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The utility of apparent diffusion coefficient values in predicting liver fibrosis in chronic hepatitis B

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ABSTRACT

Aim: We aimed to determine the relationship between apparent diffusion coefficient (ADC) values obtained from diffusion-weighted images, histopathological fibrosis, and activity stages in patients with chronic hepatitis B infection.

Material and Method: A total of 30 patients with chronic hepatitis B admitted to our hospital between September 2012 and June 2014 were included in the study. All patients underwent biopsy and abdomen MRI examination before the treatment. Diffusion examinations at five different b-values (50, 300, 500, 700, and 1000 s/mm²) were added to the abdominal MRI examination.

Results: The hepatic ADC values at all b-values were negatively correlated with fibrosis stages ($p<0.001$ for all b-values). The ADC values at b-values 300 and 1000 were significantly lower in patient groups with histological activity indices 1 and higher compared to the patient group whose activity index was 0 (at b-value 300 $p<0.034$, and at b-value 1000 $p<0.027$). The ADC values at b-values 50, 500 and 700 were not significantly in patient groups with histological activity indices 1 and higher compared to the patient group whose activity index was 0. Hepatic ADC was a significant predictor of stage 2 or greater and stage 3 or greater fibrosis, with sensitivity of 81%-100% and 81%-96% , and specificity of 84,2%-100% and 100% (ADC with all b values).

Conclusion: The ADC values have high sensitivity and specificity in indicating liver fibrosis in chronic hepatitis B infection. We suggest that the addition of diffusion-weighted MR images into liver MRI examination might reduce the requirement for liver biopsies in patients with chronic hepatitis B.

Keywords: Apparent diffusion coefficient, diffusion MRI, hepatitis B, fibrosis, liver, histological activity index

INTRODUCTION

Approximately 400 million people worldwide have chronic hepatitis B infection (1). Hepatitis B infection poses a high risk in terms of the development of liver fibrosis, cirrhosis, and hepatocellular cancer. The early diagnosis and treatment of liver fibrosis in patients with chronic hepatitis B can prevent the progression to cirrhosis (2). The liver biopsy is used as the indicator of the severity of the disease and to detect signs of antiviral therapy in chronic viral hepatitis. However, liver biopsies have some drawbacks, including the invasiveness of the procedure, complications resulting from the procedure, and inadequate sample amounts on some occasions. Therefore, there is a need for a non-invasive method for the detection of liver fibrosis and inflammatory activity in patients with chronic viral hepatitis. In the literature, numerous non-invasive tests that predict the degree of liver fibrosis in chronic hepatitis B have been proposed, but the tests are not as highly sensitive and specific as histopathological examination and have various limitations. Ultrasonography, computed tomography, and conventional MR imaging do not have sufficient sensitivity to show liver fibrosis and early cirrhosis (3).

In diffusion-weighted MR imaging (DWI), signal intensity is inversely related to the degree of diffusion of water molecules. The apparent diffusion coefficient (ADC) is a numerical value for quantitative measurement of proton diffusion given as square millimeter/second. Low ADC shows restricted diffusion of protons. DWI is affected by tissue perfusion, but using high b-values reduces the effect of perfusion on ADC values while fibrosis restricts the diffusion of water. Taouli et al. (3,4) have reported that reduced ADC values were associated with cirrhosis.

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The aim of our study was to quantitatively assess the relationship between ADC values obtained from diffusion-weighted images, histopathological findings, and activity stages of the liver in patients with chronic hepatitis B.

MATERIAL AND METHOD

The study was conducted with the permission of the Noninvasive Clinical Education Planning Board of 3rd step Training and Research Hospital in Ankara (Date: 09.01.2014, Decision No: 2014/352). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

Patients

A total of 30 patients who were diagnosed with chronic hepatitis B and admitted to our hospital between September 2012 and June 2014 and whose ultrasound examinations were insufficient, causing dynamic liver MR images to be taken were included in our study. Patients with a clinical diagnosis of cirrhosis were not able to undergo liver biopsy and were excluded from the study. In addition, patients that had comorbid malignant diseases and patients with non-hepatitis B diseases that could lead to viral and non-viral chronic hepatitis, such as hepatitis C and autoimmune hepatitis were excluded. Moreover, patients that had more than 10% histopathologically detected steatosis were also excluded from the study. Patients were diagnosed with chronic hepatitis B based on the clinical findings and results of laboratory evaluations. All of the patients were HBs Ag positive, anti-HBc Ig G positive, anti-HBe positive and HBV DNA levels were higher than 2000 UI/ml. Serological tests for hepatitis D and hepatitis C were negative in all of the patients. All patients underwent a biopsy and pre-treatment abdominal MRI examination. Patients that were scheduled to undergo additional diffusion examinations were asked to sign an informed consent form.

