Original Article

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Transient Elastography and its Correlation with Biochemical Scores in patients with Metabolic associated fatty liver disease

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Abstract

Background: Metabolic-associated fatty liver disease (MAFLD) is a recently terminology to refer to the diseases within the field of fatty liver disease. The aim of this study is to evaluate the value of transient elastography (TE) in MAFLD patients and its correlation with clinical and biochemical scores for assessment of liver fibrosis.

Methods: This study was carried out on 97 patients with MAFLD. All patients had undergone pelvi–abdominal ultra-sound as a screening tool, transient elastography to determine degree of steatosis/fibrosis, laboratory work up and calculation of FIB-4, APRI, NAFLD fibrosis score (NFS).

Results: Based on the results of transient elastography, the studied MAFLD patients were classified into two groups; group (1) included 62 patients without fibrosis (F0 ≤ 6 KP) and group 2 included 35 patients with fibrosis (> 6 KP). There was significant increasing as regarding FIB4, APRI, and NFS in MAFLD patients with fibrosis versus patients without fibrosis, while controlled attenuation parameter (CAP) does not show significant difference. In patients with fibrosis (group 2) there was statistically significant positive correlation of LSM with FIB4, NFS (P< 0.0001), APRI (P= 0.001), while a non-significant negative correlation of LSM with CAP was detected (P = 0.2), furthermore, there was statistically significant correlation of LSM with age, 2 hours postprandial blood sugar, HbA1c, triglycerides, serum creatinine, uric acid and platelets.

Conclusion: In MAFLD patients, transient elastography is a simple, non-invasive and inexpensive method that correlates with other non-invasive assessment scores of liver fibrosis.

Introduction

Non-Alcoholicfatty liver disease (NAFLD) is the leading cause of liver disease worldwide and is estimated to affect 25% of the global population [1]. The histological definition of NAFLD is the presence of triacylglycerol (TAG) droplets in > 5 % of hepatocytes, in the absence of excessive alcohol consumption or the use of steatogenic drugs [2].

Histologically, NAFLD ranges in severity from steatosis alone (NAFL) to steatohepatitis (NASH), where steatosis is associated with hepatocellular injury, inflammation and fibrosis. Approximately 40% of patients with NAFLD will develop progressive fibrosis, which can result in cirrhosis [3, 4]. Recently, a consensus of international experts proposed to overcome the current nomenclature (NAFLD) and adopt the acronym Metabolic-Associated Fatty Liver Disease (MAFLD), which was mainly defined as liver fat deposition along with obesity, diabetes, or combined metabolic disorders. This change emphasized the importance of metabolic disorder complicated with fatty liver regardless of the heterogeneous etiology since the exclusion of other liver diseases was no longer required [5,6]. Unlike NAFLD, MAFLD does not require the exclusion of other etiologies of liver disease, for example excessive alcohol consumption or viral hepatitis[7]. MAFLD diagnosis would be based on the detection of hepatic steatosisand at least one of the following three metabolic conditions overweight/obesity, type 2 diabetes, and metabolic dysregulation (met when at least two features are present among, increased waist circumference, arterial hypertension, hypertriglyceridemia, low HDL-C, prediabetes, insulin resistance, and subclinical inflammation[6]. There is abundant evidence that fibrosis is the major determinant of adverse outcomes in patients with MAFLD[8,9].

Liver biopsy remains the gold standard test to diagnose and stage of liver fibrosis, but it has many well-documented limitations. Therefore alternatives to liver biopsy have been investigated, such as clinical scoring systems, TE, and MRI, which can be used repeatedly because of high safety[10].

