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Assessment of Liver Stiffness by Transient Elastography in Diabetics with Fatty Liver – A Single Center Cross Sectional observational Study

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Abstract
Background:*Non-alcoholic fatty liver disease (NAFLD) is emerging as a significant cause of chronic liver disease among patients with otherwise no risk factors for cirrhosis. Diabetes mellitus is an important predisposing factor for development and progression of NAFLD. Assessment of liver stiffness by transient elastography in Diabetic patients with fatty liver could provide a non-invasive estimate of the presence of underlying liver disease at a fairly early stage.*
Aim: *To assess the prevalence of the various stages of liver fibrosis in patients with Type 2 Diabetes mellitus and fatty liver on ultrasonography and to study its correlation with biochemical and metabolic parameters****Materials and methods:*** *Overall 60 patients (age group 20-80 years) with history of Diabetes mellitus and evidence of fatty liver on ultrasonography were enrolled in the study. They underwent biochemical evaluation and their liver stiffness was assessed with Transient Elastography. The liver stiffness measurements of the patients were analysed and correlated with clinical and biochemical parameters*
Results: *Significant proportion of patients with Diabetes mellitus and fatty liver had higher degrees of fibrosis as assessed by Transient Elastography. The BMI, AST, ALT, FBS and TGL levels were significantly higher in the groups of patients with higher degrees of fibrosis (F3/F4).*
Conclusion:*Among Diabetic patients with fatty liver disease, higher degrees of liver fibrosis was seen in a significant number of patients. Transient Elastography is an effective non-invasive tool for assessing extent of fibrosis in patients with Diabetes mellitus and Fatty liver.*
Keywords:*Diabetes Mellitus, Fatty liver, Fibrosis, Transient Elastography*

I. Introduction

Non-alcoholic fatty liver disease represents a spectrum of conditions characterized histologically by macrovesicular hepatic steatosis, steatohepatitis and cirrhosis and occurs in those who do not consume alcohol in amounts generally considered to be harmful to the liver. NAFLD is associated commonly associated with obesity, Type 2 Diabetes Mellitus, dyslipidemia and insulin resistance, all that are features of metabolic syndrome. The prevalence of NAFLD in Diabetic patients is estimated to be around 40 – 75% with regional and gender based differences[1]. Type 2 Diabetes Mellitus patients with NAFLD, when compared to non-diabetic patients, have a higher chance of fibrosis and have greater risk of progression to cirrhosis. Studies have shown that presence of fatty liver in diabetics may be associated with an increase in the cardiovascular risk and general mortality

For monitoring prognosis of patients with NAFLD, assessment of liver fibrosis is essential especially among high risk patients such as diabetics. Liver biopsy is the gold standard for evaluation of liver fibrosis but has potential disadvantages in being invasive, painful and associated with life-threatening complications and hence cannot be routinely be applied to all patients with NAFLD for assessing of liver fibrosis. Several non-invasive methods for assessment of liver fibrosis are now available, one among which is Transient Elastiography. TE is a non-invasive, easy and repeatable modality which allows rapid, reliable and accurate assessment of liver stiffness thus making possible appropriate staging of liver disease and can effectively reduce the number of cases being referred for liver biopsy.In the present study, we decided to assess the pattern of liver stiffness in diabetic patients with fatty liver on ultrasonography and to study the correlation with clinical and biochemical parameters

II. Materials And Methods

In this descriptive epidemiological study, patients referred to the Gastroenterology out-patient clinic at Government peripheral hospital were included from August 2016 to March 2017. Inclusion criteria were patients with history of Diabetes mellitus at least 1 year duration with evidence of fatty liver on Ultrasonography between age 20 and 80 years of age, negative viral hepatitis and HIV serologies, consuming less than 20 grams of alcohol per day in the past one year and exclusion of Wilson's disease and auto immune hepatitis. The exclusion criteria were BMI $\geq$ 30, taking medications known to cause fatty liver (such as corticosteroids, estrogen, amiodarone, etc.), history of IV drug abuse, extra hepatic cholestasis (based on ultrasound or bilirubin $\geq$ 5) and evidence of focal liver mass in ultrasonography.

