How Good Is Trans Abdominal Ultrasound for Evaluating NAFLD in the General Population? A Cross-Sectional Study

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Abstract- Nonalcoholic fatty liver disease (NAFLD) is one of the most common cause of liver test abnormality and chronic liver disease in the world and can increase liver related mortality. Association of NAFLD with metabolic syndrome increase mortality due to cardiovascular disease too. NAFLD is categorized histologically into the nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Liver biopsy has been known as gold standard of evaluating NAFLD, but this procedure is invasive. It is time to replace available and easier way to diagnose, and predict the prognosis for better management of NAFLD. This study was comparing the result of transabdominal ultrasonography with Fibroscan as a new and accurate method for evaluating severity of fatty liver disease. This was a cross-sectional study that was conducted using 101 patients with NAFLD. All patients who had TUS by one experienced radiologist and fibro scan at the same time were included. Visual liver echogenicity was basis of grading in TUS. Fibro scans results are based on controlled attenuation parameters (CAP) which is not operator dependent. Other information, such as age, waist, and BMI, were also gathered. TUS has a low value for the diagnosis of liver fibrosis in NAFLD patients and predicting prognosis. TUS has a good correlation with fibroscan in grade 0 and 1of fatty liver, but in grade 2 and 3 of fatty liver, we can not rely on TUS for accurate grading.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver disease in the world. According to various publications, NAFLD is associated with an increase in the probability of liver related morbidity and mortality and of cardiovascular heart disease and diabetes. The prevalence of NAFLD in the adult population worldwide ranges around 10 to 35 percent, being the highest in males, although the prevalence among females increases after menopause (1). In other studies, the prevalence of NAFLD in the USA was estimated to be 30%, and in Italy, 25%; it seems this condition is the main cause of abnormal liver enzymes (2). In a systematic review and meta-analysis, the Middle East and South America have the highest prevalence of NAFLD (3). A study in Iran showed that the prevalence of NAFLD was 21.5%. It was also confirmed in 31% of autopsy cases in another city of Iran (4,5). NAFLD is more common in patients aged 40 to 49, but it can be found in any age group (2).

The American College of Gastroenterology and the American Gastroenterological Association categorized NAFLD histologically into the nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Nonalcoholic fatty liver disease is liver steatoses with no injury to the hepatocellular, whereas nonalcoholic steatohepatitis (NASH) is with the hepatocellular injury with or without fibrosis.

There are different tests with different sensitivities and specificities for the diagnosis of liver disease. Among these tests and methods, liver biopsy (LB) has been known as a reference for diagnosis and grading of NAFLD. LB is an invasive procedure with some disadvantages for patients rather than this precision to find the steatosis disease. Some disadvantages are the

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possibility of pain, bleeding, infection, and even mortality. Its accuracy for assessing steatosis and fibrosis is limited because of sampling errors and variations in interpretation among pathologists (6,7). Histologic lesion of NASH distributed unevenly in the liver (6). Transabdominal ultrasonography (TUS) is one of the diagnostic tools for NAFLD. Even with real time ultrasonography in NAFLD, large inter and intraobserver reliability has been reported (8). In a meta-analysis of 28 studies, the mean sensitivity of ultrasonography (USG) for the identification of Steatosis compared with liver biopsy ranged from 73% to 91%. The mean specificity ranged from 69.6-85.2% (7). For mild steatosis on liver biopsy (0%-10% steatosis), however, sensitivity dropped to 62.2%-82.1% and specificity to 76.2-94.7 (7). TUS has a limitation in diagnosis cirrhosis and stage of fibrosis too. It is important to diagnose NAFLD before fibrosis through the use of an accurate and noninvasive method.

Another instrument that is novel with advanced technology is transient electrography and fibroscan for diagnosing steatosis and liver stiffness or fibrosis. Controlled attenuation parameter (CAP) on fibroscan is a noninvasive, quantitative, non-ionizing method and can simultaneously evaluate steatosis in NAFLD. Fibroscans are simple and noninvasive quantitative estimation methods of liver steatosis and fibrosis, particularly in large populations with a high risk of NAFLD who need screening. It also has the major advantage of not being operator dependent.

In a comparison of liver stiffness using a fibroscan with liver biopsy, cutoff values of 6.3 kPa in fibroscan considered equal to ≥F2, and 8.3 kPa equal to ≥F3, and 10.5 kPa for F4 with a sensitivity ≥of 90%. (9) There are 22.6% false-negative and 24% false-positive results for severe fibrosis (10).

