastography (TE) (Fibro scan®). The aim of this study is to assess hepatopathy among diabetics using TE and to correlate the degree of hepatopathy with the associated risk factors.
Methods: Type 2 diabetes mellitus patients were assessed for liver stiffness using TE. Liver stiffness was correlated with the associated risk factors. Authors recruited 100 patients from diabetic clinic in tertiary care teaching hospital.
Results: About 55% of males and 39% of females had increased liver stiffness. 14% of males and 11% of females had severe fibrosis(F3-F4). Body mass index, waist circumference, fasting blood sugar levels, and liver enzymes, had significant positive correlation with liver stiffness whereas triglyceride levels, high-density lipoprotein levels, and duration of diabetes mellitus did not correlate with liver stiffness.
Conclusions: Diabetic patients have high prevalence of NAFLD and advanced fibrosis. Those with obesity and dyslipidaemia are at particularly high risk. Type 2 diabetes mellitus patients with hepatopathy can be easily identified using TE scan eliminating the need for liver biopsy. The establishment of a national program for the recognition of NAFLD is essential to reduce the risk of liver disease progression.

Keywords: Transient elastography, Fibro scan, Liver stiffness, Non-alcoholic fatty liver disease, Type 2 diabetes mellitus

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) causes serious hepatic damage and can lead to fibrosis, cirrhosis and liver cancer. NAFLD are especially frequent among patients with diabetes mainly type 2.

With India being the "Diabetes capital of the world", nonalcoholic fatty liver disease (NAFLD) is becoming the most common cause of liver dysfunction in the country.[1] It covers a wide spectrum, ranging from simple steatosis, which is generally non-progressive, to non-alcoholic steatohepatitis (NASH), that can progress to cirrhosis, liver failure, and hepatocellular carcinoma.[2]

The rates of severe liver fibrosis detected by Fibroscan are as high as 15% in patients hospitalized for diabetes. Identification of patients with advanced liver fibrosis helps them to be screened for complications, namely varices and hepatocellular carcinoma. Transient elastography (TE) [Fibro Scan®; Echosens, Paris, France] has been shown to be accurate in the estimation of

hepatic fibrosis without the drawbacks of liver biopsy, which is the gold standard.

Prevalence and factors related to the increased risk of NAFLD in diabetic patients in southern Tamil Nadu, India has never been studied before. Data regarding the profile of liver fibrosis in the population has also been unknown.

The purpose of the study was to assess the liver involvement among type 2 diabetes mellitus (T2DM) patients using TE and to correlate it with associated risk factors. The aims and objectives of this study authors to assess the hepatopathy among T2DM patients in southern Tamil Nadu based on liver stiffness using TE, to correlate the liver stiffness with the associated risk factors, namely, duration of diabetes, waist circumference, fasting triglyceride (TGL) levels high-density lipoprotein (HDL) levels, fasting blood sugar (FBS) levels ,body mass index (BMI), aspartate transaminase (AST) levels and alanine transaminase(ALT) levels.[2,3]

METHODS

A cross-sectional study was performed on the patients attending the diabetic outpatient department in Tirunelveli Medical College and Hospital, Tirunelveli, Tamil Nadu, India during October-November 2017. The sample size was 100.

Inclusion criteria

- Patients either newly diagnosed to have T2DM as per WHO[3]/ADA[4] criteria or on oral antidiabetic drugs.

Exclusion criteria

- Men consuming more than 20g of alcohol per day.[5]
- Women consuming more than 10g of alcohol per day.[5]
- Secondary cases of hepatic steatosis.
- Positive hepatitis B surface antigen or anti-hepatitis C virus antibody.
- Clinical and radiological evidence of other concomitant chronic liver diseases.

The study was approved by the institutional ethics committee. Patients attending the diabetic outpatient department satisfying the inclusion and exclusion criteria were recruited for the study after obtaining fully informed written consent. Consecutive sampling was performed.

Liver stiffness was assessed using Fibro scan-402® (M probe, Echosens, Paris) by an experienced examiner in all patients. Patients were in dorsal decubitus position, with the right arm in maximal abduction, above the head. After gel application, the probe was positioned perpendicular to the skin surface over one of the intercostal spaces adjacent to the right lobe of the liver (typically the 9th to 11th intercostal space, on the right mid-axillary line). A portion of the parenchyma free of large vessels, >6cm thick, was chosen; liver stiffness was measured at a depth of 25-65mm, in a 1 cm×4cm area. At least 10 valid measurements were obtained, with a success rate, defined as the number of valid acquisitions divided by the attempts, >60%, and a ratio of the interquartile range to the median of 10 measurements ≤0.3.

