

Noninvasive evaluation of hepatic fibrosis in patients with hepatitis C using elastography

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Background

Evaluation of the static elastography as a noninvasive method for predicting liver fibrosis in patients with hepatitis C virus as an alternative modality for liver biopsy.

Materials and methods

A group of 35 patients with chronic hepatitis C virus were subjected to biological tests, abdominal ultrasonographic examination, liver biopsy with a histopathological estimation of score of activity and fibrosis, and liver stiffness measurement by means of elastography of the left lobe of the liver.

Results

Our study showed that there is a significant association between the elastography score and the grade of fibrosis ($P=0.001$). A significant positive relationship was found between the activity stage and the elastography score ($r=0.625$ and $P=0.01$). Elastography has been shown to have a reasonably high sensitivity, specificity, and diagnostic accuracy 100, 48.27, and 57.14% and 87.5, 96.3, and 94.29% for fibrosis grades 0, 1, 2 and 5, 6, respectively. No statistically significant relationship was found between the diameter of the anterior abdominal wall and the accuracy of elastography. However, 63.6% of those with bright liver texture had an incorrect elastography score, whereas 42.9% of those with a normal liver texture had the correct elastography score, and this association was statistically significant ($P=0.039$).

Conclusion

Transient elastography indicates whether the liver is normal or cirrhotic; however, it has a low accuracy in the assessment of moderate stages of fibrosis (stages II, III, and IV). Bright liver affects the accuracy of elastography in assessing the degree of fibrosis, whereas anterior abdominal wall diameter does not.

Keywords:

elastography, hepatitis C virus, liver biopsy, ultrasonography

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Introduction

Hepatitis C virus (HCV) infection is a major health problem in Egypt, where the seroprevalence is 10–20-fold higher than that in the USA [1]. Egypt has the highest prevalence of HCV worldwide, ranging from 6% to more than 40% across regions and demographic groups [2]. At present, liver biopsy is considered the ‘gold standard’ to evaluate the grade of liver fibrosis [3]. Although liver biopsy is a generally accepted procedure, a major criticism of liver biopsy and an important stimulus to the development of noninvasive techniques is the small portion of the liver that is assessed [4]. The specimen obtained by standard liver biopsy techniques represents just 1/50 000 of the liver, and typically, only 16% of such biopsies exceed the optimal length of 25 mm required for an adequate histological assessment [4]. Furthermore, recent evidence indicates that even advanced fibrosis (not cirrhosis) is reversible. Spontaneous resolution of liver fibrosis can occur after successful treatment of the underlying disease. Therefore, there is a need for reliable, simple, and noninvasive methods to assess liver fibrosis [5].

More recently, assessment of liver fibrosis by a noninvasive method on the basis of physical measurements, called transient elastography (TE), has been proposed [6]. There are two types of elastography: static elastography and dynamic elastography.

This study was carried out to examine the usefulness of static elastography as a noninvasive technique for the evaluation of hepatic fibrosis in patients with HCV, as an alternative modality to liver biopsy.

Materials and methods

Patients

A group of 35 patients with chronic HCV hepatitis, positive HCV Ab by ELISA and/or positive HCV RNA by PCR (23 men and 12 women, mean age 41.5 ± 9.8 years), attending the Kasr El Aini University Hospital outpatient clinic were recruited after approval of the institutional ethical committee. Patients with a prothrombin concentration less than 60%, ascites, encephalopathy, other

causes of hepatitis, and patients with an ultrasonographic picture suggestive of cirrhosis or hepatocellular carcinoma were excluded from the study.

All patients in the study were subjected to biological tests, abdominal ultrasonographic examination, liver biopsy with a histopathological estimation of the score of activity and fibrosis, and liver stiffness measurement (LSM) by means of elastography of the left lobe of the liver.

Liver biopsy

Guided by a high-resolution machine (Hitachi 7500; Hitachi Medical Corporation, Tokyo, Japan), a tru-cut sonar-guided liver biopsy was performed using 18G needles. Histopathological scoring of activity and fibrosis was performed.

Transient elastography

Elastography of the left lobe of the liver was carried out using Hitachi 7500 (Hitachi Medical Corporation). The probe scanned vertically from the epigastrium to observe a sagittal section of the left hepatic lobe. The elasticity score was estimated according to the following scores.

Score 1: The entire colored area of the region of interest is distorted uniformly light green. *Score 2:* Partially mottled blue regions are shown in the light green-colored area. *Score 3:* Light green and blue are mixed in the colored area (almost a 50–50 mix). *Score 4:* Most of the colored area is shown as blue.

Statistical analysis

Patients' data were analyzed using SPSS 17.0 for windows 7. Quantitative variables were expressed by mean and SD (Standard deviation), compared using unpaired Student *t*-test and Mann-Whitney test. Spearman rank order test was used for correlating quantitative variables. Qualitative variables were expressed by numbers (Frequency) and percent compared between groups using χ^2 -test sensitivity, specificity, PPV and the NPV were calculated. *P* value was considered to be significant if less than 0.05.

