Comparative Study between Fibroscan and Liver Biopsy Results in Chronic HBV Egyptian Patients: A Single Center Pilot Study

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Abstract

Objective: Recent reports have shown that liver stiffness measurement using Fibroscan allowed accurate prediction of hepatic fibrosis in patient with chronic hepatitis C but few reports are published for chronic hepatitis B especially in Egypt. The study aimed to compare and validate the results of fibroscan versus liver biopsy among chronic HBV patients who are not candidates for treatment according to Egyptian Guidelines.

Methods: Thirty one chronic HBV patients not candidates for treatment were included in our study. Patients who were histologically confirmed with liver biopsy within recent 6 months were enrolled. Inclusion criteria were males and females above 18 years, HBeAg positive or negative cases with HBV DNA by 2000IU/ml with normal or fluctuating liver enzymes. Exclusion criteria included concomitant HCV infection, evidence of liver disease induced by other causes, and age less than 18 years. Patients were subjected to liver biopsy and fibroscan study. Both liver biopsy and fibroscan were performed and interpreted in Hepatology And Pathology Departments at National Hepatology and Tropical Medicine Research Institute, Cairo (NHTMRI).

Results: The mean age of our patients was 35.4. Study population showed male predominance as the number of males was 25 cases (80.6%) while the number of females was 6 (19.4%). The mean ALT was 35.01U/L and the mean AST level was 30.89U/L. HBV DNA levels were quite variable with a minimum of 188IU/ML and a maximum of 80,162,000 IU/ML with a mean of 2,613,521. Liver biopsy results showed that 4 cases had a fibrosis score of (F0), 19 cases (F 1), 5 cases (F2), and only 3 cases (F3). Fibroscan results coincided with liver biopsy cases in all 4 cases with F0. Eleven cases with an F1 biopsy result had a less fibroscan result of F0, 5 cases had an increased fibroscan score of F2 and only three cases coincided with liver biopsy. Fibroscan results coincided with liver biopsy in 4 cases out of 5 in F2 liver biopsy group. The 3 cases that showed a liver biopsy result of F3 had a less fibroscan result of F2.

Conclusion: Liver stiffness assessment was found to be correlated with liver fibrosis however the results of liver biopsy were not similar to fibroscan results. Most of the cases had a fibroscan result less than liver biopsy results by Metavir score. Only cases with Metavir score of F0 and most of F2 coincided with fibroscan results.

Key Words: HBV – Egyptian patients – Liver biopsy – Fibroscan – Histopathological changes.

Introduction

CHRONIC hepatitis B virus infection (HBV) poses a serious global health problem based on the approximately 350 million individuals suffering from chronic hepatitis B (CHB) infection worldwide [1].

Approximately 1 million patients die of liver failure, cirrhosis and hepatocellular carcinoma (HCC) as a result of HBV infection each year [2]. Approximately 10-20% of patients with chronic hepatitis B (CHB) infection have liver cirrhosis at first presentation, and an additional 20-30% of patients will eventually develop this condition and its complications within one or more decades [3].