Demographic data of all patients were collected (including age, gender, duration of diabetes, age of onset of diabetes, BMI, medication history (DM and non-DM), alcohol consumption, past history of jaundice, blood transfusion or surgery, associated diseases). Patients underwent biochemical investigations (LFTs, FBS, PPBS, Lipid profile) and viral serology. Transient elastography was performed for all patients using M probe with the patient in fasting state. The test is performed with the patient in the supine position with the right arm completely abducted and the breath held in inspiratory apnea. The target liver tissue was selected using ultrasound guide and vibrating waves sent to the liver. For each patient, measurement was done 5 times and the mean was calculated. The liver stiffness measurement was expressed in terms of kilopascal (kPa).

The values obtained for liver stiffness were compared with the clinical and biochemical parameters of the patients. Data obtained were analysed using SPSS version 19. Chi square test was used to compare demographic data; ANOVA was used to compare the liver stiffness, liver biochemistry, lipid profile and BMI in the groups. Significant levels in this study were considered as ≤ 0.05

III. Results

A total of 112 diabetic patients with fatty liver were enrolled in the study during the designated study period. Among whom 52 patients were excluded due to significant alcohol use, positive viral serologies or BMI > 30 (as siginificant subcutaneous fat led to interference with waves from the M probe) or due to intake of medications causing fatty liver (steroids, estrogens). The remaining 60 patients were included in the study and their clinical, biochemical parameters and liver stiffness were analysed. The mean age of the patients included in the study was 54.12 (± 11.394). The other parameters were analysed and tabulated. (Table 1)

Table 1: Demographic and biochemical data of patients included in the study

Gender Male Female	 24 (40%) 36 (60%)
Duration of Diabetes mellitus (years)	7.38 (± 4.203)
Age at onset of Diabetes mellitus (years)	46.37 (± 10.17)
Medication history Single OHA Multiple OHAs Insulin±OHA	 27 (45%) 21 (35%) 12(20%)
BMI	26.602 (± 2.427)
T. Bil	0.803 (± 0.399)
AST	34.22 (± 16.475)
ALT	35.97 (± 19.798)
Fasting Blood Glucose	155.53 (± 35.836)
T. Cholesterol	192.10 (± 25.040)
Triglycerides	169.70 (± 42.14)
Ultrasonography Fatty liver Grade I Grade II	 59(98.3%) 1 (1.7%)
Liver Stiffness score	7.95 (± 4.102)

The distribution of the patterns of fibrosis among the patients was noted (Figure 1) and it was found that 34% patients had significant liver stiffness on fibroscan (F3/F4) while 28% had no fibrosis on fibroscan.

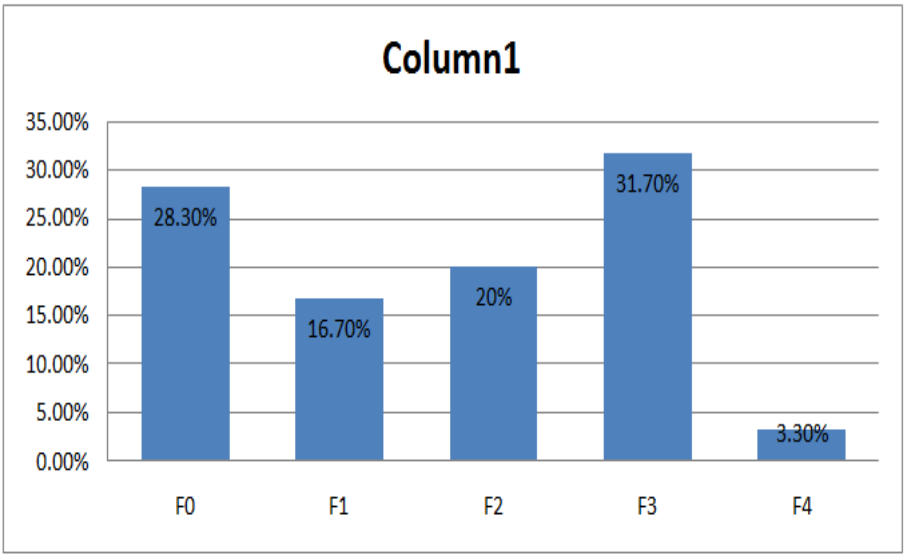

Figure 1: Frequency of the stages of fibrosis among the patients screened

The mean values of the liver stiffness measurements were calculated for both genders and it was found that there was no significant difference in the liver stiffness between male and female patients with diabetes mellitus and fatty liver. (Table 2)

