**ORIGINAL ARTICLES**

**RELEVANCE OF TRANSIENT ELASTOGRAPHY (FIBROSCAN®) IN EVALUATION OF HEPATIC B VIRUS CHRONICALLY INFECTED PATIENTS**

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**REZUMAT**

**Scop:** Hepatitile cronice virale pot fi evaluate invaziv (puncţie biopsie hepatică-PBH), fie non-invaziv: elastometrie impulsionială (EI). Am urmărit valoarea durităţii hepatice (DH) la purtătorii de AgHBs faţă de subiecţii sănătoşi şi comparat valoarea medie a DH la pacienţii cu hepatită cronicită B (HBV) versus cei cu hepatită cronicită C (HCV).

**Material şi metodă:** Am evaluat 526 pacienţi, pe o perioadă de 12 luni, împărţii în 4 loturi: 63 pacienţi cu HBV, 120 purtători de AgHBs, 191 pacienţi cu HCV și 152 voluntari sănătoşi, folosind EI (FibroScan®-Echosens, Paris, Franţa). PBH a fost efectuată în aceeaşi zi.

**Rezultate:** Am descoperit o valoare crescută a DH în cazul purtătorilor de AgHBs (DH medie 5,7 ± 2,2 kPa) comparativ cu grupul sănătos (DH medie 4,8 ± 1,3 kPa), p=0,0002. Surprinzător, la 20 (16,6%) din purtători, valoarea DH a fost peste 7 kPa, necesitând evaluare suplimentară. Valoarea medie a DH la pacienţii cu HBV a fost 8,13 ± 3,86 kPa, nefiind semnificativ diferită faţă de cea din HCV: 8,45 ± 4,96 kPa (p=0,9432). A existat o corelaţie directă semnificativă între valoarea DH determinată prin EI şi stadiul fibrozei stabilit prin PBH (r=0,490, p<0,0001) la pacienţii cu HBV.

**Concluzii:** Purtătorii inactivi de AgHBs prezintă valori mai crescute ale DH comparativ cu indivizii sănătoşi. PBH este necesară la cei 16,6% purtători inactivi de antigen HBs care au prezentat valori ridicate ale DH.

**Cuvinte cheie:** fibroscan, duritate hepatică, virus hepatic B

**ABSTRACT**

Chronic viral hepatitis can be evaluated either invasively (liver biopsy), or non-invasively: transient elastography (TE). This paper aims to evaluate liver stiffness (LS) for inactive virus B carriers and healthy subjects, and compare mean LS value in chronic viral B hepatitis (HBV) versus chronic viral C hepatitis (HCV).

**Material and methods:** We evaluated 526 patients during 12 months, divided into 4 groups: 63 HBV patients, 120 inactive virus B carriers, 191 HCV patients and 152 healthy volunteers using TE (FibroScan®-Echosens, Paris, France). Both HBV and HCV patients underwent liver biopsy the same day.

**Results:** We discovered an extremely statistically significant higher value for LS in case of inactive virus B carriers (mean LS 5.7 ± 2.2 kPa) versus healthy subjects (mean LS 4.8 ± 1.3 kPa), p=0.0002. Surprisingly, 20 (16.6%) of carriers had a LS mean value >7 kPa, requiring extensive evaluation. LS mean value in HBV patients was 8.13 ± 3.86 kPa, a value not statistically different from value obtained in HCV patients: 8.45 ± 4.96 kPa (p=0.9432). We found a significant direct correlation between LS value obtained through TE and the stage of fibrosis established by liver biopsy (r=0.490, p<0.0001) for HBV patients.

**Conclusions:** Inactive virus B carriers had higher values for LS compared to healthy persons. Both HBV and HCV patients had similar values for each and every stage of fibrosis. Liver biopsy is required for the 16.6% cases of inactive virus B carriers discovered with high LS value.

