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Utility of diffusion-weighted MRI for assessing liver fibrosis in patients with chronic active hepatitis

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PURPOSE
We evaluated the utility of quantitative diffusion-weighted magnetic resonance imaging (DW-MRI) for assessing both the relationship between the degree of fibrosis and the histological activity index (HAI) in chronic hepatitis (CH) cases and attempted to determine whether the apparent diffusion coefficient value (ADC) could be used as a reference for the degree of fibrosis detected by histology.

MATERIALS AND METHODS
The study population consisted of 55 CH patients (Group I) and a control group of 30 volunteers (Group II). Group I consisted of 31 CH-B (CHB), 18 CH-C (CHC) and 6 non-alcoholic steatohepatitis patients. DW-MRI of the liver with b values of 0, 500 and 1000 s/mm² was performed, and liver biopsies of the patients were obtained two weeks later. The ADC value, degree of liver fibrosis and HAI were compared within Group I, and the ADC values of both groups were compared with each other.

RESULTS
The ADC was lower in Group I than in Group II ($P < 0.05$). The ADC of the left lobe lateral (LL) ($P < 0.05$), left lobe medial (LM) and right lobe anterior (RA) segments ($P < 0.01$) in Group I were lower than those of Group II. There was no relationship between HAI and the ADC of LL, LM, RA and right lobe posterior (RP) segments in Group I. Additionally, there was no correlation between fibrosis scores and ADC in Group I, whereas there was a negative correlation between fibrosis scores and ADC values of the LL (28.3%) and RP (29.5%).

CONCLUSION
CH patients had lower ADC values. There was no correlation between ADC values and fibrosis stages or ADC and HAI values. Quantitative DW-MRI was not useful in determining the degree of fibrosis in liver tissue.

Key words: • liver fibrosis • diffusion-weighted magnetic resonance imaging • chronic hepatitis

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In contemporary medicine, percutaneous liver biopsy is the gold standard both for evaluating changes in fibrosis in early or late stages of diffuse liver disease and for distinguishing necroinflammatory grades (1–3). However, it is an invasive procedure and has certain contraindications that can lead to complications such as pain, hemorrhage, biliary peritonitis, penetration of abdominal organs, pneumothorax and death (4). Estimated mortality rates due to needle biopsies range from 0.009% to 0.12% (4–7). Additionally, biopsies are sensitive to sample size and analysis errors due to the heterogeneous distribution of fibrosis (8–10). Therefore, alternative non-invasive diagnostic methods have been suggested. Serological tests (e.g., the FibroTest) (11), new serum markers (12, 13), and ultrasound-based elastography (14) have been developed as diagnostic tools for liver fibrosis. It has been shown that diffusion-weighted magnetic resonance imaging (DW-MRI) may be beneficial in diagnosing fibrosis; however, the first DWI studies demonstrated contradictory results (15–20).

Diffusion is the spontaneous movement of random microscopic molecules in a solution, and this movement can be quantified by the average diffusion coefficient rate. DW-MRI is sensitive to this microscopic movement (21, 22), which can be measured by the apparent diffusion coefficient (ADC); thus, the diffusion of fluid is measured by the ADC (21). Because microscopic movements affect molecular diffusion and microcirculation of blood in the capillary network, the ADC is often higher than expected in biological tissues. Diffusion and perfusion both affect the ADC (18, 21, 22). MR diffusion quantifications can be affected by a number of factors including perfusion, cellular structure and permeability (22). ADC values are lower in patients with chronic liver disease, and diffusion restriction caused by proteoglycan and glycosaminoglycan (collagen fibers in the liver) deposits might explain this phenomenon (15, 17, 18, 23). There are a limited number of studies that have considered whether fibrosis may affect the diffusion correlation between hepatic ADC and the degree of liver fibrosis (16, 19, 24). In those studies, liver ADC values were compared with histological grades (15, 16, 19). There are various histopathological grading systems to evaluate necroinflammation. In clinical practice, the Knodell scoring system has long been used to grade fibrosis. The Knodell scoring system is based on the degree of fibrosis and necroinflammatory activity as follows: F0, none; F1, portal fibrosis; F2, bridging fibrosis with few septa; F3, bridging fibrosis with many septa; and F4, cirrhosis. Intralobular degeneration, focal necrosis, periportal ± bridging necrosis, and portal inflammation are the necroinflammatory parameters that determine the severity of the activity. The total histological activity index (HAI) is a combined score that consists of the mean amount of necrosis, inflammation and fibrosis as demonstrated by the following formula: HAI (Knodell score, 0–22) (25).