Studies have demonstrated that the risk of liver disease progression in patients with CHB is associated with elevated HBV DNA levels [4,5]. Therefore, the goal of therapy for CHB patients is to delay or prevent progression of liver disease by suppressing long-term HBV DNA replication [6]. Most guidelines recommend treatment of chronic HBV for those with high HBV DNA 2000 and persistently elevated liver enzymes. Recent studies suggest that the upper limits of normal for ALT levels should be decreased to 30IU/l for men and 19IU/l for women. HBV infected patients with ALT values close to the upper limit of normal were found to have abnormal histology and can be at increased risk of mortality from liver disease especially those above the age of 40 years [7].
Because liver complications usually develop in patients with advanced liver fibrosis and cirrhosis, the early detection of advanced liver fibrosis and cirrhosis and the assessment of their severity for the design of optimal surveillance and intervention strategies are important. Although liver biopsy (LB) has been the gold standard for assessing liver fibrosis to date [8], it is prone to sampling error and interpretational variability [9]. Recently, liver stiffness measurement (LSM) using transient elastography (FibroScan) has been introduced for assessing liver fibrosis with accurate, reproducible, and reliable results [10]. Furthermore, because liver stiffness measurement (LSM) can be expressed numerically as a continuous variable, clinicians can grade the degree of liver fibrosis, even in patients with cirrhosis. The non-invasive assessment of fibrosis in chronic hepatitis, especially of viral etiology, is accepted more and more, partially replacing liver biopsy (LB) in some countries [11]. Transient elastography Fibroscan (FS), Echosens, France is a reproducible, non-invasive and rapid method for measuring liver stiffness. It is based on sonographic measurement of the propagation velocity of an elastic shear wave induced by the device itself: the faster the wave, the stiffer the medium. Studies of patients with hepatitis C virus (HCV) infection have shown that wave velocity correlates with the degree of liver fibrosis, and that elastography can accurately detect both early fibrosis and advanced fibrosis [8]. However, few data is available on the use of this method in patients with chronic hepatitis B, especially in Egypt.

**Patients and Methods**

Thirty-one chronic hepatitis B patients regularly attending HBV specialized clinic at National Hepatology and Tropical Medicine Research Institute, Cairo (NHTMRI) on twice weekly basis were recruited. Patient enrollment started from January 2013 to December 2013. Patients were not candidates for HBV treatment according to Egyptian guidelines for HBV which states that (Inclusion criteria for treatment Age 18 years, HBsAg (+ve) for more than 6 months, HBV DNA 2000IU/ML, ALT elevation above upper limit of normal on 2 successive occasions within 3-6 months.

**According to the egyptian guidelines, liver biopsy is used to guide treatment decisions for patients who show:**

- HBV DNA 2000IU/ML with persistently normal ALT.
- HBV DNA <2000IU/ML with persistently elevated ALT.
- HBV DNA <2000IU/ML with normal ALT and there is clinical evidence of liver disease or a family history of HCC. Treatment is recommended for those with A2 and/or F2 or more (Metavir score) (Released by National Committee for Control of Viral Hepatitis (NCCVH) at 31/3/2013, (Unpublished data).

Those patients are only candidates for follow-up by regular investigations for liver profile and HBV DNA every 3 to 6 months according to every case individually. Inclusion criteria for our patients were adult males and females above 18 years old, HBeAg positive negative, HBV DNA by 2000C IU/ml with normal or fluctuating liver enzymes.

Exclusion criteria included concomitant HCV infection, evidence of liver disease induced by other causes, and age less than 18 years.

After obtaining the ethical committee approval, a written informed consent was taken from all subjects after explaining the goals of our study to further assess their condition and the possibility of offering them therapy for chronic HBV if results showed advanced fibrosis or activity scores.

The clinical parameters collected included present and past medical history, biochemical parameters; ALT, AST, albumin, total bilirubin, platelet count, and prothrombin conc. Serological markers included hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), HBeAg, HBeAb and hepatitis C virus antibody (HCV Ab) and quantitative HBV DNA testing.

**Liver histology:** Patients who had already had liver biopsy in the previous 6 months before the study were enrolled without the need for a second biopsy. The other patients underwent NBL prospectively. Needle biopsy of the liver was done by a trained hepatologist. The samples were fixed in paraffin and stained with hematin-eosin and Masson Trichrome stain to detect fibrosis. The slides were all read by an experienced pathologist in pathology department in our institute. The size of the biopsy specimens was noted. Liver fibrosis and necroinflammatory activity were assessed with the METAVIR scoring system. Fibrosis was therefore scored on a scale from 0 to 4 (F0=No fibrosis, F1=Portal fibrosis without septa, F2=Portal fibrosis and few septa, F3=Numerous septa without cirrhosis, F4= Cirrhosis), and activity on a scale from 0 to 3 (A0= None, A1=Mild, A2=Moderate, A3=Severe).

