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Original article

Non-invasive assessment of liver fibrosis in patients with hepatitis C: Shear wave elastography and colour Doppler velocity profile technique versus liver biopsy

Ehab F. Moustafa [a,*], Nahed Makhlouf [a], Sahar M. Hassany [a], Ahmed Helmy [a], Ahmed Nasr [a], Moustafa Othman [b], Hany Seif [b], Manal Darwish [c], Howayda Hassan [d], Mohamed Hessen [a]

[a] Assuit University, Tropical Medicine & Gastroenterology Department, Assiut, Egypt
[b] Assuit University, Radiology Department, Assiut, Egypt
[c] Assuit University, Public Health and Community Medicine Department, Assiut, Egypt
[d] Assuit University, Pathology Department, Assiut, Egypt

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ABSTRACT

Background and study aims: Determination of the presence and degree of liver fibrosis is essential for the prognosis and treatment of patients with chronic hepatitis C. Non-invasive methods of assessing fibrosis have been developed to reduce the need for biopsy. We determined the efficacy of shear wave elastography (SWE) and colour Doppler velocity as non-invasive methods for the assessment of liver fibrosis compared to liver biopsy among patients with chronic hepatitis C virus (HCV) infection.

Patients and methods: In total, 117 patients with chronic HCV infection and 50 healthy age- and sex-matched control subjects were included. For each patient and control, abdominal ultrasonography, Doppler ultrasonography of the right portal vein (PV), and SWE were performed, whereas liver biopsy was performed for patients.

Results: The mean value of the right PV maximum velocity was lower in patients with different stages of fibrosis than in controls ($p < 0.001$). The mean value of liver stiffness determined by SWE was significantly higher in patients with different stages of fibrosis than in controls. Cutoff values for liver stiffness determined by SWE for assessing fibrosis stages were F2 $\geqslant$ 4.815, F3 $\geqslant$ 6.335, and F4 = 7.540 with a sensitivity of 84.6%, 96.2%, and 100.0%; specificity of 88.5%, 93.8%, and 100.0%; positive predictive value (PPV) of 93.6%, 98.0%, and 100.0%; negative predictive value (NPV) of 74.2%, 88.2%, and 100.0%; and overall accuracy of 85.9%, 95.6%, and 100.0% [area under the ROC curve (AUC): 0.89, 0.96, and 1.0], respectively. Cutoff values for the right PV maximum velocity for assessing fibrosis stages were F2 < 23.4, F3 < 21, and F4 < 20 with a sensitivity of 65.0%, 57.4%, and 57.1%; specificity of 59.8%, 76.4%, and 75.5%; PPV of 33.8%, 58.3%, and 32.0%; NPV of 84.4%, 75.7%, and 89.7%; and overall accuracy of 61.1%, 69.5%, and 72.5% (AUC: 0.614, 0.696, and 0.625), respectively.

Conclusion: SWE is effective for the non-invasive assessment of liver fibrosis in patients with HCV infection. SWE provides a more accurate correlation with liver fibrosis stage than colour Doppler velocity profile for the assessment of liver fibrosis, especially in advanced stages (F3 and F4).

Introduction

The global prevalence of hepatitis C virus (HCV) infection is estimated to be 2.2%, which corresponds to approximately 170 million HCV-positive individuals [1].

Egypt has the highest prevalence rate of HCV infection in the world, making it the most challenging public health problem in the country. Studies show that 14.7% of the Egyptian population carries HCV antibodies and 9.8% have an active infection [2].

Accurate and precise estimation of the degree of liver fibrosis is important for determining the prognosis, surveillance, and treatment of patients with chronic HCV. Non-invasive methods of assessing fibrosis have been developed to reduce the need for biopsy [3,4].

Liver histologic analysis remains the reference standard for the assessment of liver fibrosis despite the intra- and interobserver variability in staging. A biopsy specimen of 25 mm in length has

* Corresponding author.
E-mail address: ehab_mostafa99@yahoo.com (E.F. Moustafa).

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>20% chances of being misdiagnosed with false-positive or false-negative results for fibrosis staging compared to large surgical biopsies, and there is a significant grey zone for intermediate stages [5]. In addition, liver biopsy is a painful technique that is not well accepted by patients, has morbidity and mortality risks, and is not an ideal method for following patients [6]. Moreover, classical estimates of diagnostic test accuracy [sensitivity, specificity, area under the receiver operator characteristic (ROC) curves (AUROC) and predictive values] are false or very limited.

Thus, non-invasive methods for assessing liver fibrosis are of great clinical interest. In the last decade, techniques to non-invasively estimate the stages of liver fibrosis have become commercially available. These techniques have the capability to evaluate differences in the elastic properties of soft tissues by measuring tissue behaviour when a mechanical stress is applied. Ultrasound and magnetic resonance have been used for elasticity imaging [7].

A few studies have evaluated real-time shear wave elastography (SWE) for assessing liver fibrosis by measuring liver stiffness in patients with chronic HCV infection [8].