Risk factors

Duration of diabetes mellitus, waist circumference, fasting TGL, HDL, blood pressure, FBS, BMI, AST and ALT levels.

The IBM statistical package for the social sciences (SPSS®) version 20 was used for statistical analysis. Results were considered significant at $p<0.05$.

RESULTS

Authors considered 100 patients with T2DM satisfying the above criteria. 53 were males and 47 were females. The measurement of liver stiffness was successful in all the patients. 14% of male patients and 11% female patients had severe fibrosis according to a liver stiffness >8.7 kPa.

Using TE, cutoff values considered for F1 fibrosis was >5.6 kPa; F2 fibrosis was >6.65 kPa; F3 fibrosis was >8kPa; F4 fibrosis was >17 kPa.[6] The distribution of liver stiffness among males and females is shown in (Table 1).

Table 1: Liver stiffness measurement by transient elastography (Fibro scan®).

Fibrosis	Males (%)	Females (%)
F0	45	61
F1	29	20
F2	12	8
F3	11	6
F4	3	5

About 55% of males and 39 % of females had increased liver stiffness.14% of males and 11% of females had severe fibrosis (F3-F4).

The distribution of duration of diabetes among males and females is shown in (Table 2).

Table 2: Duration of diabetes in males and females.

Duration of diabetes	Males (%)	Females (%)
Newly diagnosed	6	3
<1 year	6	12
1 year to 5 years	45	35
5-10 years	25	32
>10 years	18	18

Waist circumference cutoff of 90cm for males and 85cm for females are used as the criteria for metabolic syndrome in the Indian population.[7] Among males, 48% had waist circumference >90cm and 52% had waist circumference <90cm. Among females, 56% had waist circumference > 85cm and 44% had waist circumference <85cm. The distribution of BMI among males and females is shown in (Table 3).

Table 3: BMI in males and females.

BMI (kg/m^2)	Males (%)	Females (%)
<18.5 Underweight	8	-
18.5-22.9 Normal	23	24
23-24.9 Overweight	30	18
≥25 Obese	39	58

The distribution of glycemic control among males and females is shown in (Table 4).

Table 4: Glycemic control among males and females.

Glycemic control	Males (%)	Females (%)
FBS<100mg/dL adequate	7	5
FBS:100-125mg/dL impaired	20	13
FBS≥126mg/dL poor	73	82

Among males, 45% had HDL<40mg/dL. Among females, 92% had HDL<50mg/Dl. Among males, 38% had TGL≥150 mg/dL. Among females, 57% had TGL≥150 mg/ dL

Correlation with risk factors

As the duration of diabetes increased, liver stiffness did not increase, as seen in (Table 5).

Table 5: Cross tabulation of duration of diabetes with liver stiffness.

Duration of diabetes	Liver stiffness					p value
	F0	F1	F2	F3	F4	
	Patients (%)					
Newly diagnosed	2	1	1			0.599*
< 1 year	5	1	1	1		
1 year to 5 years	22	9	5	4	1	
5 years to 10 years	14	7	2	2	3	
> 10 years	7	7	2	2	1	

*Pearson chi-squared test

As the waist circumference increased, liver stiffness significantly increased (correlation value =0.243, p=0.002). As the BMI increased, liver stiffness increased (p<0.01) as seen in (Table 6).

Table 6: Cross tabulation of BMI with liver stiffness.

BMI (Kg/m^2)	Liver Stiffness					p value
	F0	F1	F2	F3	F4	
	Patients (%)					
<18.5 Under weight	1	3				0.007*
18.5-22.9 Normal	17	3	1	1	1	
23-24.9 Overweight	11	6	5	1	1	
>=25 Obese	23	13	3	7	3	

*Pearson chi square test

Liver enzymes had mild but significant correlation (p<0.05) with increase in liver stiffness. FBS had significant correlation (p<0.001) with increase in liver stiffness. Triglycerides and HDL had no correlation with liver stiffness as seen in (Table 7).

Table 7: Correlation of metabolic parameters with liver stiffness.

