The clinical value of the apparent diffusion coefficient of liver magnetic resonance images in patients with liver fibrosis compared to healthy subjects

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ABSTRACT

Background: Fibrotic tissue forms following chronic inflammation in the liver, which may progress over time to cirrhosis. Liver biopsy is the gold standard for the diagnosis of liver fibrosis, and there has been a considerable interest in developing noninvasive methods. Objectives: In the present study, we evaluated the efficacy of the apparent diffusion coefficient (ADC) of the liver in the diagnosis and staging of liver fibrosis. Patients and Methods: This case–control study was conducted on 40 patients with chronic liver disease and 31 healthy controls who were subjected to diffusion-weighted magnetic resonance imaging (MRI). Diagnostic values for different stages of fibrosis were determined using receiver-operating characteristic (ROC) curves based on the sensitivity and specificity. Results: Of 37 patients in the case group, 12 were males (32.4%) and 25 (67.5%) were females, whereas in the control group of 31 patients, 11 were males (35.5%) and 20 (64.5%) were females. In the ROC analysis, area under the curve separating stage one or lower fibrosis from stage two or greater fibrosis groups with a $b$-value of 600 s/mm² was 0.893 (98% confidence interval (CI): 0.795–0.955), and that with a $b$-value of 1000 s/mm² was 0.946 (98% CI: 0.813–0.946). Conclusion: Our results are in line with the previous studies, which showed that liver ADC values could be considered as a method for the diagnosis and staging of liver fibrosis.

Keywords: Apparent diffusion coefficient, biopsy, diffusion, fibrotic tissue, liver

Introduction

Liver fibrosis is a wound-healing response induced by chronic damage, which is defined by the accumulation of extracellular fibers such as collagen, glycosaminoglycans, and proteoglycans. Liver fibrosis is generally caused by viral infections, alcohol, drug use, fatty liver, and autoimmune and metabolic diseases. Although liver fibrosis in the early stages is reversible, the progressive form can lead to cirrhosis. The point at which liver fibrosis become irreversible is not fully understood, but even in the early stages of cirrhosis, it may be reversible;¹⁻³ therefore, diagnosis of fibrosis in its early stages is crucial.

Liver biopsy is currently considered as the gold standard for assessing fibrosis,⁶ but liver biopsy has some limitations: it is an aggressive procedure, it may lead to complications, and it is usually not favored by patients. Besides, biopsy only extracts a small part of the liver parenchyma, and since fibrosis is not distributed equally across the liver, it is exposed to sampling variation errors.⁷⁻⁹ There is also interobserver and intraobserver variability in the samples.⁴⁻¹⁰ Therefore, noninvasive assessment of hepatic fibrosis was considered. Two major groups of
noninvasive methods are available: (1) serologic tests such as the fibro test and (2) imaging techniques such as ultrasonic elastography and magnetic resonance-based imaging. The diffusion-weighted (DW) imaging technique, a type of magnetic resonance imaging (MRI), is sensitive to the diffusion of water molecules in tissues. The accumulation of extracellular fibers in fibrotic livers can restrict the diffusion of water molecules, which can be displayed on DW images, and its value can be measured quantitatively on apparent diffusion coefficient (ADC) maps. Previous studies have shown that hepatic ADC in patients with liver cirrhosis is lower than that of controls. Research on the relationship between DW images and fibrosis stages has revealed various results.

The present study evaluates the clinical value of DW imaging in the diagnosis and staging of liver fibrosis.

**Patients and Methods**

**Study design and population**

In this case–control study, from October 2015 to October 2017, 40 patients (above 18 years) with impaired liver enzymes who were referred to an interventional radiologist for liver biopsy and 31 healthy controls were subjected to DW MRI. Control groups included individuals who were referred for MRI for reasons other than liver disease and did not have a history of liver disease. To evaluate the liver, before DW imaging, in-phase and out-phase sequences were taken. People with fatty liver or liver disease. To evaluate the liver, before DW imaging, in-phase and out-phase sequences were taken. People with fatty liver or liver mass were excluded.

