ORIGINAL ARTICLE

Diagnosis of liver fibrosis using FibroScan and other noninvasive methods in patients with hemochromatosis: A prospective study

Diagnostic de la fibrose hépatique par FibroScan et marqueurs sériques au cours de l’hémochromatose : étude prospective

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Summary

Background. — The role of hepatic iron overload in the development of hepatic fibrosis in patients with hemochromatosis is well-established. Transient elastography (FibroScan) is a new noninvasive, rapid, reproducible bedside method, allowing assessment of liver fibrosis by measuring liver rigidity.

Objectives. — The aim of this prospective study was to evaluate liver fibrosis with FibroScan and other noninvasive biochemical methods in patients with hemochromatosis (C282Y homozygosity) compared with control patients.

Patients and methods. — From January 2004 through October 2006, all consecutive patients with hemochromatosis were evaluated for liver fibrosis using noninvasive methods (FibroScan and biochemical markers). These patients were compared with patients who had chronic cytolysis and no fibrosis on liver biopsy.

Results. — One hundred and three consecutive patients (57 cases and 46 controls) were fully investigated. Median FibroScan values were similar in both groups, 5.20 kPa versus 4.9 kPa, respectively. No differences were observed between cases and controls for all biochemical markers. A strong correlation was observed between FibroScan and many biochemical markers.

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Liver fibrosis and hemochromatosis

Introduction

Hemochromatosis (HFE-linked iron overload) is the most common inherited autosomal—recessive disorder, affecting about one in 300 individuals of Northern European ancestry [1–3]. Hemochromatosis is associated with mutation of the HFE gene [4]. The mutation is a single-base change that results in the substitution of tyrosine by cysteine at position 282 of the HFE protein (C282Y). Other mutations such as the H63D and S65C mutations have been described [4]. These mutations may have clinical significance only in conjunction with other genetic or environmental factors.

Liver biopsy is no longer considered essential for diagnosis of hemochromatosis. Nevertheless, it still provides an assessment of liver fibrosis. Liver biopsy is generally restricted to patients with hemochromatosis and to those suspected of having significant fibrosis or cirrhosis, although ferritin, platelet and aspartate aminotransferase (AST) levels are sufficient to make a diagnosis of cirrhosis in more than 80% of patients [5]. Liver biopsy can also be used by the clinician to assess iron overload, but there is wide variability in measures of hepatic iron load from hepatic biopsy [6]. Moreover, a rapid, noninvasive and cost-effective technique based on magnetic resonance imaging (MRI) is now available for assessing iron load [7]. Thus, liver biopsy is not required for the evaluation of liver iron load.

The accuracy of liver biopsy for assessing fibrosis has also come under question because of sampling errors, and intra- and interobserver variability, that can lead to over- or underestimation of the stage of fibrosis [8–10]. For this reason, more accurate noninvasive methods, including routine biochemical (APRI, FIB-4, GUCI) and surrogate serum fibrosis markers (FibroTest, Hepascore, Forns score, Lok score), have been developed [11–17]. Transient elastography (FibroScan) is a rapid, noninvasive and reproducible method recently developed for measuring liver rigidity. Recent studies have reported the good performance of FibroScan for the diagnosis of fibrosis and cirrhosis in patients with hepatitis C virus (HCV) infection, with or without human immunodeficiency virus (HIV) infection, in patients with chronic cholestatic disease or under treatment with methotrexate [18–24]. In France, either FibroScan or FibroTest is now recommended for the initial evaluation of liver fibrosis in HCV-naïve patients with no other disease [25]. To our knowledge, however, the usefulness of FibroScan and biochemical markers has never been evaluated in patients with hemochromatosis.
The aim of this prospective study was to evaluate liver fibrosis using FibroScan and other noninvasive biochemical methods in patients with hemochromatosis (C282Y homozygosity) and to compare them with control patients.