Table 2: Comparison between mean scores of liver stiffness in both gneders

	Mean score of liver stiffness	P value
Gender	Mean ± SD	0.64
Male	7.60 ± 4.53	
Female	8.18 ± 6.37	

The clinical and the biochemical parameters among the different categories of fibrosis were anlaysed and it was found that the difference was significant for BMI, AST, ALT, fasting blood sugar and TGL levels. (Table 3)

Table 3: Comparison of clinical and biochemical parameters between the liver stiffness groups

	F0	F1	F2	F3	F4	P value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age	55.35 ± 10.03	53.70 ± 9.10	51.58 ± 11.55	54.16 ± 14.16	60.50 ± 6.364	0.848
Duration of Diabetes	6.24 ± 3.75	8.10 ± 3.48	7.17 ± 4.67	7.68 ± 4.24	12.01 ± 8.48	0.401
Age of onset of Diabetes	49.12 ± 9.67	45.60 ± 9.37	44.42 ± 10.69	45.32 ± 10.96	48.50 ± 2.12	0.731
BMI	25.12 ± 2.14	25.54 ± 2.05	27.99 ± 1.97	27.43 ± 2.34	28.25 ± 2.05	0.002
AST	26.24 ± 6.25	34.10 ± 22.54	30.58 ± 13.22	42.26 ± 17.72	48.10 ± 19.80	0.027
ALT	23.71 ± 10.51	29.40 ± 13.02	33.67 ± 15.42	50.95 ± 23.18	44.50 ± 9.19	0.001
FBS	132.94 ± 30.25	140.80 ± 34.70	167 ± 39.63	176.63 ± 25.45	152.01 ± 21.21	0.001
T. Chol	191.76 ± 18.45	187.90 ± 38.63	193. 02 ± 31.48	193.21 ± 19.13	200 ± 16.97	0.971
TGL	147.59 ± 39.65	171.30 ± 37.73	176.75 ± 44.90	178.63 ± 39.29	222.50 ± 30.40	0.050

Based on the AST/ALT ratio, patients were divided into 2 groups: AST/ALT ratio < 1 (29 patients) or > 1(30 patients) and the mean liver stiffness measurements were compared between the two groups and it was not found to be statistically significant (Table 4)

Table 4: Comparison of liver stiffness based on the AST/ALT ratio

	Mean score of liver stiffness	P value
AST/ALT ratio	Mean ± SD	0.71
< 1 (29/60)	8.6 ± 5.73	
>1 (31/60)	7.34 ± 4.68	

The correlation of liver stiffness with clinical parameters was calculated using Pearson's correlation and the liver stiffness were found to have a statistically significant positive (but weak) correlation with BMI, AST, ALT, FBS and TGL levels (Table 5)

Table 5: Assessment of correlation of liver stiffness with clinical and biochemical parameters

	Pearson's correlation coefficient	P value
Age	0.052	0.690
Duration of Diabetes	0.179	0.171
Age of onset of Diabetes	-0.023	0.860
BMI	.273	0.035
AST	0.386	0.002
ALT	0.421	0.001
FBS	0.254	0.050
T. Chol	0.091	0.491
TGL	0.371	0.004

IV. Discussion

The results of the present study conducted in patients with Diabetes mellitus and fatty liver show that liver stiffness measurement by Transient Elastography is an effective non-invasive method for assessment of liver fibrosis in NAFLD. Our findings indicate that in Diabetic patients with sonographic evidence of fatty liver, a significant proportion of patients had higher degrees of fibrosis as shown by liver stiffness measurements by Transient Elastography. In addition, our study shows that age, gender, duration of diabetes, age at onset of diabetes and cholesterol levels were not associated with the degree of fibrosis while the BMI, AST, ALT, FBS and TGL levels had a significant correlation with the degree of fibrosis as assessed by liver stiffness measurements.

In a multicenter study by Kalra et al conducted in 2013 (Sprint) in India, it was found that the prevalence of NAFLD in the population was 56.5% of Diabetic patients were found to have NAFLD, with a higher incidence in females, advanced and in patients with elevated and borderline elevated aminotransferases. However the extent of fibrosis was not assessed in this study either by biopsy or by other non-invasive methods.

