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Original Research Article

Relationship between grey scale sonographic grades of fatty liver and shear wave elastographic values: an observational study

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ABSTRACT

Background: Due to the growing public health menace of metabolic syndrome, the Non-Alcoholic Fatty Liver Disease (NAFLD) has been recording a burgeoning global rise. The prognosis of NAFLD is largely depends upon its histological stage. Simple steatosis has a fairer prognosis, while Non-Alcoholic Steatohepatitis (NASH) has a poorer prognosis with tendency to progression into fibrosis and end stage liver disease. Until now, the diagnosis of varying grades of NAFLD has been dependent upon liver biopsy, which is indisputably the most reliable tool to distinguish between simple steatosis, steatohepatitis, and end stage liver disease. The sonographic grading of NAFLD is primarily based on subjective findings, the results of which may vary between different observers. Hence, there is a need to identify a reliable non-invasive objective substitute. To compare the sonographic grades of fatty liver on gray scale with liver stiffness (Kpa) values of shear wave elastography. Also, an attempt to establish objective criteria for grading of fatty liver with improved accuracy and increased specificity.
Methods: Cross sectional, observational study comprising of 240 adults referred for routine abdominal sonography. All patient underwent gray scale sonography and shear wave elastography and results were analysed.
Results: A significant positive correlation was found between various grades of NAFLD as assessed subjectively on grey scale sonography to the liver stiffness in kilopascal (Kpa) using shear wave elastography.
Conclusions: Shear wave elastography being an objective imaging tool is a reliable modality compared to grey scale sonography in diagnosis of NAFLD and has the capacity to carry out quantitative evaluation of liver parenchyma in vivo.

Keywords: Fatty liver, Non-alcoholic fatty liver disease, Non-alcoholic steatohepatitis, Shear wave elastography

INTRODUCTION

The non-alcoholic fatty liver disease (NAFLD) is on a global rise with prevalence rates of 15-30% in the western population and 9-32% in Indian population.[1,2] Spectrum of disorders ranging from simple steatosis to lobular inflammation with variable degrees of fibrosis, non-alcoholic steatohepatitis (NASH), NAFLD can be a forerunner of cirrhosis and hepatocellular carcinoma, conditions associated with grave clinical outcome.[3-5] The prognosis of NAFLD depends on histological stage. Simple steatosis with benign slow progression has a better prognosis while NASH has poor prognosis because of its early progression into end stage liver disease. Hence, the pivotal issue in the management of patients with NAFLD is the diagnosis of steatohepatitis and fibrosis at an early possible stage.

Although, liver biopsy is indisputably the gold standard for diagnosing NAFLD, being an invasive technique biopsy carries its own limitations.[4] The preferred first line of investigation among clinicians for making the diagnosis of a fatty liver disease, therefore continues to be noninvasive methods such as serum markers and imaging modalities like gray scale ultrasonography.

Gray Scale Sonography (USG), a subjective and qualitative assessment has been the most common modality used in the evaluation of a fatty liver.[6] It is safe, radiation-free, easily available, inexpensive and cost-effective and can determine the fatty infiltration of liver based on increased echogenicity of the liver parenchyma.[5,6]

Gray scale sonographic assessment of changes in echogenicity of liver only allows a semi quantitative estimation of the degree of hepatic steatosis and suffers from the lacuna that it cannot make with precision a histopathological quantification of steatosis.

The newer elastographic technique allows for objective assessment of tissue parenchyma based on a physical parameter that measures tissue elasticity or stiffness in kilopascal (kPa). It gives indirect information about pathological alterations like inflammation and fibrosis.

The elastography technique has also been evolving over time. Commencing with conventional transient elastography (TE), it has now transited to shear wave elastography. The latter has advantage of being quantitative with advantage that it does not require separate equipment and can be combined with a conventional US, thus saving time and cost.[7]

It can be performed quickly in 2-5minutes as a part of routine liver sonographic examination. It is operator independent, reproducible, carries high spatial resolution, and has the ability to perform a quantitative evaluation of elasticity in kPa without manual compression artefacts.

The present study was carried out to assess the liver stiffness in fatty liver disease with shear wave elastography and further to correlate these liver stiffness values with gray scale sonographic grades of fatty liver, to determine if elastography can act as a reliable non-invasive tool to grade NAFLD.