SWE relies on the generation of shear waves that are determined by the displacement of tissues induced by the force of a focused ultrasound beam or by external pressure. The shear waves are lateral waves, with a motion perpendicular to the direction of the force that has generated them. They travel slowly (between 1 and 10 m/s) and are rapidly attenuated by tissue. The propagation velocity of the shear waves correlates with the elasticity of the tissue; that is, it increases with the increasing stiffness of the liver parenchyma [9]. Pawluś et al. reported that patients with hepatitis B and C but without significant liver fibrosis have stiffer spleens than healthy controls, and there is no correlation between liver and spleen elasticity [10].

The use of colour Doppler ultrasonography (CDU) for the diagnosis and staging of chronic liver disease has been based on the hypothesis that alteration of liver haemodynamics because of chronic inflammatory changes may indirectly reflect histological alterations. Therefore, positive correlation studies have usually referred to the velocity ratios of the hepatic artery (HA) to the portal vein (PV) or the resistivity index of the HA. However, the role of CDU remains controversial in terms of its reproducibility and the statistical significance [11].

In the present study, we aimed to assess the efficacy of SWE and CDU as non-invasive methods for the assessment of liver fibrosis compared to liver biopsy among patients with chronic HCV infection in Egypt. We compared these methods by assessing the grade of hepatic fibrosis by each method. Thus, ultimately, liver biopsy can be replaced with new non-invasive imaging modalities.

Patients and methods

During two years period, 117 patients with chronic HCV infection and 50 healthy age- and sex-matched control subjects were included in the study. For each patient and control, complete medical history was obtained and physical examination was performed. Liver function tests, complete blood count (CBC), and abdominal ultrasonography were also performed for all patients and control subjects, whereas HCV Ribonucleic acid (RNA) was detected by quantitative polymerse chain reaction (PCR) for all patients. Patients with hepatitis B virus (HBV) co-infection and those receiving treatment for HCV infection were excluded from the study.

The study protocol was approved by the ethical committee of Faculty of Medicine, Assiut University. All participants provided written informed consent. This study was not sponsored by any real-time SWE manufacturer.

Abdominal ultrasound and Doppler examination

The apparatus used was Philips iU22 Ultrasound Diagnostic Apparatus with a diagnostic probe frequency of 3.5–5.0 MHz. All patients fasted for 8 h before examination and were asked to breathe evenly when being examined. Conventional B-mode ultrasound examination was performed to assess liver and spleen size, the echo from the surface and parenchyma, and the inside diameter of the PV. The probe was placed where the right PV was best shown. The blood flow in the right PV was measured using colour Doppler flow imaging. After the image was frozen, the mean velocity, maximal velocity, and flow volume in the right PV were measured (Fig. 1).

Shear wave elastography

A Philips iU22 Ultrasound Diagnostic Apparatus with a diagnostic probe frequency of 3.5–5.0 MHz and mechanical index of 0.8 was used in this study with a convex broadband probe (SC6-1) as recommended. Shear waves were created in liver tissue from the acoustic radiation force generated by focalized ultrasound pulses. By capturing a circular region of interest (ROI) in a SWE image, the mean and standard deviation of the elasticity within the ROI can be displayed. A SWE box size of 3.5–2.5 cm was used. SWE measurements were performed on the right lobe of the liver through intercostal spaces with the patient in the supine position and the right arm maximally abducted. The upper edge of the SWE box was placed 1.5–2 cm from the Glisson's capsule of the liver and in an area of parenchyma that is free of large vessels. The entire real-time SWE examination lasted approximately 5 min per patient. Mean and median of 10 SWE measurements for each patient and healthy control were calculated (Fig. 2). The operator was blinded to the histopathological results. Using this technique, liver stiffness values in healthy volunteers were reported to be <4.0 kPa (1.15 m/s) [12,13].

Liver biopsy

Liver biopsy was performed in all patients. Liver biopsies were obtained using an 18-gauge or larger needle (one or two thin cores ranging from 1 to 2 cm in length), then immersed in 10% buffered formalin, routinely processed, and embedded in paraffin wax. Serial thin sections (each 4 μm) were mounted on slides, stained with hematoxylin and eosin, silver, and trichrome stains. Slides were examined by an expert histopathologist without prior knowledge of patients' clinical characteristics and serum measurements. At least six portal tracts must be included in sections for proper interpretation.

Fibrosis was staged on a 5-point scale according to METAVIR scoring system [14]:

F0: no fibrosis, **F1:** portal fibrosis alone, **F2:** portal fibrosis with rare septae, **F3:** portal fibrosis with many septae, and **F4**: cirrhosis. The presence of stage F2, F3, or F4 was termed "significant fibrosis," whereas the term "advanced fibrosis" was reserved for stage F3 or F4. Scoring was performed on two separate occasions that were 2 months apart and was independently evaluated by the author. Readings were combined to obtain a final figure.

Statistical analysis

A computerised system of recording ultrasound and Doppler ultrasound was developed for inputting information. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 (SPSS Inc., Chicago, IL). Continuous variables were represented as mean values, standard deviations, and median values. Analysis of variance was used to

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