PROSPECTIVE COMPARISON OF TRANSIENT ELASTOGRAPHY AND LIVER BIOPSY FOR THE ASSESSMENT OF FIBROSIS IN CHRONIC HEPATITIS C INFECTION

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Transient elastography; Biopsy; Hepatic fibrosis

Abstract
HCV is a worldwide problem and the need to assess the degree of fibrosis is the cornerstone in its treatment. Liver biopsy has been used for years to assess the degree of fibrosis and activity but recently many non-invasive methods have emerged to replace it as aspartate transaminase/platelet ratio (APRI), abdominal ultrasonography measuring caudate/right lobe ratio and hepatic stiffness (Fibroscan).

Purpose: Correlate the accuracy of Transient Elastography (Fibroscan) in comparison to liver biopsy as a non-invasive method for fibrosis assessment in chronic hepatitis C patients.

Methods: The study was done on 50 patients with chronic HCV [32 males and 18 females] for which liver biopsy and fibroscan were performed.

Results: There was positive correlation of liver biopsy with fibroscan score, there was moderate agreement (matching) between liver biopsy and fibroscan the lowest matching were in F0 and the highest were in F3.

Conclusion: Fibroscan has a good matching with liver biopsy in the detection of hepatic fibrosis and follow up of its progression.

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1. Introduction

Chronic hepatitis C (HCV) is a global health problem that affects more than 170 million people worldwide (1), particularly in Egypt, where high prevalence rates were reported...
reaching up to 20% (2). Diagnosis and treatment of patients with chronic hepatitis mostly rely on the staging of liver fibrosis. Antiviral therapy is proposed if moderate to severe (METAVIR stages F2 and F3) fibrosis is present (3).

Liver biopsy (LB) has traditionally been considered the gold standard for pretreatment evaluation of liver fibrosis in patients with chronic hepatitis C (CHC). However, LB is an invasive procedure with several shortcomings (intra- and inter-observer variability of histopathological interpretation, sampling errors, high cost) and the risk of rare but potentially life-threatening complications. In addition, LB is poorly accepted by patients and it is not suitable for repeated evaluation. Furthermore, the prevalence of CHC makes LB unrealistic to be performed in all patients with this disease who are candidates for antiviral therapy (4). This has raised the need for developing other techniques that are less injurious and of equal accuracy to skip the step of liver biopsy.

Some of the invented methods as aspartate transaminase/platelet ratio (APRI), abdominal ultrasonography measuring caudate/right lobe ratio and hepatic stiffness (Fibroscan) have been adopted to avoid biopsy.

In this study we evaluate the diagnostic accuracy and clinical usefulness of fibroscan in predicting two conditions – significant histological liver fibrosis (METAVIR ≥ F2) and cirrhosis (F4) in patients with chronic viral hepatitis in comparison to the liver biopsy.

2. Patients and methods

The study was done on 50 chronic HCV patients with the age of the patients ranging from 19 to 56 year old with mean age 37.6 ± 10 diagnosed by seropositivity for HCV antibodies and HCV RNA by PCR. Patients were recruited from NHTMRI outpatient clinics for assessment prior to Interferon therapy. Inclusion and exclusion criteria are those for interferon therapy.

Patients were subjected to the following:

1. Full history taking.
2. Clinical examination.

3. Laboratory investigations: CBC, AST, ALT, serum bilirubin, serum albumin, prothrombin time, prothrombin concentration &INR, viral markers HBs Ag, HCV Ab and PCR of HCV.
4. Abdominal ultrasonography to assess the presence of liver cirrhosis and ascites, portal vein and splenic size.
5. Liver stiffness measurement using the transient elastography (fibroscan) (Fig. 1).

6. Ultrasound guided liver biopsy was performed using a semi-automatic true-cut needle (16 G) and liver biopsy was fixed in formalin and embedded in paraffin.

– Liver fibrosis staging and activity grading was evaluated according to the METAVIR scoring system. The used fibroscan device was (Echosens, Paris, France) located at the NHTMRI done by the same expert with experience of more than 500 cases.

– Fibrosis was staged on a 0–4 scale as follows: F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis with rare septa; F3 = numerous septa without cirrhosis; and F4 = cirrhosis.

– Activity (A) was graded as follows: A0 = no histologic necro-inflammatory activity; A1 = mild activity; A2 = moderate activity; and A3 = severe activity. (The French METAVIR Cooperative Study Group, 1994).