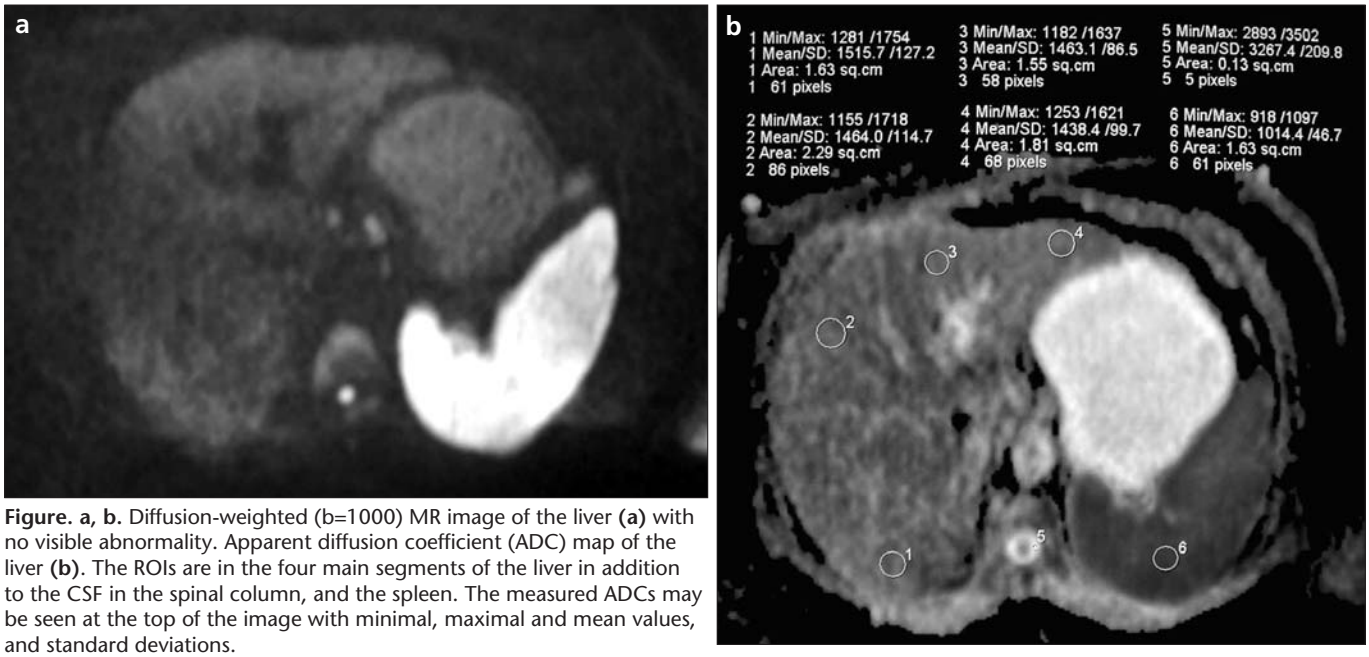

Figure. a, b. Diffusion-weighted (b=1000) MR image of the liver **(a)** with no visible abnormality. Apparent diffusion coefficient (ADC) map of the liver **(b)**. The ROIs are in the four main segments of the liver in addition to the CSF in the spinal column, and the spleen. The measured ADCs may be seen at the top of the image with minimal, maximal and mean values, and standard deviations.

In this study, we sought to determine a) the value of quantitative DW-MRI as a non-invasive method for measuring liver fibrosis, and b) whether ADC might be used as a reference standard for liver biopsy among patients with chronic liver disease.

Materials and methods

Study population

This prospective study was conducted between June 2007 and May 2008. The study was approved by the local ethics committee, and written consent was obtained from all participants. Exclusion criteria were alcohol addiction or the existence of focal malignant lesions in the liver. Chronic active hepatitis was diagnosed on the basis of a pertinent clinical history, the results of liver chemistry tests, and the results of a percutaneous liver biopsy. Fifty-five chronic hepatitis cases (Group I) and thirty volunteers with normal laboratory results and radiological imaging findings (Group II) were included in the study. The liver biopsy was performed percutaneously in chronic hepatitis patients under ultrasound guidance, and the patients were followed up at least six months prior to the biopsy. Group I consisted of 31 chronic hepatitis B (CHB) patients, 18 chronic hepatitis C (CHC) patients and 6 non-alcoholic steatohepatitis (NASH) patients. Liver biopsies were evaluated by an experienced pathologist using Knodell scores (25). The degree of liver fibrosis (stage) and the HAI scores in Group I and the ADC values of both groups were compared.