Results

On the basis of the HAI score, the patients of our study were categorized into three groups: group I ($n = 21$): 71% men, with a fibrosis score of 0, 1, or 2, group II ($n = 6$): 66.6% men, with a fibrosis score of 3 or 4, and group III ($n = 8$): 50% men, with a fibrosis score of 5 or 6.

In this study, it was found that the elastography score is related to many parameters in the patients. The first is the total bilirubin, where a statistically significant mild positive correlation was found, with $r = 0.37$. Moreover, a significant association was found with the liver texture by abdominal ultrasonography, where an elastography score of 3 was associated with a coarse liver texture, whereas an elastography score of 1 was associated with a normal liver texture; this association was statistically significant ($P = 0.001$). Furthermore, on comparing the elastography scores with the liver texture grades detected by ultra-

sonography, it was found that the mean elastography score in patients with a coarse liver texture (2.83 ± 0.41) and in those with a high speckling liver texture (2.5 ± 0.58) was greater than that of normal liver texture (1.64 ± 0.5) ($P = 0.0001$ and 0.04 , respectively). Also, it has been reported that the diagnostic accuracy of elastography is significantly affected by the liver texture detected by ultrasonography, where 63.6% of those with a bright liver texture have an incorrect elastography score, whereas 42.9% of those with a normal liver texture have a correct elastography score; this association is statistically significant ($P = 0.039$). Age also tends to affect the diagnostic accuracy of elastography, where, the mean age of patients with a bright liver texture (46.64 ± 7.06) has been found to be higher than those with a normal liver texture (38.36 ± 7.85), and this difference is statistically significant ($P = 0.01$). However, on studying the influence of anterior abdominal wall thickness by ultrasonography on the elastography score, it has been reported that there was no statistically significant relationship between the diameter of the anterior abdominal wall and the accuracy of elastography. For other ultrasonographic findings, a statistically significant ($P = 0.001$) association was found between the elastography score of 3 and the portal vein diameter of at least 13 mm, as well as a significant positive relationship between the splenic size and the elastography score ($r = 0.42$).

Liver biopsy was performed in all the studied groups, and its results were compared with those of abdominal ultrasonographic findings and elastography scores, and on analyzing the results of the liver biopsy, it was found that there was no statistically significant difference between the stage of activity in the normal liver texture group (1.5 ± 1.2) and that of the high speckling liver texture group (5 ± 3.56) ($P = 0.14$), and the same was found for the fibrosis stage between both the normal liver texture (4.43 ± 2.06) and the high speckling group (3.5 ± 1.29) ($P = 0.306$).

Although the result was different for elastography, where a significant association was found between the elastography score and the fibrosis stage, 75% of patients with an elastography score of 3 had fibrosis stage VI and 33.3% of patients with an elastography score of 2 had fibrosis stage II; this association was statistically significant ($P = 0.001$).

Moreover, a significant positive relationship was found between the stage of activity and the elastography score ($r = 0.625$ and $P = 0.01$). Elastography has been shown to have a reasonably high sensitivity, specificity, and diagnostic accuracy for fibrosis at both ends of the spectrum (groups I and III).

Discussion

The assessment of liver fibrosis is important for the staging and prognosis of chronic hepatitis [7]. Moreover, in viral hepatitis, the extent of liver damage is often an important factor to either start or postpone antiviral treatment [8].

Liver biopsy is still considered to be the gold standard for the assessment of liver fibrosis, but it has many disadvantages, which include the risks of complications and the risk of sampling errors with underestimation of fibrosis. Moreover, it is not feasible to repeat liver biopsies frequently, and the extent of liver damage can increase at relatively fast rates. The present study was carried out on 35 patients with chronic liver disease using TE scanning of the left lobe of the liver to measure liver stiffness as a noninvasive alternative for liver biopsies.

On performing TE, it was found that it closely matched the results of ultrasonographic examination, where increasing elastography score grades were associated with a coarse liver texture and vice versa, but on studying the results of liver biopsy, it was found that the accuracy of TE scores in diagnosis is affected by the ultrasonographic findings, where 63.6% of patients with a bright liver texture on ultrasonography had a mismatched elastography score whereas only 42.9% of those with a normal liver texture on ultrasonography has matched elastography scores, indicating that bright liver does affect the accuracy of elastography in assessing the degree of fibrosis, whereas the thickness of anterior abdominal does not interfere with the diagnostic accuracy of TE. Moreover, using TE, the predictability of patients with a fibrosis score of 0, 1, or 2 (group I), and a score of 5 or 6 (group III) was more accurate, sensitive, and more specific than those of patients with a score of 3 or 4 (group II), indicating that the fibrosis score does affect the accuracy of TE, and that TE has been shown to have a reasonably high sensitivity and specificity for fibrosis at both ends of the spectrum. TE appears to be useful to determine whether the liver is normal or cirrhotic.