The study protocol was fully explained to the patient and informed consent was obtained from all of them before enrollment. This study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences.

**Tissue sampling**

Ultrasound-guided liver biopsy was performed from the fifth segment of the liver by interventional radiologists. Three samples of liver were obtained. Samples were studied by a 10-year experienced pathologist. The pathologist was blinded to the imaging findings. Fibrosis stages were described based on the METAVIR score as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

**MR images**

MRI was performed at 1.5 Tesla (Optima, General Electric Health Care, Milwaukee, WI, USA), with a 16-element phased-array torso coil. The parameters for routine MRI sequences were as follows: coronal two-dimensional fast imaging employing steady-state acquisition: repetition time (TR)/echo time (TE) = 4/2.2 ms; flip angle = 70°; field of view (FOV) = 48 × 48 cm; axial 3D dual echo (in phase – out phase): TR/TE = 6/4 – 2 ms; flip angle = 12°; FOV = 48 × 48 cm. Respiratory-triggered DW images were obtained by using single-shot spin-echo echo-planar (SS-SE-EPI). The image parameters for DW-MRI at b-values of 600 and 1000 s/mm² were as follows: FOV: 35 × 30; matrix size: 128 × 128; TR: 2000–4000 ms; TE: 60–70 ms. Number of excitation time (NEX): 10; flip angle = 90°; section thickness: 6 mm; phase-encoding direction: anteroposterior; direction of motion probing: phase, frequency, and section.

**ADC calculation**

According to the protocol and parameters listed, for each b-value, six axial images were taken. Automatic voxel-by-voxel analysis on a workstation (Functool, General Electric Medical System, Milwaukee, WI, USA) was used to obtain gray-scale-coded ADC map images for b-values of 600 and 1000 s/mm². ADC map images were evaluated by a radiologist who was blinded to biopsy results. Three out of six axial images of the liver that were of better quality were selected. The ADC values were measured by locating six round region of interest (ROIs) approximately 1 cm in diameter, excluding large vessels and motion artifacts and 1 cm away from the liver capsule. ROIs were placed in six different parts of axial liver images (two in the posterior part of the right lobe, two in the anterior part of the right lobe, one in the medial part of the left lobe, and one in lateral part of the left lobe). The average ADC values of ROIs was considered as the final ADC value of the liver. These calculations were performed for each b-value independently, and liver ADC was calculated separately according to each b-value.

**Statistical analysis**

Analysis was performed using the SPSS-19 and MedCalc-15 software. On the basis of ADC values, each followed a normal distribution, and a parametric t-test was used (independent-samples t-test). The ADC values and biopsy findings were analyzed using an independent-samples t-test, analysis of variance, and Tukey’s post hoc test. Diagnostic values for different stages of fibrosis were determined using receiver-operating characteristic (ROC) curves based on the sensitivity and specificity determined based on METAVIR score.

**Results**

The case group consisted of 40 patients who were referred for liver biopsy because of impaired liver enzymes, and 31 liver disease-free individuals who were referred to the same center for MRI formed the control group. Both the case and control groups were subjected to DW-MRI. According to biopsy results, one patient had hemochromatosis, one patient had Wilson's disease, and another had normal results without fibrosis. As the deposition of metals in hemochromatosis and Wilson's disease may affect MRI signals, these two patients were excluded. Furthermore, patients who had normal liver biopsy results were excluded too. Consequently, the case group was decreased to 37 patients [Table 1]. Of 37 patients in the case group, 12 were males (32.4%) and 25 (67.5%) were females. Hence, in the control group of 31 patients, 11 were males (35.5%) and 20 (64.5%) were females. The mean age of the case group was...
40.70 ± 13.50 years and the mean age of the control group was 39.42 ± 12.67 years.