Unfortunately, ultrasound is neither sensitive nor specific to reveal fibrosis, except in advanced stages where signs of cirrhosis are evident[11]. In the last years, some clinical/laboratory scores have been created to assess the risk of NASH evolution and the need of biopsy in these patients [12]. Among all, NALFD fibrosis score seems to predict well the presence of significant fibrosis [11, 13-15]. NAFLD fibrosis score is calculated using a standardized formula that include variables as age, BMI, ALT , AST,

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presence or not of fasting hyperglycemia or diabetes mellitus II, platelet count , and serum albumin[13].
Transient elastography (FibroScan) evaluates liver stiffness using pulse-echo ultrasound. It has demonstrated great value in assessing fibrosis in chronic hepatitis C, and it might also be useful in NAFLD patients, although with less accuracy[16]. A meta-analysis of the use of TE in patients with NAFLD suggests that TE has excellent diagnostic accuracy for cirrhosis, good accuracy for F3, but modest accuracy for F2 [17]. Despite this, TE can rule out cirrhosis with a high NPV(~ 90%) [8]. The aim of this study is to evaluate the value of transient elastography and its correlation with clinical and biochemical scores in patients with metabolic associated fatty liver disease.

Materials and methods

This study was carried out on 97 patients (28 males and 69 females) with MAFLD aged between (30-66) years old recruited from out and inpatient clinic of Tropical medicine department, Mansoura University, Dakahlia, Egypt between June 2018 and May 2021. The study was approved by Mansoura university Institutional ethical Committee and carried out in accordance with the guidelines of the Helsinki Declaration (1975).

Diagnostic Criteria of MAFLD.
MAFLD is diagnosed based on an pelvi–abdominal ultra-sound sure hepatic steatosis with the existence of any one of the three aforesaid metabolic conditions; diabetes mellitus, overweight/obesity (BMI ≥ 25 kg/m2), or metabolic dysregulation (MD) [6]. MD in this study was defined as the presence of at least two of the following criteria, waist circumference ≥102 cm in men and 88 cm in women; blood pressure ≥130/85 mmHg or specific drug treatment; plasma triglycerides ≥150 mg/dL or specific drug treatment; plasma HDL-cholesterol < 40 mg/dL for men and <50 mg/dL for women or specific drug treatment; prediabetes (fasting glucose levels 100 to 125 mg/dL, or 2-hour postload glucose levels 140 to 199 mg/dL or HbA1c 5.7% to 6.4%; homeostasis model assessment (HOMA)-insulin resistance score ≥2.5[6].
Inclusion criteria. The study included patients aged 18 years old and above with body mass index (BMI) more than 25 and evidence of any grade of fatty liver on ultrasonography (USG). All subjects had undergone: detailed history taking, clinical examination, baseline anthropometric measurements, including the height and weight for calculating the body mass index (BMI)were recorded and waist circumference (using a measuring tap placed in a horizontal plane around the abdomen at the level of the iliac crest. The measurement was made at the end of expiration).
Exclusion criteria. Any chronic liver disease not fulfill the criteria for diagnosis of MAFLD based on the accepted critera[6].

Laboratory Work. Including, liver function tests (ALT, AST, serum Albumin , serum bilirubin and prothrombin Time), serum creatinine, serum uric acid, complete blood count, virology markers (HBs Ag, HCV Ab), fasting and 2h post prandial blood sugar& HbA1c, serum cholesterol , triglycerides, HDL and LDL. Finally, calculation of non-invasive scores for the assessment of liver fibrosis including. FIB-4, NFS, APRI.
Radiology Work:
1. Pelvi –Abdominal Ultra-Sound as a screening tool. All patients fasted overnight or for greater than 6hr before the sonography examination using a multifrequency (2–5 MHz) convex transducer by a single experienced sonologist who was blinded to the transient elastography results of the patients
2. Transient Elastography (TE).
TE using FibroScan® was performed by an experienced hepatologist using an XL probe, in patients who fasted for at least 6 hours prior to examination, in the supine position, with the right arm in full abduction, on the mid-axillary line with the probe tip placed in the 9thto 11th intercostal space with a minimum of 10 measurements [18].
Liver stiffness (LS) values were regarded as valid if the following criteria were met:

a) Number of valid measurements at least 10.
b) A success rate above 60%.
c) An interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median LS measurements (M) value (IQR/M ≥30%) [18].

