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Can Transient Elastography be a reliable method for assessing liver fibrosis in Non Alcoholic Steatohepatitis (NASH)?

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Abstract

The **aim** of our study was to evaluate the severity of liver damage in non-alcoholic steatohepatitis (NASH) patients, by means of Transient Elastography (TE), using prespecified cut-off values of liver stiffness (LS) measurements. **Patients and methods:** Our retrospective study included 478 NASH patients. Ten LS measurements were performed in each patient by means of TE, by using a standard M-probe. A median value expressed in kilopascals (kPa) was calculated. Reliable measurements were defined as: median value of 10 LS measurements with a success rate (SR) ≥60% and an interquartile range (IQR) <30%. Patients were divided into 3 categories using prespecified TE cut-offs for LS: <7.9kPa (absence of severe fibrosis); values ranging between 7.9 kPa and 9.6 kPa ("gray zone" in which biopsy is recommended); and > 9.6kPa (severe fibrosis). **Results:** Reliable measurements were obtained in 81.6% of NASH patients. Female gender, older age and higher BMI were associated with an impossibility to obtain reliable TE measurements. Three hundred and ninety patients with reliable LS measurements were included in the final analysis. Of those, 70.8% had no severe fibrosis, 10.8% were in the "gray zone" in which biopsy is recommended and 18.5% had severe fibrosis. **Conclusions:** In 81.6% of our NASH patients we were able to obtain reliable LS measurements by means of TE, using a standard M-probe. In our study, approximately 30% of NASH patients had LS measurements compatible with severe fibrosis and should be evaluated for urgent measures to prevent disease progression.

Keywords: NASH, Transient Elastography, liver fibrosis, liver stiffness

Introduction

The incidence of nonalcoholic steatohepatitis (NASH) has significantly increased in the last years with modern lifestyle changes [1]. It has become the third indication for liver transplantation in the USA [2], showing the importance of its early diagnosis and treatment. In this moment liver biopsy (LB) is still the "gold standard" for the diagnosis of NASH. In the study of West et al [3] the mortality rate during LB was 1:10,000 diagnostic biopsies, and complications risk increased in patients with advanced fibrosis [4]. Another problem regarding LB is the specimen length: in order to be relevant, it should be at least 2 - 4 cm [5]. Unfortunately, in general practice, the liver specimen is suboptimal, in 15-30% of cases being uninterpretable due to the small size [6,7].

Non-invasive modalities for liver fibrosis evaluation have became more and more popular in the last 10-15 years. Transient elastography (TE) is a non-invasive, ultrasound based method for liver stiffness evaluation. Its good applicability was demonstrated in patients with chronic viral hepatitis (especially chronic hepatitis C) [8,9], but also in other etiologies of chronic hepatopathies [10,11].

The **aim** of our study was to evaluate the severity of liver damage in NASH patients, by means of TE, using prespecified cut-off values of liver stiffness (LS) measurements.

Patients and methods

Patients

Our retrospective study included 478 patients with NASH, examined in our Department between 2007-

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2012. The diagnosis of NASH was established based on: ultrasound examination (moderate or severe liver steatosis - "bright liver" with posterior attenuation); biological tests (increased aminotransferases level); no history of alcohol abuse; negative markers for viral hepatitis B or C; presence of one or more etiological factors (such as obesity, type II diabetes mellitus, hypertriglyceridemia).

No patient had focal liver lesions or ascites on abdominal ultrasound examination.

The study was approved by the local Ethics Committee and was in accordance with the Helsinki Declaration of 1975.

Transient elastography (TE)

In all patients TE was performed with a FibroScan® device (EchoSens, Paris, France) using a standard M-probe, by four experienced physicians (more than 500 examinations each). It uses a 5-MHz ultrasound transducer mounted on the axis of a vibrator. The vibrator generates a painless vibration (amplitude 2 mm and 50 Hz frequency) similar to a „flick", generating shear waves that propagate through the skin and the subcutaneous tissue into the liver. The shear wave velocity is directly related to the liver stiffness, evaluated by using Young modulus and expressed in kiloPascals-kPa [12].

In all patients TE measurements were performed in the right liver lobe, by intercostal approach, in supine position with the right arm in maximal abduction. The operator, assisted by an ultrasonic time-motion image, located a liver portion of at least 6 cm thick, free of large vascular structures. Once the measurement area had been located, the operator pressed the probe button to start an acquisition. Measurements which did not have a correct vibration shape or a correct follow up of the vibration propagation were automatically rejected by the software. Ten successful measurements were performed on each patient and a median value expressed in kPa was calculated.