**Key words:** transient elastography, liver stiffness, hepatitis B virus

**INTRODUCTION**

Chronic viral B infection represents an important public health problem, worldwide, that needs to be combated through different means: first of all, by an adequate prophylaxis, as well as by treating efficiently all cases of chronic viral B hepatitis in order to diminish the number of potential sources of further infection.

We will discuss noninvasive evaluation of liver stiffness (LS) through transient elastography (TE) for inactive virus B carriers as well as patients with chronic viral B hepatitis. Liver fibrosis appears as a response to viral aggression translating itself in accumulation...
of fibrillar components of the extracellular matrix; it evolves, as time passes, towards liver cirrhosis and hepatocarcinoma. The entire process of fibro-genesis is dynamic and has a great potential for reversibility. It can be evaluated through invasive methods like percutaneous liver biopsy, the gold standard for liver fibrosis classification, sustaining a small rate of complications though. The fragment obtained from liver biopsy allows the evaluation of the 1/50.000 part of the liver volume, being well known that the distribution of liver fibrosis is heterogeneous.

Nowadays, new methods of non invasive evaluation are available such as: the evaluation of LS through TE (FibroScan® or FibroTest-ActiTest, with no side effects, easy tolerated by the patient, with a good reproducibility, uninfluenced by the subjects’ age and with similar results to those obtained by percutaneous liver biopsy. After the year 2000, these noninvasive tests were furthermore exploited; it is already acknowledged the role of TE in the evaluation of patients with chronic viral C hepatitis.

Recently new efforts are being made in order to establish an algorithm for the assessment of chronic viral B hepatitis as well as for nonalcoholic steatohepatitis. It is already proven that there is a good correlation between the measurements obtained by the use of FibroScan® and the fibrosis established through liver biopsy in the case of viral B liver cirrhosis. A meta-analysis based on 7 studies proved that TE offers good results in the case of significant fibrosis: sensibility 70% (95% CI, 67-73%), specificity 84% (95% CI, 80-88%), PPV 4.2 (95%CI, 2.4-7.2), NPV 0.31 (95%CI, 0.23-0.43). Moreover, there is a great advantage for using TE in the evaluation of inactive virus B carriers, as it can early detect a possible reactivation of the disease or it facilitates the discovery of other causes that can lead to liver destruction. The method has its own disadvantages, being well known the fact that the value of LS can be influenced also by other causes, other than liver fibrosis, for example major variation in ALT serum levels.

The aims of this paper are, on one hand, to evaluate liver stiffness (LS) of inactive virus B carriers compared to healthy subjects and on the other hand, to compare the mean value of LS in case of chronic viral B hepatitis versus chronic viral C hepatitis.

MATERIALS AND METHODS

Our study included:
- 63 patients diagnosed with chronic viral B hepatitis based on the persistence of positive HBsAg for more than 6 months (10 women, 53 men, average age 50 ± 11 years);
- 191 patients with chronic viral C hepatitis (130 women, 61 men, average age 41.4 ± 13.2 years);
- 120 inactive virus B carriers (62 women, 58 men, average age 40.1 ± 13.2 years);
- A control group formed by 152 healthy subjects, without any known liver diseases (87 women, 65 men, average age 45.3 ± 17.6 years).

The diagnosis of inactive virus B carriers was based on the following criteria: persistent normal ALT and AST serum levels, positive HBsAg, negative HBeAg, HBV DNA viral load <2.000 UI/ml. All patients were evaluated during a 12-month period in the Department of Gastroenterology and Hepatology of the Emergency Clinic County Hospital from Timisoara.

We performed a prospective study in order to observe the correlation between the value of LS obtained by using the device FibroScan® (EchoSens-Paris, France) and the stage of liver fibrosis established by ultrasound-guided percutaneous liver biopsy. All patients were evaluated by TE and the liver biopsy was performed in the same day, on 53 patients diagnosed with chronic viral hepatitis. We mention that an informed consent was signed by each and every patient before the liver biopsy was performed.

