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Research article

MR elastography is effective for the non-invasive evaluation of fibrosis and necroinflammatory activity in patients with nonalcoholic fatty liver disease

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ABSTRACT

Objectives: To evaluate the performance of magnetic resonance elastography (MRE) in diagnosing and staging hepatic fibrosis in patients with histologically confirmed nonalcoholic fatty liver disease (NAFLD) and in distinguishing simple steatosis from nonalcoholic steatohepatitis (NASH).

Methods: Ninety subjects (49 NAFLD patients and 41 healthy volunteers) were prospectively enrolled. Liver stiffness measured by MRE was correlated with the grade of fibrosis and/or inflammation determined by liver biopsy. Correlations, ROC (receiver operator characteristic) curves and diagnostic performance were evaluated. The study was approved by the local ethics committee.

Results: The area under the ROC curve (AUROC) of MRE in discriminating healthy from NAFLD individuals was 0.964 ($P < 0.0001$), and that for distinguishing advanced (F3-F4) from absent/mild fibrosis (F0-F2) was 0.928 ($P < 0.0001$). The use of a threshold > 4.39 kPa resulted in a sensitivity of 90.9% and a specificity of 97.3% for diagnosing advanced fibrosis. For discriminating NASH from simple steatosis, the AUROC was 0.783 ($P < 0.0001$), and the threshold, 3.22 kPa.

Conclusions: MRE is an effective, non-invasive method for detecting/staging hepatic fibrosis in NAFLD. This method has good performance in discriminating normal from NAFLD subjects and between the extreme grades of fibrosis. NAFLD patients with inflammation and without fibrosis have higher liver stiffness than those with simple steatosis.

1. Introduction

Chronic liver disease associated with cirrhosis is a major cause of death worldwide, accounting for approximately 2% of world mortality [1]. Its incidence has steadily increased, especially with the recent epidemic of obesity and nonalcoholic fatty liver disease (NAFLD) [2,3]. NAFLD has an average global prevalence estimated at 6% to 35%, depending on the population, ethnicity and methods used for diagnosis [4]. Most patients have simple steatosis, while a small subset have nonalcoholic steatohepatitis (NASH), with or without fibrosis [3]. The prevalence of NASH in the general population is estimated at 3% to 5% [4]. The latter condition is associated with type 2 diabetes mellitus and is considered by some authors to be involved with "metabolic syndrome" [5].

Simple steatosis has a good prognosis, with little or no progression; however, individuals with associated inflammation may develop fibrosis, cirrhosis and hepatocellular carcinoma [3–5]. It is believed that in the future, NAFLD-related cirrhosis will become the most common indication for liver transplantation and that fibrosis stage will become a predictor of mortality from cardiovascular disease [6,7].

Abbreviations: MR, magnetic resonance; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholicsteatohepatitis; LS, liver stiffness

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The detection of liver fibrosis at early stages can be helpful in preventing its progression to cirrhosis, and some reversal of such fibrosis is possible with appropriate treatment [3]. Liver biopsy is still considered the standard for detecting and grading fibrosis. However, it is invasive and subject to sampling errors and intra- and interobserver variability [8,9]. A liver biopsy fragment represents approximately 1/50,000 of the parenchymal volume [10].

Scores including the platelet count, serum aminotransferase levels and acute phase proteins have been proposed for evaluating liver fibrosis. However, none of them have demonstrated accuracy in distinguishing between intermediate fibrosis stages, and their usefulness remains controversial [3]. Morphological imaging methods have low sensitivity in detecting early stages of fibrosis and are only specific for advanced fibrosis/cirrhosis [11,12].

There is therefore a need to establish a non-invasive quantitative method that is sufficiently sensitive and specific to be used in clinical evaluation of patients at risk of liver fibrosis development and those with pre-established fibrosis requiring evaluation of a therapeutic response. Magnetic resonance (MR) elastography is an interesting method due to its high accuracy in the evaluation of liver fibrosis and also due to the possibility of evaluating a large area of the parenchyma with good reproducibility [13,14]. The objective of this study was to evaluate the performance of MR elastography in diagnosing and staging liver fibrosis in patients with histologically confirmed NAFLD and in distinguishing between simple steatosis and NASH.

2. Materials and methods

2.1. Patients

This was an observational study with prospective inclusion of patients with NAFLD. It was approved by the Research Ethics Committee of the Institution (CAAE-01699512.1.0000.5149) and all subjects agreed to participate and signed informed consent forms.