Hepatic elastography. We used a Fibroscan FS (Echosens, Paris, France) The device is available at NHTMRI. The success rate of the examination is calculated as the ratio between the number of
measurements validated by the machine and the total number of attempted measurements during the same examination. The median value of the validated measurements is taken to represent liver stiffness. The interquartile range (IQR) represents the interval around the median that contains 50% of valid measurements. To be considered interpretable and valid, the examination must include at least 10 measurements with a success rate of at least 66%, and the IQR must not exceed 33% of the result of the examination.

Statistical analysis:
Data were entered in MS Excel 2010 sheet. Data cleaning was done and then the data was transformed to Statistical Package for the Social Sciences (SPSS) version 20.0 for statistical analysis. Frequency and percent were used to present qualitative variables and mean±standard deviation was used to present quantitative data. The chi-squared test was used to estimate difference between results of Liver biopsy and fibroscan.

Results
Our study included 31 chronic HBV patients. The mean age of our patients was 35.4. Study population showed male predominance as the number of males was 25 cases (80.6%) while the number of females was 6 (19.4%). The mean ALT was 35.01U/L and the mean AST level was 30.89 U/L. HBV DNA levels were quite variable with a minimum of 188IU/ML and a maximum of 80,162,000IU/ML with a mean of 2,613.521 (Table 1).

HBeAg negative cases represented the majority of our patients as their number was 29 cases (93.5%) and only 2 cases were HBeAg positive (6.5%). As part of our inclusion criteria, all our cases were HCV antibody negative. Results of abdominal ultrasound revealed that 8 cases (25.8%) had normal ultrasound result, 8 cases (25.8) had hepatomegaly, 9 cases (29%) had bright liver and 6 cases (19.4%) had coarse liver (Table 2).

Liver biopsy results showed that 4 cases had a fibrosis score of (F0), 19 cases (F 1), 5 cases (F2), and only 3 cases (F3) (Table 3).

Fibroscan results coincided with liver biopsy cases in all 4 cases with F0. Eleven cases with F 1 biopsy result had a less fibroscan result of F0, 5 cases had an increased fibroscan score of F2 and only three coincided with liver biopsy results. Fibroscan results coincided with liver biopsy in 4 cases out of 5 in F2 liver biopsy group. The 3 cases who showed a liver biopsy result of F3 had a less fibroscan result of F2 (Table 4).

Table (1): Description of study subjects in relation to age and some blood parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>21.00</td>
<td>54.00</td>
<td>35.48</td>
<td>10.43</td>
</tr>
<tr>
<td>ALT</td>
<td>11.00</td>
<td>88.00</td>
<td>35.01</td>
<td>18.39</td>
</tr>
<tr>
<td>AST</td>
<td>19.00</td>
<td>66.00</td>
<td>30.89</td>
<td>10.37</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.34</td>
<td>1.20</td>
<td>0.67</td>
<td>0.22</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>0.29</td>
<td>11.00</td>
<td>4.52</td>
<td>2.67</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>2.30</td>
<td>5.00</td>
<td>4.14</td>
<td>0.48</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>70.00</td>
<td>100.00</td>
<td>86.66</td>
<td>9.12</td>
</tr>
<tr>
<td>Serum creatine</td>
<td>0.10</td>
<td>1.60</td>
<td>0.87</td>
<td>0.28</td>
</tr>
<tr>
<td>Platelets</td>
<td>96.00</td>
<td>315.00</td>
<td>227.74</td>
<td>47.99</td>
</tr>
<tr>
<td>HBV DNA IU/ML</td>
<td>188.00</td>
<td>80,162,000.00</td>
<td>2,613,521.7419</td>
<td>14,392,736.87708</td>
</tr>
<tr>
<td>Stiffness</td>
<td>3.00</td>
<td>10.90</td>
<td>6.67</td>
<td>2.49</td>
</tr>
</tbody>
</table>

Table (2): Abdominal ultrasound.