The results of our study are in agreement with the results obtained by Zioli *et al.* [9] for group III, for which the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 86, 96, 78, and 97%, respectively. However, they are not in agreement with our results for groups I and II; the sensitivity, specificity, PPV, and NPV were 56, 91, 88, and 56% respectively, for group I and 86, 85, 71, and 9.3%, respectively, for group II.

Also, the results of this study are in agreement with the results obtained by Castera *et al.* [10] for group III, for which the sensitivity, specificity, PPV, and NPV were 87, 91, 77, and 95%, respectively. However, it is not in agreement with our results for groups I and II; the sensitivity, specificity, PPV, and NPV were 67, 89, 95, and 48%, respectively, for group I and 73, 73, 87, and 81%, respectively, for group II.

Moreover, the results of this study are in agreement with the results obtained by Friedrich-Rust [11] for group III, who reported a specificity and NPV of 90.7 and 80%, respectively. However, it is not in agreement with our results for groups I, II, and III; the sensitivity, specificity, PPV, and NPV were 80, 61.1, 63.2, and 78.6%, respectively, for group I, 67.6, 67.7, 52.3, and 80%, respectively, for group II, and the sensitivity and PPV were 29.2 and 50%, respectively, for group III.

Our results are in agreement with the results published by Cross *et al.* [12], who concluded that the noninvasive markers and, particularly, fibroscan were effective tests for the prediction of cirrhosis in chronic hepatitis. In a study carried out by Wang *et al.* [13], 214 patients with chronic HCV hepatitis, 88 patients with chronic HBV hepatitis, and 18 patients with chronic HBV and HCV hepatitis were evaluated by liver biopsy TE, and ultrasonography. Ultrasonography scores, including those obtained after assessment of liver surface, liver parenchyma, intrahepatic vessels, and spleen index, were used to assess the degree of hepatic fibrosis. LSMs as determined by TE correlated significantly with hepatic fibrosis scores, necroinflammatory activity, and ultrasonography scores in multivariate analysis.

Fransen van de Putte *et al.* [14] reported that in 10 patients, LSM and biopsy showed corresponding results, whereas in eight other patients, only one difference in fibrosis stage was observed (often with very small differences in kPa between the LSM result and the nearest limit of the biopsy fibrosis stage). Also, they reported that alanine aminotransferase levels did not appear to be associated with discrepancies between the results of LSM and biopsy in our patients. They also reported that ultrasound was found to be highly specific, but not very sensitive to predict cirrhosis. As a consequence, no further investigations are necessary when cirrhosis is found on ultrasound, but further investigations may be considered if ultrasound is normal, depending on clinical judgment. They concluded that the LSM using fibroscan appears to be a valuable noninvasive addition to clinical practice in patients with chronic viral hepatitis. This is not totally in agreement with our results, and may be attributed to the different Fibroscan device (Echosens, Paris, France) used in their study.

Finally, the results of this study are in agreement with those obtained by Foucher *et al.* [15] for group III; the sensitivity, specificity, PPV, and NPV were 77, 97, 91, and 92%, respectively. However, this is not in agreement with our results for groups I and II; the sensitivity, specificity, PPV, and NPV were 64, 85, 90, and 52%, respectively, for group I and 65, 95, 90, and 80%, respectively, for group II.

TE has been shown to have a reasonably high sensitivity and specificity for fibrosis at both ends of the spectrum. Thus, the greatest clinical utility of TE will be its ability to determine whether the patient has cirrhosis, because, in our study, the sensitivity, specificity, PPV, and NPV were 87.5, 96.3, 87.5, and 96.3%, respectively, for group III and 100, 48.27, 28.57, 100%, and 26.32, 0.00, 23.81, 0.00% among groups I and II, respectively.

Conclusion

Elastography is a rapid, safe, acceptable, and noninvasive marker of fibrosis assessment, providing a new way to monitor patients with chronic liver disease, particularly HCV infection. However, the results of elastography must be interpreted according to the results of clinical examination, laboratory, sonography results, and liver histology.

In clinical practice, high elastography values may be accurate in assessing the severity of liver disease, to suspect the presence of complications and, consequently, in providing a follow-up program. TE (static elastography) has been shown to have a reasonably high sensitivity and specificity for fibrosis at both ends of the spectrum. TE appears to be useful to determine whether the liver is normal or cirrhotic; however, it has low accuracy in assessing moderate stages of fibrosis (stages II, III, and IV).

Bright liver affects the accuracy of elastography in assessing the degree of fibrosis, whereas the anterior abdominal wall diameter does not.

The drawback of our study is the size of the liver biopsy sample as an inadequate sample study would underestimate the efficiency of TE in detecting advanced fibrosis [16]. Moreover, further studies on a large number of patients are required to determine the accuracy of this technique in assessing the degree of liver fibrosis.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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