Variables	Correlation value	P value
TGL	-0.015	0.897
HDL	0.093	0.428
FBS	0.568	<0.001
AST	0.276	0.017
ALT	0.282	0.014

DISCUSSION

Paralleling the increasing prevalence of obesity, diabetes mellitus, and the metabolic syndrome in the general population, NAFLD has become the most common cause of chronic liver disease worldwide.[8] Since liver fibrosis can be reversible, its early detection is fundamental.[9]

NAFLD indicates the presence of fatty infiltration of the liver, defined as fat exceeding 5-10 % of weight and frequently taken as >5-10% macrosteatotic hepatocytes.[10]

Ludwig J et al, coined the term NASH in 1980 to describe a cohort of middle-aged patients with elevated serum liver enzyme levels who had evidence of alcoholic hepatitis on liver biopsy specimens in the absence of alcohol consumption.[11] Matteoni CA et al, introduced the term "non-alcoholic fatty liver disease".[12]

Liver biopsy is the gold standard for the diagnosis of NAFLD. But it has several drawbacks: invasive, expensive, has poor acceptance, prone to inter-observer variability, has poor repeatability, and has a risk of rare but severe complications including hemorrhage and even death. Because a standard liver biopsy sample only represents approximately 1/50,000 of the whole liver mass, sampling bias may also occur, given the uneven distribution of fibrosis in the liver in patients with

NAFLD.[13] Stage of fibrosis is based on the 5-point scale proposed by Brunt et al, and recently modified by Kleiner et al.[14,15] Briefly, stage 0 = absence of fibrosis; stage 1 = perisinusoidal or portal fibrosis; stage 2= perisinusoidal and portal/periportal fibrosis; stage 3 = septal or bridging fibrosis; and stage 4= cirrhosis. With the high prevalence of NAFLD in the population and the majority having simple steatosis or low-grade NASH, liver biopsy may not be an appropriate investigation for many of these patients.[16]

TE is a dynamic quantitative technique, which uses acoustic waves ("thumps"-50Hz), generated by an external driver. The speed at which the low amplitude shear waves propagate through the liver parenchyma is correlated with liver stiffness, measured in kilopascals. It ranges from 2.5 kPa to 75 kPa; mean value in normal adults is 5.81±1.54 and 5.23±1.59 kPa, for men and women respectively.[17] Advantages include repeatability, rapid use, relative simplicity, ease of use, patient acceptance, more representative (TE assesses a sample area about 100 times bigger than a biopsy sample). Limitations include decreased accuracy in the setting of obesity, narrow intercostal spaces, extrahepatic cholestasis, hepatic venous congestion and acute inflammation. The obesity problem has been partially solved by the development of XL probe. Severity of fibrosis correlates with the histologic score of Brunt.[18]

Worldwide, the pooled prevalence of NAFLD in type 2 diabetes mellitus patients was 54%.[19] In India, according to SPRINT study conducted by Kalra S et al, the prevalence of the disease was found to be higher in females (60%) than in males (54.3%) T2DM patients; with prevalence of NAFLD varying from 44.1% in western India to 72.4% in northern states.[20] Mohan V et al, found using modified adult treatment panel III (ATP III) criteria that prevalence of NAFLD was 32% among urban South Indians.[21]

Present study, done in south India, shows a prevalence of 55% among males and 39% among females.14% of males and 11% of females had severe fibrosis (F3-F4).

Abnormal waist circumference was linked to higher prevalence of NAFLD, in the study done by Cheng PN et al.[22] Authors also found significant correlation of liver stiffness with waist circumference ($p<0.01$).

Yen YH et al, state elevated BMI as an independent factor associated with clinically relevant fibrosis in patients with metabolic risk factors associated with NAFLD.[23] Authors also found significant increase ($p<0.01$) in liver stiffness with BMI, findings which were compatible with those of previous studies.[24]

Mohan V et al, found that prevalence of NAFLD increases with increasing severity of glucose intolerance.[21] Present study also revealed that poor glycemic control has significant correlation ($p<0.001$) with increase in liver stiffness.

Prasetya IB et al, found that HDL and triglyceride levels do not show any significant association with NAFLD, nor was the duration of T2DM. Present study also showed similar results.[25]

Elevations in AST more than ALT has also been associated with more advanced fibrosis and are in part related to delayed clearance of AST relative to ALT or to mitochondrial injury associated with more advanced fibrosis.[26-28] Sanyal D et al, found that subjects with NAFLD had significantly higher ALT, AST than subjects without NAFLD.[29] Present study also points out that liver enzymes have mild but significant correlation ($p<0.05$) with increase in liver stiffness.[7]

CONCLUSION

About 55% of males and 39 % of females had increased liver stiffness. 14% of males and 11% of females had severe fibrosis (F3-F4). BMI, waist circumference, FBS, and liver enzymes had significant positive correlation with liver stiffness whereas TGL, HDL, and duration of diabetes did not correlate with liver stiffness. Introduction of transient elastography in clinical practice may reduce the proportion of patients who require liver biopsy to diagnose mild disease. The establishment of a national program for the recognition of NAFLD is essential to reduce the risk of liver disease progression.

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