– Biopsy specimens were classified according to the length of the specimen into three groups:1-Ideal biopsy: Specimen length ≥ 1.5 cm or the presence of 10 portal tracts, 2-Subideal biopsy: Specimen length ≥ 1 and < 1.5 with ≥ 6 portal tracts and <10 portal tracts and 3-Not accepted < 1 cm.

2.1. Ethical considerations

The patients gave a written consent for the procedures after explaining the risk/benefit ratio as well as expected hazards and interventions.

2.2. Statistical analysis

Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. Description of

Fig. 1 (a) Duplex image showed coarse hepatic echo-texture, wavy surface and patent PV with increased diameter and hepatofugal flow.
(b) Fibroscan score: F4 (34.3 K pascal).
variables was presented as follows: Description of quantitative variables was in the form of mean and Standard Deviation (SD). Description of qualitative variables was in the form of numbers (No.) and percents comparison between quantitative variables was carried by Repeated measures Analysis of Variance (ANOVA) test for comparing between more than two groups of independent variables. Results were expressed in the form of P-values.

3. Results

The study was carried on 50 patients with chronic HCV with the age of the patients ranging from 19 to 56 year old with mean age 37.6 ± 10. Concerning the hepatic function tests total bilirubin were (0.74 mg/dl ± 0.25 mg/dl) AST level were (50.4 ± 35.99), ALT level were (49.54 ± 36.98), serum albumin g/dl were (4.14 ± 0.36 g/dl) prothrombin concentration were (87.7% ± 10.9%) and INR (1.04 ± 0.21). Concerning other lab finding TSH were (1.69 m IU/L ± 0.93), serum creatinine were (0.83 mg/dl ± 0.19), serum HB were (13.67 g/dl ± 1.43), platelets were (228,900 ± 61,900) and AFP were ng/ml 5.97 ± 13.65 (Table 1).

There was positive correlation between the fibroscan and liver biopsy. In fibroscan score 8 patients (16%) were F0, 27 patients (54%) were F1, 6 patients (12%) were F2, 5 patients(10%) were F3 and 4 patients (8%) were F4. In biopsy 3 patients (6%) were F0, 31 patients (62%) were F1, 7 patients (14%) were F2, 6 patients (12%) were F3 and 3 patients (6%) were F4. Comparing between F0 score of biopsy there was fair agreement between fibroscan and biopsy (the kappa measure was 0.359). Comparison between F1 score of biopsy there also

was moderate agreement between fibroscan and biopsy (the kappa measure was 0.468). Comparison between F2 score of biopsy there also was moderate agreement between fibroscan and biopsy (the kappa measure were 0.482). Comparison between F3 score of biopsy and fibroscan there was high agreement between fibroscan and biopsy (the kappa measure was 0.737). Comparison between F4 score of biopsy and fibroscan there was moderate agreement between fibroscan and biopsy (the kappa measure was 0.41). The overall relation between all patients on all fibrosis stages when comparing both fibroscan and biopsy was moderate agreement between both (the kappa measure was 0.478). These results are illustrated in Tables 2 and 4.

4. Discussion

Liver biopsy has a distinct advantage in that commonly associated liver lesions, such as steatohepatitis and iron overload which can impact on fibrosis progression and treatment response, can be diagnosed and investigated (5). However, it also has its limitations in staging fibrosis because of the heterogeneous distribution of fibrosis in the liver and the moderate reproducibility of readings. (6) (see Table 3 and 5)

Ultrasonic transient elastography (TE), enables to assess, under active mechanical constraints, the elasticity of the liver,
which correlates with hepatic fibrosis stages. This technique is routinely used in clinical practice to assess noninvasively liver stiffness. The Fibroscan system generates a shear wave via an impulse stress applied on the surface of the skin and records a temporal series of radio-frequency (RF) lines using a single-element ultrasound probe. Under the assumption of pure elastic tissue, elasticity is proportional to the shear wave speed (7).

Fibroscan is a non-invasive test that assists liver stiffness by employing vibration controlled transient elastography to emit a shear wave through the liver and measure its velocity via ultrasound (8).

Not only liver fibrosis but also other factors contribute to liver stiffness. Liver stiffness measurement (LSM) has been consistently found to be falsely elevated in acute hepatitis, manifested as alanine aminotransferase (ALT) flares. Severe hepatic necro-inflammation may lead to LSM values well within the cirrhotic range, even in the absence of fibrosis on histology (9).

