Quantification of liver fibrosis in patients with cholestatic hepatitis using FibroScan and diffusion-weighted MRI

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Purpose

1. Purpose

Background

Although liver biopsy is still regarded as the standard reference procedure for diagnosis and grading of liver fibrosis, it has several limitations such as hemorrhage risk, interobserver variability and sampling errors [1-3]. As reported previously, liver fibrosis shows heterogeneous distribution and sampling only a small portion of tissue during biopsy could lead to incorrect staging [4-6]. Thus, there is obvious need for development of noninvasive assessment of liver fibrosis, with possibility of whole liver examination, eliminating sampling errors and reducing biopsy-related risks. Several noninvasive methods for quantification of liver fibrosis have been introduced, such as biochemical scores, transient elastography (TE) and magnetic resonance imaging (MRI) techniques [7-9]. TE is nowadays widely used as noninvasive, painless procedure that provides immediate evaluation of liver fibrosis severity [10]. Recently, among other MRI techniques applied in the evaluation of liver fibrosis, diffusion-weighted magnetic resonance imaging (DWMRI) has emerged as an important noninvasive diagnostic method [11]. DWMRI allows global liver examination with insight in distribution of liver fibrosis and detection of the most affected liver segments.

Purpose

The purpose of the current study was to evaluate usefulness of TE and DWMRI for assessment of liver fibrosis in patients with cholestatic hepatitis with reference to liver biopsy as a gold standard.
2. Materials and Methods

Patients

CONTROLS: 12 healthy volunteers (7 women, 5 men; mean age: 45 years; range: 25-65) without previous clinical history of liver disease and with negative MRI findings for focal or diffuse liver disease.

PATIENTS: 41 patients with diagnosis of cholestatic hepatitis (30 with primary biliary cirrhosis-PBC, and 11 with primary sclerosing hepatitis-PSC)

Transient Elastography

Transient elastography was performed on each patient with a FibroScan (Echosens, Paris, France). The examination was conducted over the right liver lobe, through intercostal spaces as previously described [10]. Ten successful measurements were performed per patient and the median value was accepted as each patient's personal FibroScan value (expressed in kilopascals). The success rate was automatically calculated as the ratio of the number of successful measurements and total number of measurements. Only examinations with 10 valid measurements and a success rate of at least 60% were considered reliable. A Body Mass Index (BMI) <30 kg/m$^2$ was required for each patient.

DWMRI

- MRI examinations were performed on 1.5-T MRI system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) with combination of 6-elements phased-array abdominal coil and spine array coil to optimize signal-to-noise ratio.
- All patients underwent routine upper-abdomen protocol.
- DWI was performed using respiratory triggered single-shot echo-planar imaging sequence with 5 diffusion sensitivity values (0, 50, 200, 400 and 800 s/mm$^2$). The following acquisition parameters were used: TR of 3332 ms; TE of 69 ms; matrix size of 105x192; field of view of 400 mm; receiver bandwidth of 1736 Hz/pixel; number of excitation = 2; slice thickness = 6 mm; time of acquisition of 1.37 minute. Parallel imaging technique (generalized autocalibrating partially parallel acquisition - GRAPPA) was applied to reduce the acquisition time and to improve image quality.

Image analysis
• Quantitative ADC maps were calculated on voxel-by-voxel basis using commercial workstation (Syngo, Siemens Medical Healthcare) for combination of b=0 and each of b values using equation:

\[ \ln(S_i/S_0) = -b_iADC_{0,i} \]

where \( S_0 \) and \( S_i \) correspond to signal intensities for \( b \) values 0 and \( b=i \), where \( i= 50, 200, 400 \) and 800 s/mm\(^2\) respectively.

• Eight circular regions of interest (ROI) of 12 ± 3 pixels were manually positioned on left lobe lateral (II and III), left lobe medial segments (IVa and IVb) and on right liver lobe segments (V, VI, VII and VIII) avoiding central vascular region and visible vascular structures. ADC values were measured eight times for each \( b \) value and for combination of all \( b \) values. The final ADC was calculated as the average of eight values. ADC value for the combination of all \( b \) values was calculated as the average of the mean ADC values for each \( b \) value (Fig.1, Fig 2.).
Fig. 0: Fig. 1 48-years old women with PBC (fibrosis stage 2 on liver biopsy). Breath-hold axial single-shot echo-planar diffusion-weighted MR images obtained at $b = 0$ s/mm$^2$ (A), $b = 50$ s/mm$^2$ (B), $b = 200$ s/mm$^2$ (C), $b = 400$ s/mm$^2$ (D), $b = 800$ s/mm$^2$ (E) and ADC map obtained for $b = 800$ s/mm$^2$ (F). The calculated apparent diffusion coefficient was $1.07 \pm 0.21 \times 10^{-3}$ mm$^2$/s.