Patients and methods

Inclusion criteria

From January 2004 to October 2006, all consecutive patients with hemochromatosis (C282Y homozygosity) were prospectively included in the present study. Some patients were ‘new’ patients (recently diagnosed with hemochromatosis) who had undergone noninvasive evaluation of fibrosis before the first phlebotomy. Some patients were ‘old’ patients (iron-depleted patients), treated with phlebotomy for several months or even years, who had been noninvasively evaluated for fibrosis during the follow-up of their disease. All consecutive patients with persistent, unexplained, elevated alanine aminotransferase (ALT) levels who had had a liver biopsy, but showed no fibrosis (META VIR score) and a normal or subnormal liver parenchyma were included as controls (included in the cohort CYTOL) [26]. These patients were all HBsAg-, HCV-Ab- and HIV-Ab-negative. Also, none of these patients was either an alcohol (<40 g/day for men and >20 g/day for women) or drug user, and none had autoimmune liver disease, Wilson’s disease or α1-antitrypsin deficiency. Furthermore, no patient had abnormal thyroid-stimulating hormone levels, cardiac insufficiency or neoplasia. In the control group, liver biopsy sample size was greater or equal to 10 mm. Eligible patients were at least 18 years old. All enrolled patients gave their written informed consent. Clinical data were recorded at inclusion, including age, weight, body mass index (BMI), and presence of diabetes and hypertension.

Noninvasive assessment of liver fibrosis

Liver rigidity measurement using FibroScan (EchoSens™, Paris, France) was performed as previously described [27]. A FibroScan value greater than 7.1 kPa was considered the cut-off level for significant fibrosis [19]. The following parameters were determined by the same laboratory from blood samples taken on the same day that the FibroScan examination was performed: AST; ALT; gamma-glutamyl transpeptidase level (GGT), total bilirubin, age × sex + (0.0039 × α2-macroglobulin + (0.0302 × hyaluronic acid) + (0.0691 × bilirubin) − (0.0012 × GGT)], with age in years, male gender = 1, female gender = 0, α2-macroglobulin in g/L, hyaluronate in μg/L, bilirubin in μmol/L and GGT in U/L. The Hepascore was calculated using the following equation: y = exp (4.185818 − (0.0249 × age) + (0.7464 × sex) + (1.0039 × α2-macroglobulin) + (0.0302 × hyaluronic acid) + (0.0691 × bilirubin) − (0.0012 × GGT)), with age in years, male gender = 1, female gender = 0, α2-macroglobulin in g/L, hyaluronate in μg/L, bilirubin in μmol/L and GGT in U/L. The Hepascore was calculated as follows: AST (IU/L) × Prothrombin time (%) × 100/platelet count (10^9/L) [17].

Statistical analysis

Descriptive values are expressed as percentages, and mean (± SD) or median (range) values. Results are expressed as means ± SEM. Comparisons of quantitative data were made using Student’s t test, or the nonparametric Mann–Whitney rank-sum test when the data did not exhibit a normal distribution. Qualitative data were analyzed using the chi-square test. Kendall’s tau-b coefficient of correlation and their probabilities (P) were used to evaluate the relationships between FibroScan and FibroTest, Hepascore, FIB-4, GUCI, Lok score, Forns score or APRI. For the whole study population, the odds ratio, together with the 95% confidence interval (CI) and the corresponding P value, were calculated for assessment of relative risk using logistic regression. All reported P values are two-tailed. The data were recorded and analyzed using the SPSS v14.0 software package (SPSS Inc; Chicago, IL, USA).

Results

Characteristics of patients

Sixty-one patients with hemochromatosis and 46 control patients were included. Four patients with hemochromatosis (7%) and none of the control patients were excluded because of unsuccessful liver rigidity measurement due to obesity. Demographic and clinical characteristics of the 103 analyzed patients are presented in Table 1. The majority of patients with hemochromatosis were men (57.9%), mean age was 54.3 ± 13.7 years and BMI was 25.0 ± 3.5 kg/m^2. The majority of the control patients were women (58.7%), mean age was 46.7 ± 15.3 years and BMI was 23.7 ± 4.2 kg/m^2.

Ten patients with hemochromatosis (17.5%) had recent diagnoses of hemochromatosis, and 47 patients (82.5%) were iron-depleted. The recently diagnosed patients had been evaluated for liver fibrosis before the first phlebotomy. Characteristics of patients in these two groups are presented in Table 2. In the recently diagnosed hemochromatosis patients, ferritin levels were higher than in patients under treatment: 1528 ± 1181 ng/ml versus 303 ± 594 ng/ml, P < 0.0001, respectively.