The main advantage of liver Fibroscan compared with fibrosis markers and biochemical scores is that it measures a quantitative physical parameter directly on the liver and there is no interference from extrhepatic disorders. It represents a totally different approach and therefore could be complementary to the fibrosis markers and biochemical scores to better assess liver fibrosis without using LB (10).

Halfon et al., (11) and Rossi et al., (12) found that, the diagnostic performance of liver Fibroscan appears to be equivalent to that of the best biochemical scores for patients with significant fibrosis \(F \geq 2\) and appears to be better than this test for the diagnosis of extensive fibrosis \(F \geq 3\) and cirrhosis \(F = 4\).

Our study included 50 chronic HCV patients as diagnosed by seropositivity for HCV antibodies and HCV RNA by PCR. Patients were recruited from NHTMRI outpatient clinics for assessment prior to INF therapy as a part of the National program for treatment of viral hepatitis.

In the present study, there was a positive correlation between fibroscan and biopsy as follows: By fibroscan score 8 patients (16%) were F0, 27 patients (54%) were F1, 6 patients (12%) were F2, 5 patients (10%) were F3 and 4 patients (8%) were F4. On liver biopsy, 3 patients (6%) were F0, 31 patients (62%) were F1, 7 patients (14%) were F2, 6 patients (12%) were F3 and 3 patients (6%) were F4.

On comparing F0 score of biopsy there was fair agreement between fibroscan and biopsy (the kappa measure was 0.359). Comparison between F1 score of biopsy showed moderate agreement between fibroscan and biopsy (the kappa measure was 0.468). Comparison between F2 score of biopsy revealed moderate agreement between fibroscan and biopsy (the kappa measure was 0.482). Comparison between F3 score of biopsy and fibroscan had a high agreement between fibroscan and biopsy (the kappa measure was 0.737). On comparing between F4 score of biopsy and fibroscan there was moderate agreement between fibroscan and biopsy (the kappa measure was 0.80). The overall correlation of liver biopsy with fibroscan and biopsy had a high agreement between fibroscan and biopsy (the kappa measure was 0.737). On comparing between F4 score of biopsy and fibroscan there was moderate agreement between fibroscan and biopsy (the kappa measure was 0.8). The overall relation between all patients on all fibrosis stages when comparing both fibroscan and biopsy was moderate agreement between both (the kappa measure was 0.78). This was similar to a study carried out by Rohit and his colleagues where there was significant correlation between LSM and histological fibrosis \(r = 0.58, P < 0.001\) (13). In contrast, patients with high fibroscan scores \(n = 6; > 11 \text{kPa}\) showed a severe form of liver fibrosis with CLD and portal hypertension from a clinical point of view in a study carried out by Muñoz R and his colleagues (14).

One of the limitations to liver fibroscan is ascites. Ascites is a physical limitation to the technique because elastic waves do not propagate through liquids. In addition, liver fibroscan is unsuccessful in patients with narrow intercostal spaces and in patients with morbid obesity (15). None of our patients had ascites and this is because they were selected from patients awaiting assessment for pegylated interferon/ribavirin combination therapy. None of our patients was morbidly obese (all had BMI of 26.36 ± 3.2).

We also assessed the validity of ultrasonography in the detection of fibrosis in relation to fibroscan and there was a very high statistical significance for the echotexture and the degree of fibrosis. Aube et al. (16) reported that ultrasonography had accuracy of 82%-88% to 100% in assessing the diagnosis of cirrhosis. Its value is tempered by significant interobserver variability and an inability to gather all the required measurements, because of technical limitations (17). However, ultrasonography cannot quantify fibrosis and accurately diagnose it in the absence of the stigmata of cirrhosis including shrunken liver and ascites which per se indicate cirrhosis and advanced fibrotic process and hence not accepted for assessment of hepatic fibrosis in patients waiting for combination therapy; instead it may be useful to exclude patients with advanced cirrhosis from antiviral therapy (18).

To summarize, the correlation of liver biopsy with fibroscan score there was moderate agreement (matching) between liver biopsy and fibroscan; the highest matching in F3 and lowest in F0, that means that fibroscan has a good matching with liver biopsy in detection hepatic fibrosis and follow up of its progression.

**Conflict of interest**

None declared.
References