METHODS

A cross sectional observational study was carried out in the Department of Radiodiagnosis, VMMC and Safdarjung Hospital in a period of 18months (September 15 to March 16). 240 subjects were recruited in this study group among which 105 were males and 135 were females. Chronic alcoholics and patients with concurrent splenomegaly, SOL of liver and ascites were excluded. Routine transabdominal hepatic sonography using Phillips Iu22 scanner were performed in all the subjects and were graded as grade 0, 1, 2 and 3 (Figure 1) based on the echotexture of liver.[8-10]

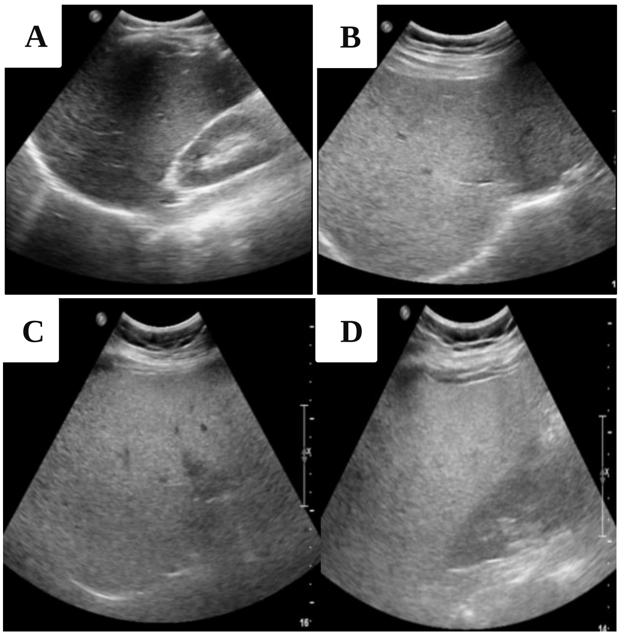

Figure 1: Grey scale sonographic image of normal liver and various grades of fatty liver. A) Grade 0/normal, B) Grade I, C) Grade II, D) Grade III.

Grade 0: Normal (Figure 1A).

Grade 1: Mild diffuse increase in liver echogenicity with clear visualization of diaphragm and intrahepatic vessels (Figure 1B).

Grade 2: Moderate diffuse increase in liver echogenicity obscuring the intrahepatic vessels and diaphragm (Figure 1C).

Grade 3: Gross increase in liver echogenicity with poor/non-visualization of intrahepatic vessels and diaphragm (Figure 1D).

ARFI shear wave elastography of the different segments of liver was performed following grey scale USG using linear array transducer of 3-5MHz frequency on the Phillips iU22 US scanner. The right lobe of the patient was examined in left lateral decubitus with the right arm in maximum abduction. The left lobe was examined in supine position with right and left arm in maximum abduction. Scanning was performed with minimal scanning pressure applied by the operator while the patients were asked to stop breathing for a moment in order to minimize breathing motion. All measurements were performed by the same radiologist and reported in kilopascals.

The tip of the transducer was covered ultrasound gel and was placed on the skin smoothly without compressing the tissue. Total of eight readings in kPa were taken at various sites to assess stiffness. Mean of quantitative values of liver stiffness was taken (Figure 2). Categorical variables were presented in number and percentage (%)

and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non-parametric test was used. Quantitative variables were compared using ANOVA/Kruskal Wallis Test (when the data sets were not normally distributed) between the groups. Qualitative variables were correlated using Chi-Square test /Fisher's exact test.

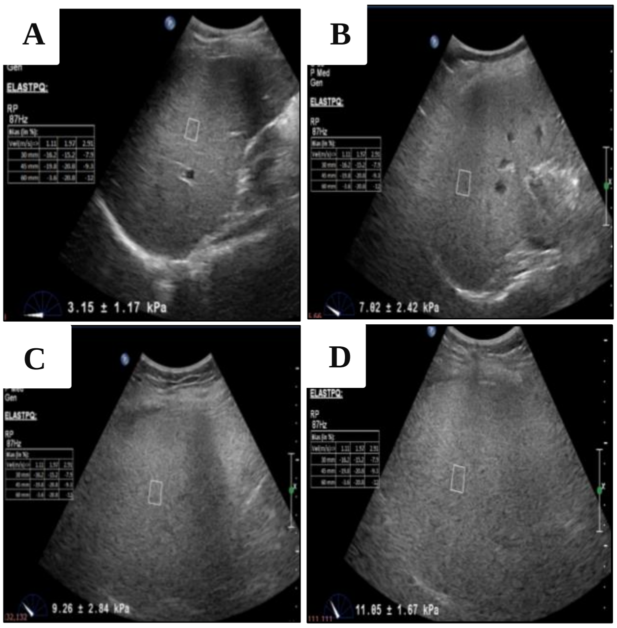

Figure 2: Shear wave elastography of the same patients as in Figure 1 showing mean stiffness values (kPa) for normal liver and various grades of fatty liver. A) Grade 0 (3.98), B) Grade I (7.48), C) Grade II (9.78), D) Grade III (1.32).