The XL probe was used in this study due to presence of morbidly obese patients. The measurement depth was between 35 and 75 mm.
Controlled attenuation parameter (CAP) was also obtained to quantify degree of steatosis
According to the manufacturer's instructions, in addition to previous studies, the stages of fibrosis (F0: 1–6, F1: 6.1–7, F2: 7–9, F3: 9.1–10.3, and F4: ≥ 10.4) were defined in kPa[19, 20]. Moreover, steatosis stages (S0: < 215, S1: 216–252, S2: 253–296, S3: > 296) were defined in dB/m [21].
Non-invasive scores for assessment of liver fibrosis
Non-invasive scores for the assessment of liver fibrosis (APRI, FIB-4, NAFLD fibrosis score) were calculated using standard formulas.
1) NAFLD fibrosis score
NAFLD Fibrosis Score = -1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m2) + 1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelet (×109/L) – 0.66 × Albumin (g/dL) [13].

Table 1: NAFLD fibrosis score and correlated fibrosis severity [13].

NAFLD fibrosis score	Correlated fibrosis severity
< -1.455	F0-F2
- 1.455 to 0.675	Indeterminate score/fibrosis
> 0.675	F3-F4

2) FIB-4
FIB-4 Score = (Age x AST) / (Platelets x √ (ALT)) [22, 23].

3) APRI

APRI = [AST/AST (ULN)] /platelet (10^9/L) [14, 22].

Statistical analysis

Statistical analysis of the data was done by using Statistical Package for Social Science (SPSS) version 25.0. The normality of the distribution was checked by Kolmogorov Smirnov test to determine parametric or nonparametric distribution. The data were presented in the form of range, median, mean, standard deviation and 95% confidence interval. Quantitative data were expressed as Mean± SD for parametric data and as median and range for non-parametric data while qualitative data were expressed as frequency and percent. For parametric data, comparisons between two groups were carried out by unpaired t-test. For non-parametric data, comparisons between two groups were carried out by Mann-Whitney. Categorical variables were compared using the likelihood-ratio v 2 test or Fisher's exact test. The results were expressed as odds ratio (OR), 95% confidence intervals (95% CI), P-values and x2-test. SPSS software version 25.0 **(SPSS, Chicago, IL)** was also used for confirming the analyses. A Spearman's correlation analysis was performed to evaluate the correlation between LSM values and other variables included in this study. Significance was considered when P value ≤ 0.05.

Results

According to the results of transient elastography, the studied patients were classified into two groups; group one included 62 patients without fibrosis (F0 ≤ 6 KP) and group 2 included 35 patients with fibrosis (> 6 KP) [19, 20]. **Table 1** shows that, MAFLD patients with fibrosis had significant increased age, female predominance, higher BMI, waist circumference, HbA1c, diabetes mellitus, cholesterol, triglyceride, platelets count and serum uric acid. However, hypertension, LDL, HDL, AST, ALT, albumin, bilirubin, INR, serum creatinine, hemoglobin and WBCs showed non-significant difference between both studied groups.

Table 2 shows that, there was significant increasing as regarding FIB4, APRI, NFS in MAFLD patients with fibrosis versus patients without fibrosis, while CAP did not show significant difference. **Table 3** shows that, there was statistically significant correlation of LSM with age, 2 hours postprandial blood sugar, HbA1c, Triglycerides, Serum creatinine, uric acid, and platelets. Furthermore, no statistical significant correlation of LSM with other biochemical parameters was detected. **Table 4** shows that, there was a statistically significant positive correlation of LSM with FIB4, APRI, and NFS while a non-significant negative correlation of LSM with CAP was detected.

Table 1. Demographic, anthropometric and biochemical data between both studied groups.