Noninvasive assessment of liver fibrosis

In the hemochromatosis patients and control patients, the median values by FibroScan were 5.20 kPa (range: 2.3–75 kPa) and 4.9 kPa (range: 2.6–7.0 kPa), respecti-
Liver fibrosis and hemochromatosis

Table 1  Characteristics of the 103 study patients.

<table>
<thead>
<tr>
<th>Caractéristiques des 103 malades.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with hemochromatosis (N=57)</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Men (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
</tr>
</tbody>
</table>
| Diabetes (%)                      | 9 (15.8)                | 2 (6.7)
| Hypertension n, (%)               | 13 (25)
| Alcohol use (drinks/week)         | 4.5 ± 10.0              | 1.1 ± 3.3   | NS |
| Platelets (g/L)                   | 241 ± 77                | 249 ± 96 | NS |
| Prothrombin time (%)              | 95.2 ± 7.4              | 95.0 ± 8.3   | NS |
| ALT (IU/L)                        | 111 ± 337               | 186 ± 165 | NS |
| GGT (IU/L)                        | 35.3 ± 37.7             | 74.3 ± 63.7 | < 0.0001 |
| AST (IU/L)                        | 36.8 ± 48.8             | 45.5 ± 34.2 | NS |
| Ferritin (ng/mL)                  | 79.8 ± 167.1            | 37.5 ± 36.4 | NS |
| Hyaluronate (µg/L)                | 538.6 ± 876.5           | 375.9 ± 595.5 | NS |

NS: not significant.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase.

Generally (P = NS). Results with the use of noninvasive methods for fibrosis evaluation are shown in Table 3. No statistical difference was observed between the two groups in any of the noninvasive tests (Table 3). Also, in both groups, a significant correlation was found between FibroScan and FibroTest values (r = 0.257, P = 0.0001), Forns score (r = 0.160, P = 0.03), Hepascore (r = 0.200, P = 0.01) and GUCI (r = 0.169, P = 0.02). However, no correlation was found between FibroScan values and the Lok score (r = 0.095, P = NS), FIB-4 (r = 0.119, P = NS) or APRI (r = 0.132, P = NS).

Noninvasive evaluations of liver fibrosis in patients with hemochromatosis are given in Table 4. Whatever the method (except for APRI and GUCI), there was no significant difference between the two groups, although a slight correlation was found between FibroScan and ferritin levels (r = 0.183, P = 0.02).

Characteristics of patients with FibroScan values greater than 7.1 kPa.

The prevalence of patients with FibroScan values greater than 7.1 kPa was 22.8% in patients with hemochromatosis (N = 13) and 0% in control patients (P < 0.0001), and their characteristics are presented in Table 5. In those diagnosed with cirrhosis, a discrepancy between FibroScan and biochemical markers was observed in only one case.

Factors associated with FibroScan values greater than 7.1 kPa.

As indicated in Table 6 and using univariate analysis, the only factor associated with FibroScan values greater than 7.1 kPa

Table 2  Characteristics of the 57 patients with hemochromatosis.

<table>
<thead>
<tr>
<th>Caractéristiques des 57 malades avec hémochromatose.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with a recent diagnosis (N = 10)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Men (%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
</tr>
</tbody>
</table>
| Hypertension n, (%)                       | 2 (25)
| Alcohol use (drinks/week)                 | 1.2 ± 1.8                     | 5.2 ± 11.1 | NS |
| Platelets (g/L)                           | 207 ± 387                     | 249 ± 81 | NS |
| Prothrombin time (%)                      | 94.6 ± 8.8                    | 95.4 ± 7.2 | NS |
| GGT (IU/L)                                | 260.2 ± 714.1                 | 81.1 ± 180.9 | NS |
| ALT (IU/L)                                | 48.9 ± 37.7                   | 32.4 ± 37.4 | NS |
| AST (IU/L)                                | 59.3 ± 86.6                   | 32.0 ± 36.1 | NS |
| Ferritin (ng/mL)                          | 1528.9 ± 1181.3               | 302.8 ± 594.2 | < 0.001 |

NS: not significant.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase.

Missing data in some cases.
was diabetes (odds ratio 4.25, 95% CI 1.04—17.46, \( P = 0.04 \)).