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Fig. 0: Fig. 2 55-years old women with PBC (fibrosis stage 4 on liver biopsy). Breath-hold axial single-shot echo-planar diffusion-weighted MR images obtained at $b = 0$ s/mm$^2$ (A), $b = 50$ s/mm$^2$ (B), $b = 200$ s/mm$^2$ (C), $b = 400$ s/mm$^2$ (D), $b = 800$ s/mm$^2$ (E) and ADC
map obtained for $b = 800 \text{ s/mm}^2$ (F). The calculated apparent diffusion coefficient was $0.89 \pm 0.13 \times 10^{-3} \text{ mm}^2/\text{s}$.

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Results

3. Results

- The mean TE values were 4.82 ± 1.11 kPa, 7.23 ± 1.87 kPa, 11.93 ± 2.57 kPa, 21.18 ± 4.57 kPa in fibrosis stages 1, 2, 3 and 4, respectively. TE values of patients with mild and moderate fibrosis (F1, F2) were significantly lower (p ≤ 0.05) than those obtained in patients with severe fibrosis (F3, F4). In addition, there was a significant difference between liver fibrosis stage 3 and 4 (p ≤ 0.05). Liver stiffness measurement was significantly positively correlated to liver fibrosis stage (ρ = 0.77; p ≤ 0.001).

- Mean ADC values in patients stratified by fibrosis stage are shown in Table 1. There was significant difference (p ≤ 0.05) between ADCs in healthy volunteers and patients with liver fibrosis and cirrhosis (stage ≥ 1), for all b values and the combination of all b values. Moreover, significant differences between ADC values of F1 versus F2 and F3 were found only for the combination of all b values. ADCs for F1 were significantly different from ADCs for F4 for all b values (p < 0.01). Comparing ADC values for F2 with advanced fibrosis stages, significant differences were found between F2 and F4 for b values 400 s/mm², 800 s/mm² and the combination of all b values. However, no significant difference was seen between F2 and F3 for all b values. A significant negative correlation was found between ADCs for different b values and fibrosis stage (#=-0.451 to -0.678; p < 0.01).

Table 1. Distribution of Apparent Diffusion Coefficients (value x 10⁻³ mm²/s) According to Liver Fibrosis Stage (n = 41)

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>b = 50</th>
<th>b = 200</th>
<th>b = 400</th>
<th>b = 800</th>
<th>b = 0-800*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.41 ± 0.55</td>
<td>2.61 ± 0.18</td>
<td>1.88 ± 0.11</td>
<td>1.73 ± 0.10</td>
<td>2.01 ± 0.11</td>
</tr>
<tr>
<td>1</td>
<td>2.57 ± 0.23</td>
<td>1.89 ± 0.11</td>
<td>1.63 ± 0.13</td>
<td>1.11 ± 0.05</td>
<td>1.80 ± 0.10</td>
</tr>
<tr>
<td>2</td>
<td>2.23 ± 0.08</td>
<td>1.78 ± 0.10</td>
<td>1.43 ± 0.16</td>
<td>1.10 ± 0.04</td>
<td>1.64 ± 0.05</td>
</tr>
<tr>
<td>3</td>
<td>2.34 ± 0.17</td>
<td>1.77 ± 0.09</td>
<td>1.34 ± 0.15</td>
<td>1.07 ± 0.03</td>
<td>1.63 ± 0.07</td>
</tr>
<tr>
<td>4</td>
<td>1.93 ± 0.12</td>
<td>1.54 ± 0.05</td>
<td>1.32 ± 0.19</td>
<td>1.03 ± 0.06</td>
<td>1.46 ± 0.05</td>
</tr>
</tbody>
</table>

NOTE: the results are expresses as the means ± SD

* Combination of b values of 0, 50, 200, 400 and 800 s/mm²
4. Conclusion

- While liver biopsy provides examination of tissue specimens from only one liver segment, TE measures liver stiffness of a hundred times bigger volume of liver parenchyma [10]. The results from the present study have shown that TE values are significantly different between mild, moderate fibrosis (F1, F2) and severe fibrosis (F3, F4). Our results are consistent with previous reports by Gomez-Dominguez et al. and Corpechot C et al. [12, 13]. According to these findings, we could assume that TE could be reliably used for differentiation of advanced fibrosis stages.

- DWMRI could be accurately used for determination of high grade fibrosis and discrimination between healthy livers and cirrhosis. This finding is in accordance with previous studies [14]. Differentiation between mild and moderate fibrosis is of great clinical significance, since these patients could benefit from antifibrotic therapy. In this study, significant differences between mild (F1), moderate (F2) and advanced fibrosis stages (F3-F4) were observed only for ADC calculated for combination of all b values (0-800 s/mm²). Similar findings have already been reported by Taouli et al. [15]. A possible explanation could be that performing DWMRI with relatively high b values (≥400 s/mm²) decreases perfusion component, with diffusion being more precisely assessed [11].

5. Limitations

- The small number of patients with PBC and PSC precludes generalized conclusions on the basis of obtained results.
- Further studies are needed to assess optimal cut off values and to evaluate if there are differences between two cholestatic diseases.
- Because technical factors and imaging parameters vary significantly between different studies, there is a need for standardization of DWMRI protocols.
6. References