	MAFLD with no fibrosis (≤ 6 KP) N= 62 patients	MAFLD with fibrosis (> 6.1 KP) N= 35 patients	P
Age	43±7	54 ± 7	< 0.0001
Sex: M/F	23/39	4/31	0.005
BMI:(Kg/m^2)	34.7 ± 4.7	36.7 ± 5.1	0.04
Waist circumference (cm)	112± 11	116.3 ± 9.5	0.04
Hba1c (%)	5.6(5 - 9.5)	7 (5.1 – 9.8)	0.003
DM: N/%	12 (18.8%)	24 (66.7%)	<0.0001
HTN: N/%	12 (18.8%)	12 (33.3%)	0.1
Cholesterol (mg/dl)	230 (121– 356)	209 (12 – 359)	0.03
Triglyceride (mg/dl)	144 (88- 267)	160(105– 310)	0.04
LDL(mg/dl)	156(111-273)	147 (69– 279)	0.2
HDL(mg/dl)	46.8 ± 7.4	44.5 ± 8.8	0.16
AST(U/L)	35 (18– 160)	35(23– 101)	0.4
ALT(U/L)	32(17– 153)	38(24– 110)	0.5
Albumin: (g/dL)	4.3(3.5 – 5)	4.3(3.6 – 4.8)	0.1
Bilirubin(mg/dl)	0.83(0.3– 1.2)	0.8(0.4– 1)	0.96
INR	1(1– 1.38)	1(1– 1.3)	0.8
Creatinine (mg/dl)	0.8(0.6–1.98)	0.9(0.7– 1.3)	0.06
Serum uric acid(mg/dl)	5.6 ± 1.5	4.9 ± 1.5	0.02
WBCs(×10^3/µL)	5.2(4.3–12.2)	5.8 (4.1–10.8)	0.1

Hemoglobin (g/dL)	12(7 – 14.8)	12(11– 14.4)	0.7
Platelets (×10^3/µL)	270 (166– 398)	230 (81– 340)	0.001

BMI, *body mass index*; **HbA1c**, *glycated hemoglobin*; **DM,** *diabetes mellitus*; **HT,** *hypertension*; **LDL,** *Low density lipoprotein*; **HDL,** *high density lipoprotein*; **ALT,** *alanine transaminase*; **AST,** *aspartate transaminase*; **Hba1c,** *glycated hemoglobin*; **HDL,** *high density lipoprotein*; **INR,** *international normalized ratio*.

Table 2: Comparison of noninvasive methods for assessment of fibrosis and steatosis between non fibrosis group and fibrosis group (classified according to LSM values)

	MAFLD with no fibrosis (≤ 6 KP) N= 62 patients	MAFLD with fibrosis (> 6 KP) N= 35 patients	P
LSM	4.65 (3– 6)	7.9 (6.3– 18)	< 0.0001
CAP	320 (247– 397)	308 (133– 397)	0.3
FIB4	0.97 (0.55-2.08)	1.5 (0.85– 7.5)	< 0.0001
APRI	0.33 (0.16– 1.43)	0.43 (0.24– 3.02)	0.002
NFS	-2.03 (-3.48- -0.06)	- 0.21 (- 2.75– 2.11)	< 0.0001

Test used: *Mann-Whitney for data expressed as median and range*; **P:** *Probability*

Table 3: Correlations of LSM with demographic, anthropometric, biochemical parameters in MAFLD patients with fibrosis.

Parameter	R	P
Age	0.612	<0.0001
Body mass index	0.191	0.06
Waist circumference (cm)	0.168	0.1
Fasting Blood Sugar	0.177	0.08
2 hours postprandial blood sugar	0.208	0.04
HbA1c	0.298	0.003
Cholesterol	-0.181	0.07
Triglycerides	0.242	0.02
Low density lipoprotein	-0.095	0.3
High density lipoprotein	0.021	0.8
AST	0.127	0.2
ALT	0.118	0.2
Albumin	-0.094	0.4
Bilirubin	-0.007	0.9
INR	-0.054	0.6
Serum creatinine	0.252	0.01
Serum Uric acid	-0.275	0.006
White Blood Cells	0.118	0.2
Hemoglobin	-0.026	0.8
Platelets	-0.291	0.003

ALT, *alanine transaminase*; **AST,** *aspartate transaminase*; **Hba1c,** *glycated hemoglobin*; **HDL,** *high density lipoprotein*; **INR,** *international normalized ratio*; **P,** *probability*; **r,** *correlation coefficient*.