Using multivariate analysis and adding ferritin levels greater than 150 ng/mL, FibroScan values greater than 7.1 kPa were associated with diabetes (odds ratio 8.39, 95% CI 1.35—52.1, \( P = 0.02 \)) and ferritin levels greater than 150 ng/mL (odds ratio 6.31, 95% CI 1.12—35.39, \( P = 0.04 \)).

### Follow-up of hemochromatosis patients

Forty-four patients were followed-up for one to two years. These patients (seven patients with a recent diagnosis of hemochromatosis and 37 iron-depleted patients) had FibroScan evaluations every year. The evolution of their FibroScan values is shown in Figs. 1 and 2. In patients with a recent diagnosis of hemochromatosis, five had initial FibroScan values less than 6 kPa that did not change after one or two years, and one patient had an initial value of 8.8 kPa that was 4.9 kPa a year later. The final patient had an initial value of 21.1 kPa that was 21.3 kPa one year later and 8.8 kPa after two years. In iron-depleted patients, FibroScan values did not change significantly; for example, two patients had initial elevated FibroScan values of 53.2 kPa and 21.8 kPa that were 70.6 kPa and 5.7 kPa, respectively, a year later.

### Table 3  Noninvasive evaluation of liver fibrosis.

<table>
<thead>
<tr>
<th></th>
<th>Patients with hemochromatosis (( N = 57 ))</th>
<th>Control patients (( N = 46 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median FibroScan value (kPa)</td>
<td>5.2</td>
<td>4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean FibroTest score</td>
<td>0.30 ± 0.29</td>
<td>0.27 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Hepascore</td>
<td>0.39 ± 0.37</td>
<td>0.24 ± 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Mean APRI score</td>
<td>0.42 ± 0.60</td>
<td>0.61 ± 0.71</td>
<td>NS</td>
</tr>
<tr>
<td>Mean FIB-4 score</td>
<td>1.46 ± 1.17</td>
<td>1.43 ± 1.86</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Forns score</td>
<td>4.40 ± 1.86</td>
<td>4.47 ± 1.36</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Lok score</td>
<td>0.33 ± 0.22</td>
<td>0.26 ± 0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Mean GUCI score</td>
<td>0.46 ± 0.74</td>
<td>0.59 ± 0.60</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant.

### Table 4  Noninvasive evaluation of liver fibrosis in patients with hemochromatosis.

<table>
<thead>
<tr>
<th></th>
<th>Patients with a recent diagnosis (( N = 10 ))</th>
<th>Iron-depleted patients (( N = 47 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>FibroScan (kPa)</td>
<td>10.2 ± 11.3</td>
<td>8.3 ± 13.9</td>
<td>NS</td>
</tr>
<tr>
<td>FibroTest</td>
<td>0.32 ± 0.36</td>
<td>0.30 ± 0.27</td>
<td>NS</td>
</tr>
<tr>
<td>Hepascore</td>
<td>0.45 ± 0.35</td>
<td>0.38 ± 0.38</td>
<td>NS</td>
</tr>
<tr>
<td>APRI</td>
<td>0.76 ± 1.19</td>
<td>0.34 ± 0.35</td>
<td>0.05</td>
</tr>
<tr>
<td>FIB-4</td>
<td>1.83 ± 1.64</td>
<td>1.38 ± 1.05</td>
<td>NS</td>
</tr>
<tr>
<td>Forns score</td>
<td>4.12 ± 1.69</td>
<td>4.46 ± 1.91</td>
<td>NS</td>
</tr>
<tr>
<td>Lok score</td>
<td>0.37 ± 0.23</td>
<td>0.33 ± 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>GUCI</td>
<td>0.93 ± 1.59</td>
<td>0.36 ± 0.39</td>
<td>0.03</td>
</tr>
</tbody>
</table>

NS: not significant.

### Table 5  Characteristics of biochemical markers of fibrosis in patients with hemochromatosis and FibroScan values > 7.1 kPa.