Transient elastography

TE was performed by three doctors with great experience, by using the device FibroScan® (EchoSens-Paris, France). The measurements were taken in the right lobe of the liver through the intercostal spaces of the patient placed in dorsal decubitus and the right arm in maximum abduction. The value for LS registered by the device can be between 2.5 up to 75 kPa. A number of 10 valid determinations are required, for each patient, in order to obtain the mean value of LS expressed in kPa.

We excluded from the study those patients who obtained a success rate bellow 60% and an interquartile range (IQR) >20% from the mean value. Mostly, this happened due to abdominal obesity, or narrow intercostal spaces that did not allow the accumulation of the needle in the liver tissue. The success rate was calculated automatically by the device as the total number of successful determinations divided to the total number of acquisitions. The IQR is interpreted as the variability of valid measurements and should not exceed 20% of the mean value.

Echo-guided percutaneous liver biopsy

We evaluated 53 patients by echo-guided percutaneous liver biopsy and by TE in the same day. Modified Menghini needles of 1.4 and 1.6 mm in diameter were used. The liver fragments were...
cataloged by their length, as well as their portal spaces, excluding those that did not fulfill the appropriate requests, i.e. length >2 cm or number of portal spaces >8 for a good quality result. In a previous study from our department, 250 liver biopsies were performed by a senior doctor and then analyzed by an experienced morpho-pathologist. The obtained results were encouraging, having the average length of the fragment of 3.08±0.87 mm and an average number of portal spaces of 14.9±7.09. In only 12.4% of cases the length of the biopsy fragment was below 2 cm.

The liver tissue fragments obtained by liver biopsy were further on analyzed by a senior morpho-pathologist who used in his description the Metavir score with the following classification:

- F0 – no fibrosis;
- F1 – portal fibrosis without septa;
- F2 – portal fibrosis and few septa extending into lobules;
- F3 – numerous septa extending to adjacent portal tracts or terminal hepatic venules;
- F4 – cirrhosis.

Even though liver biopsy is considered to be the gold standard method for the evaluation of liver fibrosis, it should not be forgotten that it still is a method that requires hospitalization, has a certain degree of discomfort for the patient, implies certain risks as well as higher costs than non invasive methods. It must be acknowledged though, the fact that this procedure produces a small rate of complications if it is placed in the hands of well trained hepatologists. Nowadays, it is a matter of establishing the accuracy of TE, when talking about the stage of liver fibrosis, with the hope that in time it will be able to replace successfully invasive methods.

RESULTS

Primarily, our goal was to establish the mean value for LS in chronic viral hepatitis B, respectively chronic viral hepatitis C. We obtained the following results: for 63 cases of chronic viral B hepatitis LS value was 8.13 ± 3.86 kPa compared to 8.45 ± 4.96 kPa for 191 cases of chronic viral C hepatitis, with no statistical significant difference between the two of them.

Later on, we subdivided the entire group into small groups according to the stage of fibrosis (F1, F2, F3, F4) and we compared the average value for LS within the cases with the same stage of fibrosis, again with no significant difference between the two forms of chronic viral hepatitis, according to existing data from Table 1, as well as Figure 1.

<table>
<thead>
<tr>
<th>Category</th>
<th>HBV Nr. cases</th>
<th>FS (kPa)</th>
<th>HCV Nr. cases</th>
<th>FS (kPa)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>63</td>
<td>8.13 ± 3.86</td>
<td>191</td>
<td>8.45 ± 4.96</td>
<td>0.9432 (NS)</td>
</tr>
<tr>
<td>F=0</td>
<td>1</td>
<td>7.4</td>
<td>4</td>
<td>5.27 ± 0.83</td>
<td>(small sample)</td>
</tr>
<tr>
<td>F=1</td>
<td>14</td>
<td>6.52 ± 1.76</td>
<td>26</td>
<td>5.41 ± 1.92</td>
<td>0.0519 (NS)</td>
</tr>
<tr>
<td>F=2</td>
<td>31</td>
<td>7.05 ± 2.05</td>
<td>97</td>
<td>7.18 ± 2.63</td>
<td>0.8153 (NS)</td>
</tr>
<tr>
<td>F=3</td>
<td>15</td>
<td>9.94 ± 4.06</td>
<td>45</td>
<td>9.75 ± 4.63</td>
<td>0.5789 (NS)</td>
</tr>
<tr>
<td>F=4</td>
<td>2</td>
<td>20.45 ± 9.26</td>
<td>19</td>
<td>16.68 ± 8.10</td>
<td>(small sample)</td>
</tr>
</tbody>
</table>