Failure of TE measurements was defined as no valid measurements obtained after at least 10 shots and unreliable measurements were considered in the following situations: valid measurements fewer than 10; success rate (SR) <60% (SR = the ratio of the number of successful measurements over the total number of acquisitions); and/or interquartile range interval (IQR) ≥30% (IQR = the difference between the 75th and the 25th percentile, essentially the range of middle 50% of the data) [13]. So, reliable measurements were defined as median value of 10 valid LS measurements with a SR ≥60% and an IQR <30%.

According to LS values obtained by means of TE, NASH patients were divided into 3 categories using the cut-offs proposed by Wong et al [11], who evaluated 246 NASH patients by means of TE (M-probe) and LB: LS <7.9kPa (absence of severe fibrosis), values ranging between 7.9 kPa and 9.6 kPa ("gray zone" in which biopsy is recommended) and respectively LS > 9.6kPa (severe fibrosis).

Statistical analysis

The statistical analysis was performed using MedCalc Software (MedCalc program, Belgium). The Kolmogrov-Smirnov test was used for testing the distribution of numerical variables. Mean value and standard deviation were calculated for numerical variables with normal distribution, while in the case of non-normal distribution median values and range intervals were utilized. Qualitative variables were presented as numbers and percentages. Parametric tests (t-test) were used for assessment of differences between numerical variables with normal distribution and nonparametric tests (Mann–Whitney or Kruskal–Wallis tests) for variables with non-normal distribution. Chi-square (X^2) test (with Yates' correction for continuity) and Fisher's exact test were used for comparing proportions expressed as percentages ("n" designates the total number of patients included in a particular subgroup). 95% confidence intervals were calculated for each predictive test and a p-value < 0.05 was considered as significant for each statistic test.

Results

The main characteristics of the subjects included in the study are presented in Table I.

Failed LS measurements were observed in 1.9% of patients, unreliable LS measurements in 16.5% of cases, so reliable LS measurements by means of TE were obtained in 81.6% of NASH patients.

Female gender, older age and higher BMI were associated with failed and unreliable TE measurements (Table II).

Table I. Main patients' characteristics.

Parameter	
Age (years)	46.4 ± 11.9
Gender: – male	n = 321 (67.1%)
– female	n = 157 (32.9%)
Body mass index – BMI (kg/m^2)	29.3 (17.5-53.6)
Distribution of patients by BMI:	
– <25kg/m^2	n = 68 (14.2%)
– 25-29.9 kg/m^2 (overweight patients)	n = 206 (43.1%)
– ≥30kg/m^2 (obese patients)	n = 204 (42.7%)

Numerical variables with normal distribution are presented as mean value ± standard deviation, while variables with non-normal distribution are presented as median values and range intervals

Table II. Factors associated with the impossibility to obtain reliable LS measurements by means of TE.

Parameter	Patients with reliable measurements n = 390 (81.6%)	Patients with failed and unreliable measurements n = 88 (18.4%)	p value
Age (years)	45.4 ± 11.9	51.2 ± 10.7	**< 0.0001**
Gender: – female	n = 118 (30.2%)	n = 39 (44.3%)	0.01
– male	n = 272 (69.8%)	n = 49 (55.7%)	0.01
BMI (kg/m²)	28.7 (17.5-53.6)	31.1 (17.6-41)	0.0004

Numerical variables with normal distribution are presented as mean value ± standard deviation, while variables with non-normal distribution are presented as median values and interquartile range

The percentage of reliable measurements was similar in normal weight and overweight patients (BMI: 25.1-29.9kg/m²): 85.2% vs. 87.3% (p=0.81). In obese NASH patients (BMI ≥30 kg/m²), the percentage of reliable measurements was significantly lower as compared with normal weight and overweight patients: 74.5% vs. 85.2% (p=0.04) and 74.5% vs. 87.3% (p=0.001), respectively.

The analysis of liver fibrosis distribution was performed in 390 NASH patients with reliable LS measurements. Of these, 70.8% had no severe fibrosis (LS values lower than 7.9 kPa), 10.8% were in the "gray zone" in which biopsy is recommended (LS values ranging from 7.9 kPa to 9.6 kPa) and 18.5% had severe fibrosis (LS values higher than 9.6 kPa).