<table>
<thead>
<tr>
<th>#</th>
<th>FibroScan value (kPa)</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.2</td>
<td>No fibrosis according to biochemical tests (except Hepascore)</td>
</tr>
<tr>
<td>2</td>
<td>7.4</td>
<td>No fibrosis according to biochemical tests (except Hepascore)</td>
</tr>
<tr>
<td>3</td>
<td>7.9</td>
<td>No fibrosis according to biochemical tests</td>
</tr>
<tr>
<td>4</td>
<td>8.1</td>
<td>No fibrosis according to biochemical tests</td>
</tr>
<tr>
<td>5</td>
<td>8.6</td>
<td>BMI = 30 kg/m²; no fibrosis according to biochemical tests</td>
</tr>
<tr>
<td>6</td>
<td>8.8</td>
<td>Significant fibrosis according to biochemical tests (except Lok, APRI)</td>
</tr>
<tr>
<td>7</td>
<td>8.8</td>
<td>Significant fibrosis according to biochemical tests</td>
</tr>
<tr>
<td>8</td>
<td>10.2</td>
<td>Severe fibrosis according to biochemical tests (except Lok, APRI)</td>
</tr>
<tr>
<td>9</td>
<td>14.4</td>
<td>Cirrhosis at liver biopsy in 1998</td>
</tr>
<tr>
<td>10</td>
<td>21.1</td>
<td>Significant fibrosis according to biochemical tests (except Lok, APRI)</td>
</tr>
<tr>
<td>11</td>
<td>38.6</td>
<td>Cirrhosis according to biochemical tests</td>
</tr>
<tr>
<td>12</td>
<td>70.6</td>
<td>Cirrhosis according to biochemical tests</td>
</tr>
<tr>
<td>13</td>
<td>75.0</td>
<td>Past history of ascites (hepatocellular carcinoma)</td>
</tr>
</tbody>
</table>

Note: biochemical tests included FibroTest, Hepascore, APRI, FIB-4, Forns score, Lok score, GUCI.
Table 6  Factors associated with FibroScan values > 7.1 kPa.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>1.67</td>
<td>0.51—5.51</td>
<td>0.40</td>
</tr>
<tr>
<td>Age &gt; 50 years</td>
<td>1.97</td>
<td>0.56—6.86</td>
<td>0.29</td>
</tr>
<tr>
<td>Body mass index &gt; 25 kg/m²</td>
<td>1.50</td>
<td>0.46—4.85</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.25</td>
<td>1.04—17.46</td>
<td>0.04</td>
</tr>
<tr>
<td>Platelets &lt; 200 g/L</td>
<td>1.29</td>
<td>0.36—4.61</td>
<td>0.69</td>
</tr>
<tr>
<td>Ferritin &gt; 150 ng/mL</td>
<td>3.84</td>
<td>0.93—15.91</td>
<td>0.06</td>
</tr>
<tr>
<td>Multivariate analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>8.39</td>
<td>1.35—52.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Ferritin &gt; 150 ng/mL</td>
<td>6.31</td>
<td>1.12—35.39</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Discussion

To our knowledge, this is the first study evaluating noninvasive methods, especially FibroScan, in patients with hemochromatosis. FibroScan and biochemical markers are efficient techniques for diagnosing significant fibrosis or cirrhosis. In our study using FibroScan and biochemical markers, no differences were observed between patients with hemochromatosis and control patients. Because of the improvement in screening for hemochromatosis in the 1990s, patients with hemochromatosis treated with phlebotomy in the 2000s do not have severe disease or severe fibrosis. Only five patients (8.8%) had FibroScan values greater than 12.5 kPa (cut-off value for the diagnosis of cirrhosis). In four of these patients, biochemical markers correlated with FibroScan values and three patients had symptoms of cirrhosis.

In the present study, for the diagnosis of significant fibrosis, we used a cut-off value of 7.1 kPa, the same as for patients with chronic hepatitis C infection [19]. However, other cut-off values have been published [20]. If we had used an 8.7 kPa cut-off value, the diagnosis of significant fibrosis would have included only eight patients with hemochromatosis (14%) and a strong correlation would have been observed for all noninvasive methods. Indeed, all patients with FibroScan values greater than 8.7 kPa had significant fibrosis, at least according to biochemical scores. Cut-off values could probably be optimized according to the etiology and type of lesion. For example, the cut-off value could be defined mainly for chronic hepatitis, with another one given for alcoholic liver disease and nonalcoholic fatty liver or steatohepatitis, where the amount of fibrosis may be different [28]. Therefore, the cut-off value for the diagnosis of cirrhosis or severe fibrosis in patients with hemochromatosis might be estimated in a study comparing liver biopsy and FibroScan. However, such a study would be difficult to set up as guidelines recommend that a liver biopsy be performed only in cases of serum ferritin levels greater than 1000 ng/mL, abnormal AST level and hepatomegaly [2].