Magnetic resonance imaging

All patients underwent MRI of the liver after six hours of fasting prior to biopsy. MRI was performed using a 1.5 T scanner (Avanto; Siemens, Erlangen, Germany) with a 33 mT/m maximum gradient capability via an eight-channel phased-array body coil. Before DWI was conducted, the following were performed: breathhold, axial 3D gradient-echo T1-weighted sequence, 2D gradient-echo T1 in-phase and out-of-phase, axial respiratory-triggered, turbo spin-echo T2-weighted sequence with fat saturation, coronal T2-weighted half-Fourier single-shot turbo spin-echo (HASTE) sequences and then diffusion weighted single-shot spin-echo echo-planar sequence with chemical shift selective fat-suppression technique; TR/TE, 4900/93; matrix, 192 × 192; slice numbers, 30; slice thickness, 6 mm; interslice gap, 35%; FOV, 45 cm; averages, 5; acquisition time, approximately 3 min; PAT factor, 2; PAT mode, parallel imaging with modified sensitivity encoding (mSENSE). DW-MRI was performed with b factors of 0, 500 and 1000 s/mm² (Fig.). Following DWI, contrast-enhanced dynamic imaging was performed when necessary with an axial 3D gradient-echo T1-weighted MR sequence during and after administration of gadopentetate dimeglumine at a dose of 0.1 mmol/kg of body weight as a bolus injection, with 20 s between each breathhold acquisition (each breathhold lasted between 20–24 s).

Image interpretation

The DWI datasets were transferred to an independent work station (Leonardo console, software version 2.0; Siemens) for postprocessing, and the ADC maps were reconstructed. An experienced abdominal radiologist placed circular regions of interest (ROI) approximately 1–1.5 cm in diameter in four segments of the liver (right lobe posterior [RP] and anterior [RA], and left lobe medial [LM] and lateral [LL] segments) to measure ADC values. For ADC calculations of the liver segments, we applied three ROIs on each segment and found the arithmetic average (3 ROIs per segment, 12 ROIs per patient). The final ADC was the arithmetic average of the 12 ROIs. Care was taken to exclude vessels and motion artifacts from the ROIs (Fig.).

Statistical analysis

The Statistical Package for Social Sciences for Windows 15.0 (SPSS Inc., Chicago, USA) was used for the analysis. Other than descriptive statistical methods, Student's t-test was used for both the comparison of quantitative data and the comparison of group parameters. An analysis of the correlation between parameters was conducted us-

ing the Pearson correlation and Spearman's rho correlation tests. The cut-off point was designated using receiver operating characteristic (ROC) analysis. The results were considered significant if they had a $P < 0.05$ value.

Results

The mean age did not differ between Groups I (45.43 ± 13.19) and II (42 ± 12.44) ($P > 0.05$). Although there was a negative correlation between the means of ADC values and ages in Group I (30.6%) ($P < 0.05$), there was not a significant difference in Group II ($P > 0.05$). The mean ADC values were lower in Group I ($1.46 \pm 0.17 \times 10^{-3}$ mm²/s) than in Group II ($1.56 \pm 0.16 \times 10^{-3}$ mm²/s) ($P < 0.05$). The mean ADC values of the LL ($P < 0.05$), LM ($P < 0.01$) and RA ($P < 0.01$) in Group I were lower than in Group II. There was no difference in RP mean ADC values between Group I and Group II ($P > 0.05$) (Table 1). There was no relationship between HAI scores, LL, LM, RA and the mean RP ADC values in Group I ($P > 0.05$). There was also no correlation between fibrosis scores and mean ADC values in Group I ($P > 0.05$). While there was a negative correlation between fibrosis scores and the mean ADC values of the LL (28.3%) and RP (29.5%) ($P < 0.05$), there was no relationship between LM and RA levels ($P > 0.05$) (Table 2).