Table 4: Correlations of LSM with noninvasive methods for assessment of fibrosis in MAFLD patients with fibrosis

Parameter	R	P
FIB4 score	**0.539**	**<0.001**
APRI	**0.32**	**0.001**
NFS score	**0.54**	**<0.001**
CAP	**-0.12**	**0.2**

APRI: *AST to Platelet Ratio Index*, **CAP:** *Controlled Attenuation Parameter*, **LSM:** *Liver Stiffness Measurement*, **P:** *probability*, **r:** *correlation coefficient*.

Discussion

A common clinical concern in patients with FLD is determination of the stage of fibrosis. Unfortunately, liver biopsy has well-known limitations and cannot be proposed for all patients, especially given the high prevalence of NAFLD worldwide [24].

The newly suggested MAFLD criteria aids to recognize extra cases of fatty liver disease at risk of adverse outcomes. MAFLD is defined as the presence of hepatic steatosis together with one or more of the next; overweight or obesity; type 2 diabetes; or two or more other metabolic risk abnormalities[25]. TE has become a leading tool in the non-invasive staging of liver disease [16, 26, 27].

In the preset study, the MAFLD patients were classified according to the results of transient elastography into two groups; group one included patients without fibrosis (F0 ≤ 6 KP) and group 2 included patients with fibrosis (> 6 KP) [19, 20]. The study demonstrated that, MAFLD patients with fibrosis had significant older age, increased HbA1c, and diabetes mellitus, versus non fibrotic group. It is important to note that MAFLD diagnosed based on diabetes alone were older and showed a higher grade of hepatic fibrosis, which is in line with previous reports that diabetes was associated with liver fibrosis and prognosis of NAFLD[28, 29]. Also in our study we found MAFLD patients with fibrosis had significant increased cholesterol, triglyceride, and serum uric acid. In accordance with these results, Huang et al found that, in the presence of more metabolic conditions associated with of MALFD increasing risk of hepatic fibrosis [30]. Another important finding in our study was significantly higher BMI and waist circumference in MAFLD/fibrotiic group. Kocand sumbul reported that waist circumference was associated with a 2.78-fold increased likelihood of Liver fibrosis [31]. Inappropriately, utmost studies assessed the hepatic fibrosis burden using Fibrosis-4 (FIB-4) index or NFS score in subjects with MAFLD [32, 33]. Though, validation of FIB-4 and NFS was still needed more evolution in a novel definition of MAFLD. Only two studies have examined the prevalence of hepatic fibrosis in MAFLD using transient elastography with limited subjects [34, 35]. In the present study, there was a statistically significant positive correlation of LSM with FIB4, APRI and NFS score. In line with our findings, Fallatah et al, [20] and Mansour et al, [36] reported a significant positive correlation between LSM detected by TE as compared to APRI, FIB-4 and NFS results. Supporting these results, Ning et al, reported that LSM, APRI, FIB-4 and NFS had shown positive correlations with the increasing degree of liver fibrosis by liver biopsy [37].

In MAFLD patients, we found a statistically significant positive correlation of LSM with age. These findings are compatible with the results of earlier study [37]. We also observe a significant correlation of LSM with Hba1c consisting with kocand sumbul who found that each 1% increment in HbA1c level was associated with 36.7% increased likelihood of liver fibrosis [31].

Regarding lipid profile, We detect a statistically significant positive correlation of LSM with triglycerides, Nobili et al. reported that NAFLD activity and fibrosis scores showed a significant positive correlation with triglyceride/HDL [38].

Regarding platelets, we observe a significant negative correlation between LSM and platelet count. Moreover, when comparing (F0, F1-4) groups there was significant decrease in platelet counts. These findings agree with several studies that reported a strong negative correlation of platelet count with stiffness [20, 36].

This study has some limitations. First is the small number of cases may reduce the statistical power to find the difference between groups. Second, is the absence of biopsy confirmation of our results. Liver biopsy and MRI were not performed on the basis of invasiveness and cost requirements, respectively.

Conclusion

Our study shows a highly significant positive correlation between LSM by TE and other non-invasive assessment scores of liver fibrosis (APRI, FIB-4 and NFS) in patients with MAFLD.

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