Mean liver stiffness for each grade of fatty liver was obtained (Figure 2). Correlation between various grades of fatty liver and liver stiffness was done with Pearson's correlation (r). Various other parameters obtained were also correlated using the same. The test results were expressed by the correlation coefficient (r) and level of significance (P) with the level of statistical significance being $P \leq 0.05$. Receiver operating characteristic (ROC) curves was plotted, and the area under the curve (AUC) was calculated to assess the optimal cut off value to diagnose fatty liver. Sensitivity, specificity, PPV and NPV of shear wave elastography to diagnose fatty liver was also obtained.

RESULTS

Among 240 subjects aged between 23 and 72 years (mean age: 42.97±10.66), majority of them were females 135 (56.25%) and 105 (43.75%) were males.

In the study, most common form after the normal liver echo texture Grade 0 (33.3%) on grey scale were the Grade I and II (48.34%) fatty liver. Distribution of subjects in various grades of fatty liver based on subjective assessment on grey scale sonography was tabulated in Table 1. The mean BMI in all the grades of fatty liver were also obtained and assessed for correlation with each grade of fatty liver and p-values were obtained. The mean BMI of normal subjects was found to be 23.7±1.8.

Table 1: Distribution of subjects in various grades of fatty liver showing frequency and percentage distribution of subjects in sonographic grades of fatty liver.

Sonographic grades	Frequency	Percentage
Grade 0	80	33.33%
Grade 1	58	24.17%
Grade 2	58	24.17%
Grade 3	44	18.33%
Total	240	100%

On objective assessment of liver parenchyma using shear wave elastography, the mean liver stiffness (shear modulus) for normal subjects was found to be 5.07±1.73 kPa with increasing mean liver stiffness with increasing grades of fatty liver. Mean liver stiffness on shear wave elastography in various grades of fatty liver is tabulated in Table 2 and depicted in Figure 3.

Table 2: Mean liver stiffness (kPa) on shear wave elastography with interquartile range (kPa) in various grades of fatty liver.

Sonographic grades	Mean stiffness (kPa)	Interquartile range (kPa)
Grade 0	5.07	3.85-5.84
Grade 1	6.84	5.46-7.94
Grade 2	9.43	8.72-10.16
Grade 3	11.96	10.21-13.55

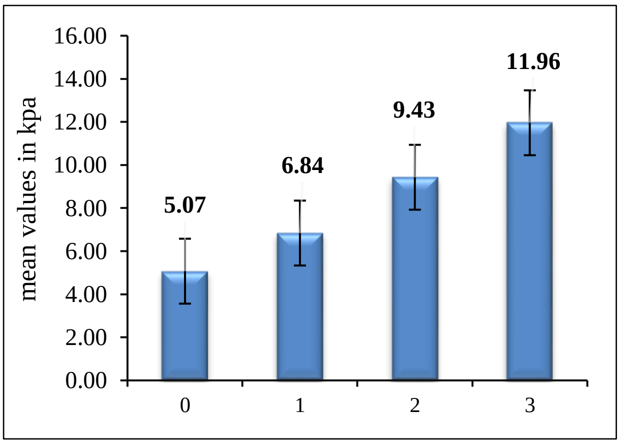

Figure 3: Mean liver stiffness values in kPa on shear wave elastography in various grey scale sonographic grades of fatty liver.

On comparing between subjective and objective assessment on grey scale sonographic grades of fatty liver and liver stiffness on shear wave elastography respectively, a significant correlation was found with correlation coefficient to be 0.822 (p value <0.0001) as shown in Figure 4.