MR scans were performed between March 2014 and July 2015. Patient inclusion criteria were age greater than 18 years and NAFLD diagnosed by liver biopsy at a maximum interval of 12 months, provided that the patients have maintained the clinical conditions observed at the time of biopsy. Exclusion criteria were: (a) other known causes of chronic liver disease and/or of hepatic steatosis — namely chronic B or C hepatitis virus infections, auto-immune hepatic disorders (autoimmune hepatitis, primary sclerosing cholangitis and primary biliary cholangitis), Wilson disease, hemochromatosis, alpha-1-antitripsin deficiency, use of steatogenic medications within the past six months, exposure to hepatotoxins, and history of bariatric surgery; (b) significant alcohol consumption – 10 g of alcohol per day in women and 20 g of alcohol per day in men; (c) pregnancy; and (d) contraindications to perform MR.

Forty-one healthy volunteers recruited by convenience at the participating institutions were also evaluated by MR. The inclusion criteria for this group were age greater than 18 years and no history of alcohol intake or liver disease. Exclusion criteria were pregnancy, contraindications to perform MR, and absence of liver steatosis at qualitative chemical shift imaging (conventional in-phase and opposed-phase imaging).

Demographic, laboratory and clinical data were evaluated, including age, gender, weight, height and blood laboratory tests performed in the last three months (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyltransferase, platelet count, albumin, ferritin and lipid profile). Gender, weight and height were recorded for the healthy volunteers. Body mass index (BMI) was calculated.

2.2. Magnetic resonance protocol

All subjects underwent MR of the liver at the Hermes Pardini Institute, after a minimum of four hours of fasting. A 1.5 T with a phased-array torso coil was used (GE SignaHDxT, GE Medical System, Milwaukee, WI). MR elastography was performed with a protocol similar to those previously described [15,16] using commercially available hardware and software (Resoudant Inc., Rochester, MN). With the patient supine, a passive acoustic driver was used on the right hypochondrium, held by an elastic strap and connected to the active driver located outside the examination room. The active driver produced acoustic vibrations of 60 Hz, which were transmitted to the passive driver and body, thereby producing shear waves. The elastography sequence (MR Touch, GE Medical System, Milwaukee, WI) was performed during the acoustic vibration transmissions with encoding of tissue motion. The acquisition parameters were as follows: axial plane; field of view (FOV), 42 cm; acquisition matrix, 256 × 64; fractional FOV, 1; flip angle, 30°; number of excitations, 1; bandwidth, 31.25 kHz; TE/TR, 21.7/50; slice thickness, 8 mm; number of slices, 4; acquisition time, 55 s, 4 apneas. Magnitude and waveform images were generated. Specialised software was then used for automatic processing of the results to obtain quantitative maps of liver stiffness (LS) (elastograms) using a multimodal direct inversion algorithm, with a confidence threshold mask that was previously described and validated [17]. Regions of interest (ROI) were drawn freehand on each of the four generated elastograms, avoiding the periphery of the liver, large blood vessels and artefacts, thereby obtaining the final LS in kilopascals, which corresponded to the mean of the four slices. All post-processing was performed by a single radiologist with 15 years of abdominal radiology experience, who was blinded to the clinical, laboratory and histopathological data (L.C.). Finally, relaxometry sequences were performed to measure hepatic iron according to a pre-established protocol [18,19]; and fat was quantified using chemical shift imaging (conventional in-phase and opposed-phase imaging), as previously described [10].

2.3. Histopathological evaluation

A pathologist (P.V.T.V.), blinded to the other test results, reviewed all the liver biopsies and graded them according to the NASH Clinical Research Network (NASH-CRN) system [20]. Considering the NAFLD Activity Score (NAS), "simple steatosis" was defined as NAS 1–2, "borderline NASH" as NAS 3–4 and "definite NASH" as NAS ≥5 [20,21]. Hepatic fibrosis was classified into five stages (F0, no fibrosis; F1, perisinusoidal or periportal fibrosis; F2, perisinusoidal and periportal fibrosis; F3, fibrous septa; F4, cirrhosis) [22].

2.4. Statistical analysis

LS was compared between different groups: volunteers, NAFLD patients without fibrosis on biopsy, those with mild fibrosis, and those with advanced fibrosis. Means or medians of LS were also compared between the different NAS histological groups. For this evaluation, the patients were stratified into three groups: simple steatosis, borderline NASH and definite NASH. Jonckheere-Terpstra, Mann-Whitney U and Student's *t*-tests were used for comparative analyses, adjusted using the Bonferroni method for multiple comparisons when needed. Correlations between LS and fibrosis stage on histology; and LS and NAS were investigated using the Spearman's method.

The variables LS, measured by elastography, NAS and BMI, which were associated with the degree of fibrosis in the univariate analysis at a significance level of 0.20, were included in the logistic regression model, using the proportional odds model.

To determine the diagnostic performance of MR elastography in differentiating between the various fibrosis stages and the volunteers,