A study by Prashanth et al in 2009, showed that in Diabetic patients with fatty liver, liver biopsy revealed fibrosis in 37.3% of patients. While the absence of correlation of age, duration of Diabetes did not correlate with degree of inflammation and fibrosis were seen similar or our study the difference was that the aminotransferases were within normal limits (but significantly higher) and were associated with steatohepatitis thought the association with fibrosis was not studied. Also unlike our study BMI did not show a correlation with the severity of NAFLD while the AST/ALT ratio was significantly higher in the severe fibrosis group.A study by Amarapurka et al in 2006, conducted on patients with Diabetes and biopsy proven NASH it was shown that though there were no definitive predictors of liver fibrosis, Ast, Alt And Ast/alt ratio may help to determine the extent of fibrosis in NASH patients.It has been shown by several studies in the past that Transient elastography is a reliable, non-invasive, rapid and reproducible method of estimating the extent of liver fibrosis in liver disease due to any etiology thereby reducing the necessity if performing a liver biopsy.

In a study conducted by Pathik et al in 2015 (2), in high risk non-alcoholic fatty liver patients it was found that in predicting the risk of fibrosis by imaging and non-invasive methods, it was found that transient elastography was an effective tool in detecting as well as assessing the extent of fibrosis. In this study, it was found that among the patients with fatty liver those who had a history of diabetes were more likely to have higher degrees of fibrosis on liver biopsy. This study showed that a liver stiffness cut-off value of 12 kPa (by transient elastography) had 90% sensitivity, 80% specificity, 72% PPV and 93% NPV in predicting stage 3 or 4 fibrosis. Unlike our study, the levels of transaminases, BMI or lipid profile did not have a statistical difference among the various stages of fibrosis in those who underwent liver biopsy. Similar to our study, the AST/ALT ratio did not have a significant difference in terms of the stages of liver fibrosis in this study.In a comparative study conducted by Hajiani et al in 2014 (1) between diabetic and non-diabetic patients with fatty liver, there was no statistical difference between the two groups in terms of age, BMI, lipid profile, and liver enzymes. However similar to our study it was shown that levels of AST, ALT and TGL had a statistical significant association with the degree of fibrosis while the FBS and BMI did not correlate with the degree of fibrosis in the diabetic patients group.

Diabetes mellitus is associated with the insulin resistance, increased visceral adipose tissue and hence predisposes hepatic steatosis and by virtue of inflammation and oxidative stress leads on to steatohepatitis and fibrosis eventually culminating in cirrhosis and hepatocellular cancer. In view of the chronic nature of this pathogenetic mechanism, early identification of fibrosis in patients with Diabetes mellitus and fatty liver will serve to isolate patients at high risk of cardiovascular as well as liver related mortality and help in their monitoring and therapy.

Liver biopsy though being the gold standard for assessing the degree of inflammation and fibrosis is met with potential disadvantages of being invasive, being associated with life threatening complications (though at a negligible) and hence cannot be applied to the vast majority of patients with NAFLD. The absence of clinical and biochemical parameters to accurately predict the presence of fibrosis necessitates a non-invasive modality to reliably assess the liver fibrosis. Transient elastography is a non-invasive, rapid, reliable and reproducible method for assessment of the extent of liver fibrosis in patients with Nalfd

Our study is not without limitations. First the sample size is small. Considering the larger prevalence of Nafld in the population, larger studies with Transient elastography can help in further establishing the role in liver stiffness measurement. Second though the superiority of transient elastography in assessing liver fibrosis has been validated in several studies, in our study it has not been compared with other non-invasive modalities. Third our study was a single centre cross sectional study. Follow-up of patients with higher degrees of fibrosis will further help in understanding the natural course of disease and also help in modifying therapy.

V. Conclusion

Given the widespread prevalence of NAFLD, significant presence of advanced fibrosis in most of the patients and absence of definite predictors of fibrosis, Transient elastography is a reliable method for screening and detection of liver fibrosis in diabetics with fatty liver; thereby paving way monitoring and aggressive treatment options with which disease progression could be controlled and complications of cirrhosis and hepatocellular carcinoma prevented.