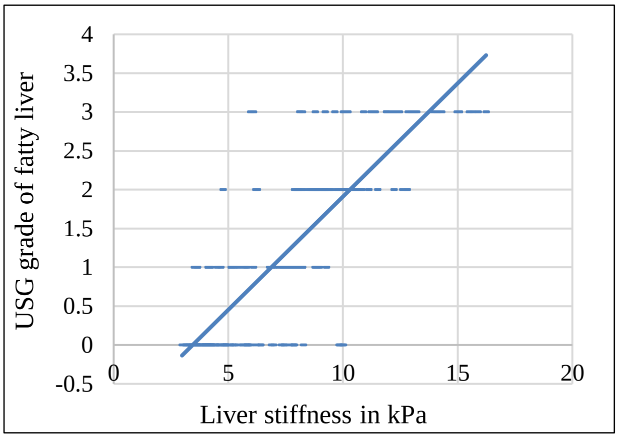

Figure 4: Statistical correlation between grey scale sonographic grade of fatty liver and liver stiffness on SWE showing strong positive correlation (correlation coefficient of 0.822).

Statistically significant correlation was found between mean values of liver stiffness in various grades of fatty liver (p value <0.0001). However, there was no significant statistical difference between mean liver stiffness values obtained for males and females among normal subjects (p value=0.172) and for each age group among normal subjects (p value=0.887).

A significant positive correlation was found between BMI and liver stiffness with correlation coefficient of 0.43 (p value= <0.0001) and also there was statistically significant positive correlation between BMI and sonographic grades with correlation coefficient of 0.342 (p value = <0.0001).

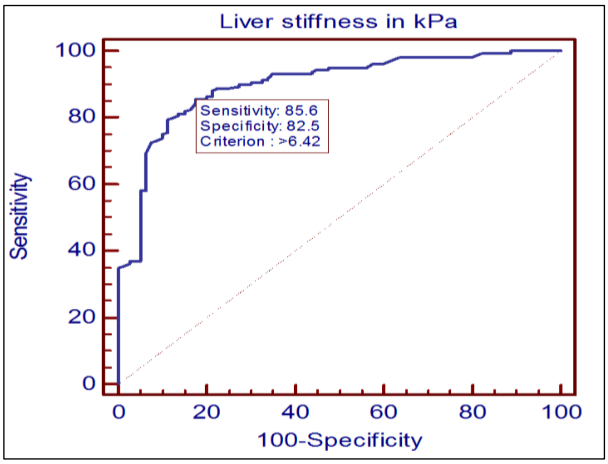

Figure 5: ROC (Receiver operating characteristic) curve: maximum accuracy of liver stiffness for diagnosis of fatty liver at a cut off value of 6.42kPa with sensitivity of 85.62% and specificity of 82.5%.

On statistical analysis of liver stiffness in 240 subjects, in various form of fatty liver the maximum accuracy of liver stiffness for diagnosis of fatty liver was found at a cut off value of 6.42 kPa (Figure 5).

For a cut off value of 6.42 the sensitivity was 85.62%, specificity was 82.5%, positive predictive value was 90.73% and negative predictive value was 74.16%.

The results of statistical measure of performance are depicted and tabulated in Table 3. The AUC value for the ROC curve was 0.899 (p <0.001, α of 0.05).

Table 3: Statistical measure of performance at a cut off value of 6.42kPa showing maximum accuracy for liver stiffness in diagnosis of fatty liver.

Statistic	Value	95% C.I
Sensitivity	85.62%	79.22-90.66%
Specificity	82.50%	72.38-90.09%
PPV	90.73%	84.93-94.84%
NPV	74.16%	63.7-82.86%

The interrater agreement of subjective and objective assessment on grey scale USG and shear wave elastography was found using a cut off of 6.42 (maximum accuracy as determined by the ROC curve for liver stiffness) for the diagnosis of fatty liver was analyzed using Cohen's kappa from the values obtained for liver stiffness is tabulated in Table 4. The kappa agreement in this study between two diagnostic modalities i.e. grey scale sonography and shear wave elastography in diagnosis of NAFLD was found out to be 0.663 (κ value) indicating good agreement which was lesser than previous study where κ value in their study was 0.87 (very good agreement).[11] In this study, the sensitivity and specificity of shear wave elastography in diagnosis of fatty liver was found to be 85.6% and 82.5% respectively with AUC for ROC curve 0.899 which was slightly lesser than the previous study.[11]

Table 4: Interrater agreement i.e. Cohen's kappa calculated between grey scale sonographic grades of fatty liver and shear wave elastography-Cohen's kappa: 0.663.