As liver blood tests in hemochromatosis are considered unreliable for detecting fibrosis or cirrhosis, the recommendation is to rely only on liver biopsy to assess the severity of liver fibrosis. The risks of liver biopsy can be reduced by operator experience and by using ultrasound guidance. However, complications such as pain, bleeding, pneumothorax, hemorrhax, bile peritonitis, hemobilia, punctured kidney or intestine, infection, anxiety and even death are not entirely avoidable [29,30]. In addition to safety issues, the reproducibility of liver biopsy is poor owing to the hete-
rogenity of liver fibrosis and sample size as well as inter-
and intrapathologist variability [8—10,31].

Few studies have demonstrated a role for noninvasive
methods in the evaluation of liver fibrosis in patients with
iron overload. Jensen et al. showed that serum procollagen-
III-peptide has little diagnostic value for assessing liver
fibrosis in hemochromatosis patients [32]. Guyader et al.
used an algorithm to predict the absence of severe fibrosis in
HFE hemochromatosis [33]. Using multivariate analysis, they
demonstrated that the combined finding of serum ferritin
less than 1000 µg/L, absence of hepatomegaly and normal
serum AST predicts a low risk of cirrhosis. They also showed
that patients with serum ferritin greater than 1000 µg/L,
elevated AST and a platelet count less than 200 g/L have an
80% chance of having cirrhosis. Morrison et al. have
shown that patients with hemochromatosis and serum ferri-
tin levels less than 1000 µg/L are unlikely to have cirrhosis
[34].

To our knowledge, the diagnostic value of biochemical
markers has never been evaluated in liver fibrosis associ-
ated with hemochromatosis. We prospectively assessed the
performance of FibroScan in comparison to serum markers
of fibrosis in patients with hemochromatosis. As liver biopsy
is not recommended for all patients with hemochromato-
sis, for ethical reasons, we did not perform a liver biopsy
as the ‘gold standard’. Although no systematic liver biops-
ies were performed in our study, we consider FibroScan
to be a reliable tool for fibrosis assessment, as seen in
previous studies of other clinical settings: HCV infection
[19,20], HIV—HCV co-infection [18] and cirrhosis of various
origin [22,28,35]. There is no reason to believe that the per-
formance of FibroScan would be different in patients with
hemochromatosis. Our results suggest that FibroScan may be
used reliably as first-line assessments of fibrosis in patients
with hemochromatosis.

Only two factors (diabetes and ferritin levels) were asso-
ciated with FibroScan values greater than 7.1 kPa. The
association between diabetes and fibrosis is well-known
even in patients with hemochromatosis [36,37]. Likewise,
ferritin levels are known to be associated with cirrhosis in
such patients [33].

No statistical difference was observed between patients
with hemochromatosis and control patients in any of the
noninvasive tests (Table 2). The control patients were well-
defined, having unexplained chronic cytolysis and no fibrosis
on liver biopsy. All control patients had FibroScan values
less than 7.1 kPa, indicating that the accuracy of Fibro-
Scan for excluding significant fibrosis was excellent in this
population. Therefore, as no difference was observed be-
 tween patients with hemochromatosis and control patients
in terms of FibroScan values, we hypothesize that FibroScan
could identify significant fibrosis in patients with hemochro-
matosis.

In conclusion, FibroScan and biochemical markers may
constitute a reliable noninvasive means of detecting liver
fibrosis. Liver biopsy could be performed only for the diag-
nosis of associated liver diseases [such as alcoholic disease,
onalcoholic fatty liver disease (NAFLD) and primary sclero-
sing cholangitis] or for patients with discrepancies between
FibroScan values and biochemical markers. Further longitu-
dinal and prospective studies are necessary to confirm these
preliminary data.

Conflicts of interest

Authors have no financial disclosure.

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