<table>
<thead>
<tr>
<th>Ultrasound feature</th>
<th>Number</th>
<th>Percent</th>
<th>Liver biopsy</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright liver</td>
<td>9</td>
<td>29.0</td>
<td>F0</td>
<td>4</td>
<td>12.9</td>
</tr>
<tr>
<td>Coarse</td>
<td>6</td>
<td>19.4</td>
<td>F1</td>
<td>19</td>
<td>61.3</td>
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<tr>
<td>Hepatomegaly</td>
<td>8</td>
<td>25.8</td>
<td>F2</td>
<td>5</td>
<td>16.1</td>
</tr>
<tr>
<td>Normal</td>
<td>8</td>
<td>25.8</td>
<td>F3</td>
<td>3</td>
<td>9.7</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>100.0</td>
<td>Total</td>
<td>31</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table (3): Liver biopsy results.

<table>
<thead>
<tr>
<th>Liver biopsy</th>
<th>F0</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>F0</td>
<td>4</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>F1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>F2</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>F3</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>19</td>
<td>5</td>
<td>3</td>
<td>31</td>
</tr>
</tbody>
</table>

Table (4): Liver biopsy results versus fibroscan.
Discussion

This is a comparative pilot study comparing the results of liver biopsy and fibroscan among chronic HBV Egyptian patients who are not candidates for treatment. Most guidelines recommend treatment of chronic HBV for those cases with HBV DNA 2000 and persistently elevated liver enzymes. Recent studies suggest that the upper limits of normal for ALT levels should be decreased to 30IU/l for men and 19IU/l for women. HBV infected patients with ALT values close to the upper limit of normal were found to have abnormal histology and can be at increased risk of mortality from liver disease especially those above the age of 40 years [7]. In our study we tried to compare the liver biopsy results (Index results) with the fibroscan results performed to the same patients within 6 months. The results of our study points to the similarity of fibrosis scores among patients with no or minimal fibrosis (F0) scores in both liver biopsy and fibroscan. On the other hand a heterogenous result was obtained in cases with F1 fibrosis score. Most of F1 cases (11 cases) had an F0 score regarding fibroscan result. Similar observations were emphasized by Sporea et al., [12]. In patients with HBV chronic infection, data regarding LS measurement for fibrosis staging are conflicting. One explanation could be that the necroinflammatory activity in HBV infection can vary with time, as well as the fact that fluctuations in aminotransferases can occur. In another study done by Seo et al., [13], LS measurements were better correlated with the fibrosis score in patients with chronic HCV hepatitis than in those with chronic HBV hepatitis (0.773 vs 0.557, p<0.001). The AUROC was larger in the group of patients with chronic HCV hepatitis (0.944, 0.982, and 0.958 for F2, F3, and F4 respectively) than in those with chronic HBV hepatitis (0.881, 0.863 and 0.850, respectively). Unlike HBV, transient elastography (TE) is a validated non-invasive tool to evaluate hepatic fibrosis in patients with hepatitis C virus (HCV) infection [14]. Also Canavan et al., [15] stated that ultrasound elastography for fibrosis surveillance is cost effective in patients with chronic hepatitis C virus in the UK.

Alterations of levels of aminotransferases can influence the LS values obtained by means of transient elastography (TE), so that LS measurements have to be interpreted in a biochemical context, otherwise there is a risk of over estimating the severity of fibrosis. Also this explains why LS measurements are not performed in acute hepatitis or during alanine aminotransferase (ALT) flares in HBV chronic hepatitis [16,17].

Conclusion:

Liver stiffness measurement could be used as a predictor for liver fibrosis in chronic HBV patients but still liver biopsy may be required to confirm treatment decisions.

Recommendations:

- Further large scale studies are required to further assess validity of fibroscan in chronic HBV patients.
- Reevaluation of the results of fibroscan during episodes of fluctuation of liver enzymes compared to resting conditions especially among chronic HBV patients.

Acknowledgement:

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References