Stiffness	Normal	Fatty liver	Total	P value	
<6.42	66 (27.50%)	23 (9.58%)	89 (37.08%)	P< 0.0001	Kappa 0.663
>6.42	14 (5.83%)	137 (57.08%)	151 (62.92%)		
Total	80 (33.33%)	160 (66.67%)	240 (100%)		

DISCUSSION

NAFLD, hepatic manifestation of the metabolic syndrome is a commonly encountered condition. It may cause early parenchymal damage due to associated inflammation and fibrotic changes resulting increase in increased liver parenchymal stiffness. Biopsy, an invasive investigation, continues to be the gold standard to assess degree of liver parenchymal damage and amount of liver fibrosis using a histological score (METAVIR Score) in NAFLD. Previous studies have shown that there is linear correlation between degree of hepatic steatosis as observed by grey scale USG with METAVIR score.[12]

The role of USG in NAFLD is for grading of fatty liver based on increase in echotexture. However, the disadvantage is that it is subjective, operator dependent, high inter and interobserver variation with low sensitivity and specificity.

It has been established in previous studies that the liver stiffness is directly proportional to degree of fibrosis. The shear wave elastography helps to diagnose, quantify steatosis as well as indirectly assess degree of fibrosis and inflammation in NAFLD can be used as primary modality for diagnosis and accurate quantitative grading of fatty liver.

In this study, author used shear wave elastography for diagnosis and quantification of fatty liver as well as compare the same with grey scale finding. The mean liver stiffness in normal subjects was found to be 5.07kPa. This is consistent with normal stiffness values given by previous studies conducted by Hyun C et al, Suh CH et al, Huang Z et al, and Arda K et al.[13-15] The mean liver stiffness in grade 1 fatty liver (6.84kPa) is higher than that of grade 0 or normal liver (5.07kPa) in this study, which is in conflict with studies conducted by Yoneda M et al, where there was lower stiffness in mild steatosis as compared to normal liver likely.[16] In this study, there is rise in liver stiffness with increase in severity of fatty infiltration. The mean liver stiffness in grade 1, grade 2 and grade 3 fatty liver was found out to be 6.84kPa, 9.43kPa and 11.96kPa respectively which is consistent with study done by Li YY et al, and on further statistical analysis it was also found out that there is positive correlation between rise in liver stiffness with increasing grade of fatty liver with correlation coefficient of 0.822. This can be explained by advancing levels of fibrosis, presence and increasing level of inflammation with hepatocyte ballooning with increasing grade of hepatic steatosis.

Among normal subjects mean liver stiffness in females (5.34kPa) was higher as compared to males (4.82kPa) which is in conflict with the study conducted by Huang Z et al, where normal liver stiffness was greater in males (5.45kPa) than in females (4.89kPa) likely due to poor nutrition and multiple pregnancy in females.[14]

No correlation between age and liver stiffness was found which was consistent with previous studies, however author found a significant positive correlation between BMI and grades of fatty liver and also between BMI and liver stiffness with correlation coefficient of 0.342 and 0.43 respectively and was similar to study conducted by Abangah G et al, in which there was a positive correlation between BMI and fatty liver.[16,17]

Grading of fatty liver was done subjectively by the grey scale ultrasound by a single radiologist. Hence, inter-observer and intra-observer variation could not be evaluated.

In this study, the subjects were from a homogenous population of Indian adults, whether the results from this study can be extrapolated to other ethnic groups remain to be further validated.

CONCLUSION

Shear wave elastography being an objective imaging tool for diagnosis of NAFLD has the capacity to carry out quantitative evaluation of liver parenchyma in vivo by assessing the liver stiffness in kilopascals (kPa). It appears to be a reliable, non-invasive, easy and quick substitute for biopsy and is reproducible, quantitative substitute for grey scale ultrasonography.

In patients with NAFLD, change in liver stiffness as measured by ARFI shear wave elastography have linear relationship with grey scale sonographic grades of fatty liver which was likely due to underlying inflammatory change and fibrosis with increase in fat deposition. A cut off value of 6.42kPa has moderately high sensitivity and specificity for diagnosis of NAFLD using ARFI shear wave elastography.

However, larger clinical prospective studies are recommended to validate accuracy of shear wave elastography and to establish threshold values for various grades of fatty liver with histopathological confirmation.

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