The mean and standard deviation of liver ADC based on the b-value of 600 and 1000 s/mm² are stratified according to the fibrosis stage in Table 2. The comparison of mean ADCs at a b-value of 600 s/mm² showed significant differences for F0 vs. F2, F0 vs. F3, F0 vs. F4, F1 vs. F3, and F1 vs. F4 (P = 0.001, P < 0.001, P < 0.001, P = 0.006, and P = 0.001, respectively); at a b-value of 1000 s/mm², they showed significant differences for F0 vs. F2, F0 vs. F3, F0 vs. F4, and F1 vs. F4, and P < 0.001, P < 0.001, P < 0.001, and P = 0.003, respectively, was reported. In other groups, the difference was not statistically significant [Table 3].

The diagnostic accuracy of ADC for assessment of hepatic fibrosis compared with liver biopsy is shown in Table 4. ROC analysis showed that hepatic ADC is a significant predictor of liver fibrosis stages. For example, to predict stage 2 or greater fibrosis compared with healthy individuals, and with increased fibrosis, ADC values showed a greater decrease.

Table 1: Causes of liver disease

| Biopsy results         | Frequency (%) |
|------------------------|---------------|
| Autoimmune hepatitis   | 25 (67.5%)    |
| Primary biliary cholangitis | 4 (10.8%)   |
| Primary biliary cirrhosis | 3 (8.1%)    |
| Hepatitis C virus      | 3 (8.1%)      |
| Hepatitis B virus      | 2 (5.4%)      |
| Total                  | 37 (100%)     |

Discussion

The diagnosis of liver fibrosis stage using a physical examination and laboratory findings is challenging. Identifying patients with F2 stage liver fibrosis and greater is of special clinical importance because only these patients benefit from antiviral drug therapy. Liver biopsy is currently the gold standard for the diagnosis and staging of fibrosis. However, liver biopsy has some limitations. Therefore, finding an alternative method has been the goal of many researchers. DW-MRI is a noninvasive, rapid imaging technique that measures the diffusion of water molecules. In fibrotic liver, the accumulation of extracellular fibers results in a reduction of water molecule motion and ADC values.

As expected, with the increase in fibrosis stage, ADC values are further reduced. Our study consistent with previous findings showed that ADC values are lower in patients with liver fibrosis compared with healthy individuals, and with increased fibrosis, ADC values showed a greater decrease.

Boulander et al. compared ADC values in 18 patients with liver fibrosis due to hepatitis C and 10 patients without liver fibrosis, using b-values of 50 and 250 s/mm². They found no significant difference between the two groups. Our findings were not in line with the above-mentioned study, as they used lower b-values than we did. When low b-values were used in DW-imaging in addition to being under the influence of diffusion, it is also under the influence of perfusion, in order to reduce the perfusion effect, the use of higher b-values is recommended. However, higher b-values reduce the signal and consequently, the signal-to-noise ratio (SNR), making images prone to artifacts; therefore, finding a proper b-value for assessment of liver fibrosis is essential.

Most studies using a b-value ≥ 500 s/mm² showed a significant correlation between liver fibrosis and the ADC values. Taouli et al. evaluated the ADC value in DW-MRI of 23 patients with chronic liver disease and seven healthy subjects using b-values of 50, 300, 500, 700, and 1000 s/mm². They observed a significant difference between the liver ADC of F2 ≤ vs. F1 ≥, and between F3 ≤ vs. F2 ≥ when the b-value was 500 s/mm² or higher. AUC to differentiate F2 ≤ from F1 ≥ and F3 ≤ from F2 ≥ using a b-value of 1000 s/mm² was 0.868 and 0.832, respectively. They concluded that using b-values of 500 s/mm² and higher can be useful in differentiating F2 ≤ from F1 ≥ and F3 ≤ from F2 ≥. In our study, there was a statistically significant difference between the ADC values of F2 ≤ vs. F1 ≥ using both b-values of 600 and 1000 s/mm². The same results were obtained when comparing F3 ≤ vs. F2 ≥. AUC to differentiate F2 ≤ from