In a study done by Carvalhana in 2013 for evaluating the diagnostic accuracy of CAP for detection and quantification of steatosis, it was found that CAP significantly correlated with steatosis. The optimal cutoff value of CAP was from range 243 dB/m for S≥2; to 303.5 dB/m for S≥4, respectively (11).

The evaluation of the liver with fibroscan is representative and independent of the operator, and it also could evaluate 100 times more volume of liver parenchyma than liver biopsy, which makes the fibroscan a representative instrument (12). The drawbacks of the fibroscan are it's an expensive method and limited availability in practice.

With disease burden and a wide spectrum of NAFLD, early diagnosis, start treatment, and management to prevent liver stiffness and monitoring changes in trials of new drugs, noninvasive and accurate diagnostic methods are needed.

The aim of this study was to evaluate the accuracy of ultrasonography in comparison to fibroscan for diagnosing different grades of fatty liver.

Materials and Methods

This cross-sectional study was conducted under the supervision of Mashhad University of medical sciences with regard to the Declaration of Helsinki and was approved by our university ethics committee. (IR.MUMS.REC.1395.110)

This study was conducted on 101 patients with NAFLD. All patients who had transabdominal ultrasonography by a single experienced radiologist who was blind to the result of fibroscan and referred for doing fibroscan were included. Fibroscans were done by one experienced operator, who was blind to the results of ultrasonography. US was performed by an expert radiologist using a scanner (Acuson X300, Siemens, Germany). The sonographic feature was based on accepted visual steatosis of a bright liver with increased contrast of liver-kidney, blurring of intrahepatic vessels and diaphragm, and categories to 4 grades (normal=0 to sever steatosis=4). Fibroscans (EchoSens, Paris, France), which were used in this study, are equipped with an L-probe for obese patients. A vibration of mild amplitude and low frequency is transmitted from the vibrator toward the liver, which induces an elastic shear wave that propagates through the liver tissue (13). The pulse-echo ultrasound acquisitions follow the propagation of the shear wave and determine its velocity. The velocity is directly related to liver stiffness (LSM); the harder the tissue, the faster the shear wave propagates. LSM is calculated from velocity and expressed in kPa (13). It has 4 grades of stiffness (S0 <237 db/m=normal, S1: 237-259 db/m, S2: 259-291 db/m, S3: 291-400 db/m). Several reports defined the cutoff values of fibrotic stages in NAFLD with the standard M probe of Fibroscans. The cutoff values for F2, F3, and F4 were 6.6–7.8, 7.1–10.4, and 10.3-22.3 kPa, respectively. (14-21).

Controlled attenuation parameters (CAP) are quantitative estimation methods of liver steatosis in Fibroscans. Other information about patients such as age, waist, and BMI were also gathered.

Statistical analysis

In this study, we used the Bivariate correlation to assess the association between Sonography and fibroscan (Kendall's tai-b method taken for assessments

correlations in ordinal variables in this study). We also conducted a linear regression analysis to predict the percent steatosis by sonographic grade and BMI. Statistical significance was assumed if $P<0.05$. All reported P are two-sided. Statistical analyses were performed using STATA (Version 11.1, SE, Texas).

Of the total of 101 participants in this study, 86 were male, and 15 were female. The median age was 43 (42 among males and 46 among females) with an interquartile range of 36-51.

The mean BMI was 28.92±4.61. Other baseline characteristics are shown in Table-1.

Results

Table 1. Mean baseline characteristics of participants

		Age	Waist Circumference (cm)	BMI	LSM	Percent Steatosis
Sex	man	43	103.3	29.1	6	57.7
	female	47	99.5	28.8	5.8	59.4
Steatosis stage	s0	33	89	21.8	4.5	7.7
	s1	48	100.2	26.9	5.4	21
	s2	44	100.5	28	6	45.6
	s3	43	104.8	30.2	6.2	71.6

LSM: liver stiffness measurement in kPa, mean BMI: Body mass index

There was a significant correlation between BMI and the grade of fatty liver disease in our study. Positive predictive value (PPV) and negative predictive value (NPV) of TUS for all grades of fatty liver, according to the fibro scan was 98.7 and 33%, respectively.

In patients with fibrosis more than 10.3 KPa (F3-F4), TUS could provide an accurate diagnosis grade of fatty liver in 11 patients (27%). We exclude patients with liver stiffness of more than 10.3 from analysis, 27 out of 57 patients who had S3 fatty liver in fibro scan were diagnosed to have grade 3 fatty liver by TUS (Sensitivity: 47.3%). Of 19 patients at stage 2, just 9 had grade 2 by TUS (47.5%). 6 (85.7%) out of 7 patients with Stage 1 in fibroscan had grade 1 by TUS.