In the CHB, CHC and NASH subgroups, there was no correlation between the mean ADC-fibrosis scores and ADC-HAI ($P > 0.05$). Although there was a positive correlation between ADC and fibrosis (28%) and a negative correlation between ADC and HAI (24.6%) in the CHB+CHC group, these correlations were not significant. A cut-off ADC value of 1.52 yielded a sensitivity of 72.73%, a specificity of 60%, a positive predictive value of 76.92% and a negative predictive value of 54.55%.

Discussion

The major complications of chronic liver disease may be life threatening. Thus, the follow-up and treatment of chronic liver diseases and pathological evaluations are of clinical importance. Percutaneous liver biopsy can cause mortality and morbidity; however, histopathological findings provide important criteria for the assessment of antiviral treatment, disease prognosis and treatment response in patients with chronic viral hepatitis (2, 26, 27). Although liver biopsy is the gold standard, it is a procedure not easily accepted by patients and can only supply a small sample for local analysis. Therefore, there is a demand for new non-invasive methods to measure liver fibrosis. Serological markers that are currently being investigated include aspartate transaminase/alanine transaminase rates, platelet count and the prothrombin index, all of which are simple tests, as well as the FibroTest, which is a more complex test (28). Additionally, imaging methods like FibroScan, Echosens (29–31), perfusion-weighted MRI (32, 33) and MR elastography (30, 31) can be used in diagnosing late-stage fibrosis and cirrhosis. In the literature, there are DW-MRI studies reporting ADC decreases due to liver fibrosis (17, 18). This decrease is probably related to constricted sinusoids and the increased quantity of connective tissue (34, 35). Other than collagen deposits, perfusion differences, cellular inflammation and apoptosis can affect fluid diffusion (23, 35, 36).

In a study consisting of 17 Child-Pugh class A cirrhotic patients with hepatitis B and 10 control patients, the ADC was significantly lower in cirrhosis patients than in the control group (34). In a different study performed on cirrhotic patients, it was concluded that liver fibrosis could be correctly determined if the maximum mean b value was optimized in the single-shot spin-echo echo-planar sequences. In that study, the initial value of the ADC threshold for diagnosing liver fibrosis was 1.31×10^{-3} mm²/s (37). A precise assessment of the ADC can be performed by detecting regional ADC variations (38). Taking ADC measurements from the right lobe posterior segment and using of high b values (500–750 s/mm²) to limit the effects of differences in perfusion are recommended for a better evaluation of fibrosis (23, 39). When low b values are used, the ADC is more strongly affected by perfusion (18, 19). In another study, b values of 200 and 400 were reported to give better results in fibrosis measurements (15). In our study, the ADC was calculated using measurements from four segments of liver lobes and b values of 0, 500 and 1000.

Treatment choice and planning are performed according to the degree of liver fibrosis in CH patients. Patients

Table 1. Comparison of the ADC values of liver segments in patients and controls

	Patients mean ± SD	Control group mean ± SD	*P*
ADC	1.46 ± 0.17	1.56 ± 0.16	0.009[a]
LL	1.56 ± 0.23	1.68 ± 0.22	0.022[b]
LM	1.45 ± 0.21	1.63 ± 0.22	0.001[a]
RA	1.34 ± 0.18	1.50 ± 0.20	0.001[a]
RP	1.47 ± 0.18	1.41 ± 0.22	0.241

Student's t-test was used: [a]$P < 0.01$, [b]$P < 0.05$
ADC, apparent diffusion coefficient; LL, left liver lobe lateral segment; LM, left liver lobe medial segment; RA, right liver lobe antterior segment; RP, right liver lobe posterior segment

Table 2. Correlations between fibrosis and HAI in patients with respect to liver segments

	HAI		Fibrosis	
	r	*P*	r	*P*
LL	-0.220	0.106	-0.283	0.036[a]
LM	-0.087	0.526	-0.092	0.506
RA	-0.034	0.805	-0.005	0.969
RP	-0.226	0.098	-0.295	0.029[a]