![Figure 1](image-url)
persons) had a mean value of LS 5.7 ± 2.2 kPa, a value that is significantly higher compared to 4.8 ± 1.3 kPa for the 152 healthy volunteers (p=0.0002), as it can be seen in Figure 2.

Figure 2. Mean values of LS in healthy subjects versus HBsAg carriers.

**DISCUSSIONS**

Transient elastography (FibroScan®) is a rapid and non painful method that facilitates an easy insight of the liver stiffness, being a surrogate marker of fibrosis. Data obtained from our study showed that inactive virus B carriers have a significantly higher value of liver stiffness compared to healthy individuals, meaning that their health status should periodically be assessed in order to early identify a possible decline in their health status; what better method than a noninvasive one should be used for that purpose? Based on this information, it is needless to say that inactive virus B carriers should be kept under continuous supervision with regular check-ups on transaminases levels, as well as DNA viral load assessment every 6 month and perhaps transient elastography once a year.

In case of disease progression further invasive investigations should be performed, such as liver biopsy, in order to give the patient the chance to antiviral therapy at the right moment, reducing thus the evolution towards cirrhosis and its complications. This might be the case of the 16.6% patients that were found with a value greater than 7 kPa by transient elastography method. Both the patient and later on the health system benefits from an accurate and rapid diagnose, as it reduces, on one hand, the patient’s sufferance and on the other hand the additional costs.

There are also some difficult situations when transient elastography can not be performed due to obesity, narrow inter costal spaces or liver steatosis. In these cases, either the success rate was below 60% or IQR greater than 30%, so we did not include those patients in the study. For these particular patients, liver biopsy should be further taken into consideration in order to have a proper health evaluation. This aspect was underlined in different articles.8,11,17

In order to compare results, we included in our study healthy volunteers with no previous known liver diseases. Their medium value for liver stiffness was 4.8 ± 1.3kPa, a perfectly normal value. Further on, we wondered if there were any significant differences in FS values depending on age. We did not find such results, so age does not seem to influence the outcome. Similar results were obtained in a previous study conducted in our department according to which the upper limit of liver stiffness in healthy individuals should be 6-6.5 kPa.7

The mean value for LS in case of chronic viral B hepatitis was 8.13 ± 3.86 kPa, a value that was not statistically different from the one obtained for patients with chronic viral C hepatitis: 8.45 ± 4.96 kPa (p=0.9432). We found a significant direct correlation between the value of LS obtained through TE and the stage of fibrosis established by liver biopsy (r=0.490, p<0.0001) for patients with chronic viral B hepatitis. This shows that transient elastography can be a reliable method when it comes to measuring liver stiffness in patients diagnosed with chronic viral B hepatitis.

**CONCLUSIONS**

1. The value of liver stiffness determined with the help of transient elastography for patients with chronic viral B hepatitis was similar to the one obtained in patients with chronic viral C hepatitis; the comparison was made for each and every stage of liver fibrosis.
2. Inactive virus B carriers expressed higher values for liver stiffness than healthy subjects.
3. Inactive virus B carriers who had “alarmingly” high values of liver stiffness (16.6% of cases) require further investigations including an eco-guided transcutaneous liver biopsy.

Transient elastometry performed with the device FibroScan® is a good, noninvasive method that allows the evaluation of both inactive virus B carriers as well as those diagnosed with chronic viral B hepatitis, making possible a repetitive follow-up of liver stiffness at the beginning of therapy as well as at its end. In the future TE can determine the selection of cases that require liver biopsy.

**REFERENCES**