Table 2: Distribution of liver ADC (value × 10³ mm²/s) stratified by fibrosis stage

| Fibrosis stage | Number (%) | ADC b 600 s/mm² | ADC b 1000 s/mm² |
|----------------|------------|----------------|-----------------|
| F0            | 31 (45.5%) | 1.545±0.097    | 1.291±0.070     |
| F1            | 10 (14.7%) | 1.472±0.087    | 1.227±0.055     |
| F2            | 10 (14.7%) | 1.384±0.108    | 1.181±0.067     |
| F3            | 12 (17.6%) | 1.315±0.131    | 1.152±0.067     |
| F4            | 5 (7.3%)   | 1.227±0.086    | 1.090±0.048     |

Table 3: Comparing liver ADC values considering various fibrosis stages

| Liver fibrosis | b=600 s/mm² | b=1000 s/mm² |
|---------------|------------|-------------|
Table 4: Area under the receiver operating characteristics curve (AUC) and criterion (ADC) observed to maximize sensitivity and specificity for quantification of liver fibrosis (se: sensitivity, sp: specificity)

| Fibrosis stage | b 600 (s/mm²) | ADC cut-off | AUC (95% CI) | se  | sp  | ADC cut-off | AUC (95% CI) | se  | sp  |
|----------------|---------------|------------|--------------|-----|-----|------------|--------------|-----|-----|
| F0 vs. F1≤     |               | 1.458      | 0.861 (0.756-0.933) | 75.68 | 87.10 | 1.223      | 0.894 (0.795-0.955) | 75.68 | 90.32 |
| ≤F1 vs. F2≤    |               | 1.404      | 0.893 (0.795-0.955) | 77.78 | 87.80 | 1.223      | 0.908 (0.813-0.964) | 88.89 | 82.93 |
| ≤F2 vs. F3≤    |               | 1.374      | 0.892 (0.793-0.954) | 82.35 | 86.27 | 1.186      | 0.889 (0.790-0.952) | 82.35 | 86.27 |
| ≤F3 vs F4      |               | 1.352      | 0.927 (0.837-0.976) | 100.00 | 82.54 | 1.140      | 0.933 (0.846-0.980) | 80.00 | 82.54 |

Kocakoc et al. studied 44 patients with chronic liver disease and 30 healthy controls, assessing the role of DW images in the diagnosis of hepatic fibrosis using three different b-values (100, 600, and 1000 s/mm²). They concluded that only ADC values obtained by a b-value of 1000 s/mm² were statistically significant. In their study, the Ishak classification scoring system for fibrosis stage was used. AUC for identification of significant fibrosis (Ishak ≥3) was 0.759, which in our study for F2 and higher at the b-value of 1000 s/mm² was 0.903. In order to increase SNR and reduce image artifacts, we increased NEX to 10, while in the Kocakoc’s study NEX was one. This and the use of different fibrosis scoring systems might explain the differences between our study and that of Kocakoc in the results when the b-value was 600 s/mm² and the AUC.

A meta-analysis included 25 studies that assessed the role of ADC values for estimation of fibrosis stages. In this study, the AUC to differentiate F ≥ 2 in b-value ≥800 and <800 s/mm² were 0.918 and 0.799, respectively; and for F ≥ 3 were 0.916 and 0.836, respectively. Their findings for b-values ≥800 s/mm² were very close to those of our study. However, for b-values <800 s/mm², our findings show better estimation results for a b-value of 600 s/mm². As very low b-values such as 50–250 s/mm² were included in their study, and considering that these are contaminated by the perfusion effect, the differences may be explained.

Study limitations
In our study, there were no tissue samples from the control group and they were selected based on clinical and MRI findings. Similar numbers of patients were not used at each stage of fibrosis, and our sample size, particularly in some stage of fibrosis (F4) was low. Further research with a larger number of patients and even distribution among different stages of fibrosis is recommended.

Conclusion
Our results show that hepatic ADC value with b-values 600 and 1000 s/mm² could be considered as a method for diagnosis and staging of liver fibrosis. Besides, using DW-MR may lead to good estimates to differentiate fibrosis stage ≥2 from ≤1, which is of clinical importance.

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Conflicts of interest
There are no conflicts of interest.
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