Spearman's rho correlation test was used: [a]$P < 0.05$
HAI, histological activity index; LL, left liver lobe lateral segment; LM, left liver lobe medial segment; RA, right liver lobe antterior segment; RP, right liver lobe posterior segment

with stage 2 fibrosis and above should receive treatment according to generally accepted guidelines in Turkey and elsewhere (23, 25, 40). Previous studies have investigated the correlation between hepatic ADC and the degree of fibrosis. Boulanger et al. (16) used DWI with b values of 50–250 s/mm^2 and found no significant difference between hepatitis C patients and the control group. The ADCs of patients with hepatitis were higher than those of controls. A possible explanation for this finding is that differences between fibrotic and non-fibrotic livers cannot be detected at small b values (<300 s/mm^2). Another study evaluated a population of 163 patients using a b value of 128 s/mm^2; the results showed a significant negative correlation between the hepatic ADC and fibrosis scores but no correlation between the ADC and inflammation grade (19). In another study similar to ours, a negative correlation between hepatic ADC and the stage of fibrosis and a weaker negative correlation between the ADC and the grade of inflammation were found. It was also found that ADC calculations exhibit a prognostic value in distinguishing advanced fibrosis and cirrhosis. However, there was no significant difference between ADC values and the stages of fibrosis in this study (38). We did not find any correlation either between the mean ADC values and fibrosis scores (r = -0.226; P = 0.097) nor ADC values and HAI scores (r = -0.206; P = 0.132). Therefore, we believe that quantitative DW-MRI is not a sufficient method for distinguishing chronic hepatitis stages and that treatment cannot be planned accordingly because it is essential that the stages of fibrosis be determined beforehand.

A study on live rats demonstrated a decreased ADC value in fibrotic livers in comparison to the controls. However, this difference was not found in dead animals and fixed tissues (35). The ADC difference among dead and living rats was related to perfusion effects. Decreased perfusion due to liver fibrosis has been seen in a number of studies (32, 35, 41, 42). In a study conducted with cirrhotic live dogs, the ADC was lower in the cirrhotic lobes than in normal lobes; however, lobal differences in the ADC values disappeared after portal vein clamping (43). Thus, the study concluded that the decrease of ADC in the liver was caused by decreases in blood perfusion effects as a result of cirrhosis (22, 35, 41). In another rat study comparing conventional morphological imaging and DW-MRI, diffuse hepatic disease could be detected earlier by DW-MRI, resulting in the suggestion of using ADC values as a marker for early diagnosis (44).

In our study, the ADC values were different among different liver lobes. This difference probably originated both from regional perfusion changes and the artifacts affecting ADC calculations caused by cardiac and intestinal motions, as well as from vascular pulsations, particularly in the left lobe of the liver (18, 23, 39). Thus, conducting liver ADC measurements from the right lobe posterior segment (39) and using multiple b values to prevent perfusional effects from affecting the ADC have been proposed (38). In another study, the authors proposed that the ADC is affected by perfusion rather than diffusion in organs that have a strong blood supply such as the liver (45, 46). The negative correlation among the ADC values of RP and LL segments and the absence of a correlation between the RA and LM segments support this view. In a group of 54 hepatitis C patients, the ADC values of 23 patients (with fibrosis stages of F2 and F3) were compared based on their elastography, FibroTest, APRI, Forns index, and hyaluronate results. This resulted in a sensitivity of 87%, a specificity of 87%, a positive predictive value of 72%, a negative predictive value of 94%, and an ADC cutoff level of 1.21 x 10^{-3} mm^2/s. When patients with F2–F4 fibrosis stages were compared to patients with F0–F1 stages and healthy volunteers, the ADC values in the F2 and F4 groups were lower. In conclusion, it was determined in this study that in cases where liver fibrosis is evident, DW-MRI is more useful to detect the degree of fibrosis than other non-invasive procedures (47). Further studies are needed to evaluate more patients and to correlate DW-MRI findings with findings obtained by newer methods of perfusion (32), MR elastography (30, 33) and serologic markers of fibrosis.

This study has several limitations. Firstly, the subgroups of the patient population were relatively small. Secondly, although high spatial resolution and less distortion are desirable for DWI of the liver, single-shot echo-planar DWI imaging is limited in these regards. Further studies involving a larger number of patients are required to evaluate the correlation between ADC values and histological scores with high-quality images.

In conclusion, ADC values are lower in chronic hepatitis cases, as reported in a number of previous studies. Although ADC values are lower in patients with advanced fibrosis, we could not find a relationship between ADC values, fibrosis stage, and HAI values that was found in other studies. These findings suggest that DWI may not be used to determine liver histology in CH patients. Because DWI is unable to show the stages of fibrosis, its use in treatment plans and follow-up is debatable.

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