Table 2 shows the accuracy of TUS in comparison to fibroscan in different grades of NAFLD.

Which is even less without excluding F4 patients.

Table 2. Contingency table for TUS and fibro scan results by excluding F4

		Steatosis Stage				Total
		s0	s1	s2	s3	
TUS	**Normal**	3	1	3	2	9
	Percent in steatosis stage	75%	14.29%	15.79%	3.51%	10.34%
	Grade 1	1	6	6	2	15
	Percent in steatosis stage	25%	85.71%	31.58%	3.51%	17.24%
	Grade 2	0	0	9	26	35
	Percent in steatosis stage	0%	0%	47.37%	45.61%	40.23%
	Grade 3	0	0	1	27	28
	Percent in steatosis stage	0%	0%	5.26%	47.37%	32.18%
Total		4	7	19	57	87
Percent in steatosis stage		100%	100%	100%	100%	100%

Discussion

Our investigation in comparing two noninvasive imaging methods in diagnosis severity and grading of NAFLD showed that when transabdominal ultrasonography was compared to transient electrography (fibroscan) blindly, TUS was not an efficient method for the screening and management of patients with a high risk of severe NAFLD.

In one study, the prevalence of fibrosis with stiffness of more than 10 kpa was 8% in NAFLD (22). In our study prevalence of fibrosis in these patients was 10.8%.

However, in a study by Ballestri *et al*., ultrasonography could rule out the diagnosis of severe NASH, with a high negative predictive value (94%) (23.

But in our study, NPV of TUS for severe steatosis

(S=3) was 53%. And only in 47.3% of severe fatty liver grade S3, TUS diagnosed as grade 3.Sensitivity, and specificity for all grade of fatty liver were 91.2% and 75%, PPV of TUS for all grade of NAFLD was 98.8%, and NPV was 27.2%, respectively.

TUS as the screening modality for detecting fatty liver disease and severity of steatosis has disadvantages when compared to the fibroscan, even though ultrasonography is the most practical option used for the detection of liver steatosis in epidemiological and screening studies today. In one study, it was found that underestimation of TUS in the prevalence of fatty liver, especially when the amount of steatosis is <20-30% in liver biopsy (24,25), and more importantly, does not offer information on the presence of liver fibrosis. In our study also there was a 71% underestimation of the severity of steatosis by TUS, especially in grade 3.

Prevalence of steatosis in obese individuals (BMI>30 kg/m2) and morbidly obese individuals (BMI>35 kg/m2) is estimated at 65-75% and 85-90% in some studies (23,11,15), respectively. 59% of our patients with BMI>30 and 69.8% with BMI > 35 had steatosis.

In a study done on 118 patients with NASH, the sensitivity of TUS in detecting mild (10%-29% hepatocytes containing fat) to severe steatosis (30%-69% hepatocytes containing fat) was 79.7% (26). In 63 patients with severe steatosis (>70% fat), the sensitivity was 98.4%. The ability to detect steatosis in patients with NASH was significantly limited by the presence of advanced fibrosis. In fact, the sensitivity of detecting moderate-to-severe steatosis in NASH with only mild fibrosis was 100%, but in almost one-quarter of NASH patients with advanced fibrosis, the US could not detect even moderate-to-severe steatosis. TUS is not able to discriminate between fibrosis, inflammation, or NASH (25,27). Therefore, TUS is very good at detecting steatosis without accurate grading of fatty liver, but coexisting fibrosis and inflammation may produce false negatives.

In our study, the accuracy of US to detect S1 and less was high, 75 % in S0 and 85% in S1 but in moderate (S=2) and severe steatosis(S=3) was 47.3% respectively and in patients with F3 and F4 false negative US was 92% and 85% respectively.

Liver biopsy is impractical in NAFLD, and imaging techniques to assess fibrosis and steatosis are an important noninvasive adjunct to LB (28).

Nonalcoholic fatty liver disease is a major health problem worldwide. Fibro scan may become a clinical tool for mass screening in high-risk patients for NAFLD and for monitoring the changes induced by treatment, and replacing TUS.

In this study, we did not have a liver biopsy as the gold standard for fatty liver. We didn't measure the fatty liver index as an alternative noninvasive method of assessing hepatic steatosis based on routinely collected parameters. Most of our study population were male, and the success rate of fibroscans is higher among males because they have less subcutaneous fat.

TUS is not good for managing severe NAFLD with a high probability of liver fibrosis and cannot predict prognosis and liver stiffness. TUS has no value for the management of NAFLD, especially in grade 3, but for grade 0 and grade 1, we use TUS for the accurate grading of NAFLD.

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