Discussion

Metabolic abnormalities become more frequent due to the Western lifestyle. Increasing caloric intake (especially from sugar) and the lack of physical activity are the main causes of obesity, one of the main enemies of modern people. Obesity, diabetes mellitus and hypertriglyceridemia increase the risk of non alcoholic fatty liver disease (NAFLD). This is a benign entity, with no risk of liver fibrosis. Despite it, a proportion of patients with NAFLD shall develop NASH, in which liver inflammation is followed by fibrosis that can progress to cirrhosis. Thus the differentiation between NAFLD and NASH is essential for treatment, but especially for prognosis. LB is the best test that evaluates liver alterations, offering information concerning the severity of fatty infiltration, inflammation and fibrosis (if present). But, obesity being a long life disease, how often should LB, an invasive method, be performed? And how many patients shall accept repetitive LBs, knowing that the treatment is the same, whatever the severity: correction of the metabolic factors (such as diabetes or hypertriglyceridemia), weight loss and physical activity?

Thus, non-invasive evaluation of liver fibrosis can be a rational solution. Biological tests (such as FibroMax or NashTest) [14,15] or elastographic methods, such as TE [11,16] or Acoustic Radiation Force Impulse elastography – ARFI [16,17] can be practical solutions.

TE is the oldest ultrasound based elastographic method used for the non-invasive assessment of liver fibrosis. In the last years, several published studies have demonstrated a good performance of TE (using the standard M-probe) for liver fibrosis evaluation in NASH patients. The area under a receiver operating curve (AUROC) for predicting significant fibrosis (F≥2) ranges between 0.78-0.86 [11,16,18,19], for predicting severe fibrosis (F≥3) between 0.73-0.97 [11,16,18,19] and for predicting liver cirrhosis (F=4) between 0.93-0.99 [11,16,19].

Our rate of reliable measurement (81.6%) is in line with the study of Castera et al [13], which included 13,369 LS measurements by means of TE, in patients with various etiologies of chronic liver diseases. Similarly with the Castera study [13], female gender, older age and higher BMI were associated with failed and unreliable TE measurements. As compared with the study of Friedrich-Rust et al [16], who evaluated 61 NASH patients, our rate of reliable measurements was much higher: 81.6% vs. 60.6%. Considering that female gender was associated with failure and unreliable TE measurements in our study and in the Castera study [13], a possible explanation for our higher rate of reliable measurements can be the much lower percentage of women in our study, as compared with the cohort evaluated by Friedrich-Rust et al (32.9% vs. 47.3%) [16]. Wong et al [11] specified only the number of cases in which 10 valid LS measurements could not be obtained (10.2%), slightly higher than in our study (8.1%).

According to our data, the percentage of reliable LS measurements was similar in normal weight vs. overweight NASH patients, while in obese patients it was significantly smaller as compared with normal weight and

overweight patients. These results are in line with those obtained by Wong et al [11].

It should be specified that the obesity problem was partially solved in TE by the recent development of a more sensitive ultrasound sensor (XL probe), which has also the ability to noninvasively quantify liver steatosis by means of Controlled Attenuation Parameter (CAP) [20, 21]. In obese patients, the rate of reliable measurements increased from 45-50% with the M-probe, to approximately 75% when the XL-probe was used [20,21]. When NASH patients were evaluated using both M and XL-probes [16], the rate of reliable measurements increased by 10% (from 60.6% to 70.4%).

Using a value higher than 9.6 kPa as the LS cut-off for severe fibrosis in NASH patients [11], 18.5% of our subjects had severe fibrosis, a proportion slightly lower than in the study of Wong et al [11]. In this cohort of patients detailed investigations should be performed and also ultrasound screening for hepatocellular carcinoma. In our study, 10.8% of patients were included in the "gray zone" (LS values between 7.9 and 9.6kPa), in which LB is recommended. In the study of Wong et al [11] 16.3% of NASH patients were included in this category and severe fibrosis was found in 60% of cases in LB. Unfortunately, due to the retrospective design of our study, we could not perform LB in these patients.

Where will the liver evaluation of patients with NAFLD progress to - probably not in the direction of liver biopsy. Encouraging results of TE for the non-invasive evaluation of liver fibrosis in this type of patients and some new data regarding ARFI [16,17] make us consider elastography as a possible method for fibrosis estimation. On the other hand, non-invasive biological tests such as FibroMax or NashTest [14,15] can play a role for fibrosis quantification in NASH and NAFLD patients.

In **conclusion**, reliable LS measurements by means of TE, using an M-probe, could be obtained in 81.6% of our NASH patients. TE can be a reliable method for liver fibrosis evaluation in patients with NASH. In our study, approximately 30% of subjects with NASH had LS values compatible with severe fibrosis and they should be evaluated in order to take urgent measures to prevent disease progression.

Conflict of interest: none

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