MR Imaging

The diffusion-weighted images were obtained by using 1.5 tesla MRI device (GE Medical System, Milwaukee, WI). A body coil was used for all experiments with participants in the supine position. Diffusion-weighted MR imaging at five different b-values was added to the abdominal MRI examination. Ten slices in the middle portion of the liver were taken (with 7-mm thickness and spacing of 1.5 mm). The following were the acquisition parameters of DW-MRI: non-breath hold single-shot spin-echo echo-planar DW-MRI, repetition time 1300, echo time minimum, matrix size 192-256, field of view 40, number of excitation 4. Parallel imaging technique using the generalized auto-calibrating partially parallel acquisition (ASSET) was used with a two fold acceleration factor.

A single radiologist who was blinded to the histology results placed a region of interest (ROI) in each lobe of the liver. Analysis of DW-MRI data was performed with the GE FUNCTOOL software (GE Medical Systems) to obtain ADC maps at each b value (50, 300, 500, 700, and 1000 s/mm²). One-cm² regions of interest (ROI) on the right and left lobes of the liver were measured from three different places, and average values were calculated. The axial echo-planar diffusion-weighted images of patients with stage 0 and stage 4 fibrosis of chronic hepatitis b at b-values 1000 s/mm² are demonstrated in **Figure 1** and **Figure 2**.

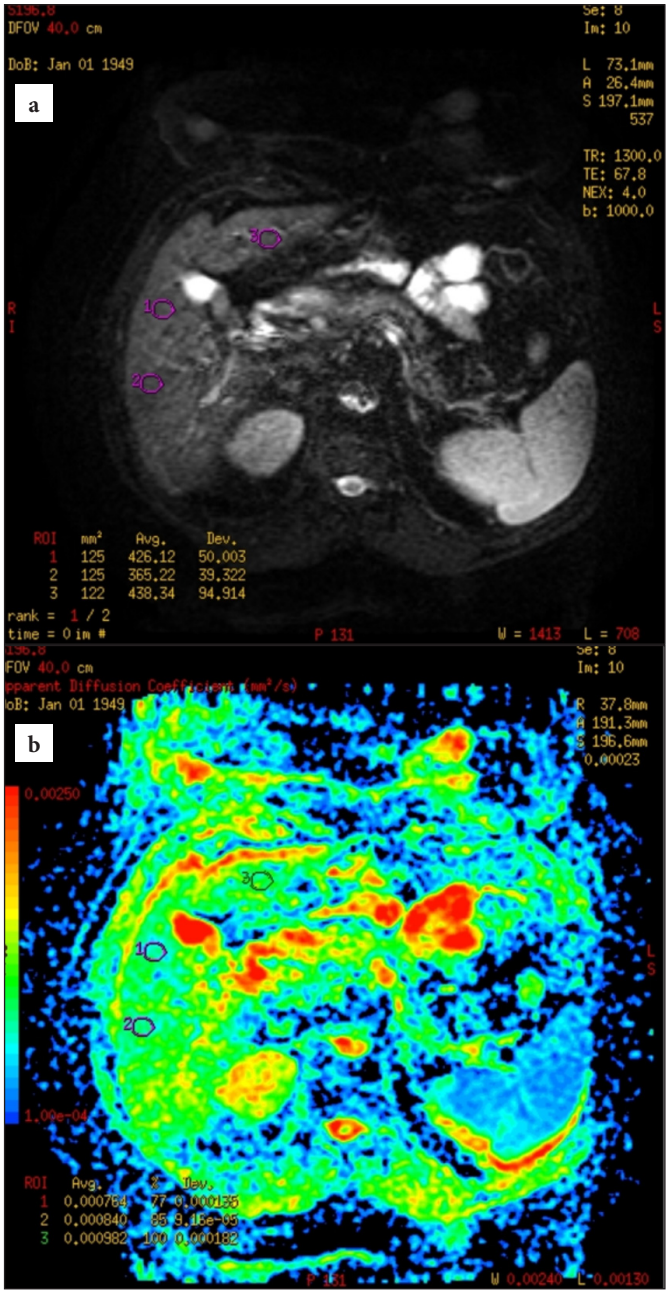

Figure 1. The axial diffusion-weighted images (a) and ADC map (b) of 46-year-old patients with stage 4 fibrosis. The mean ADC value of measurements taken from the right and left lobes of the liver was found as 0.86 x 10-3.

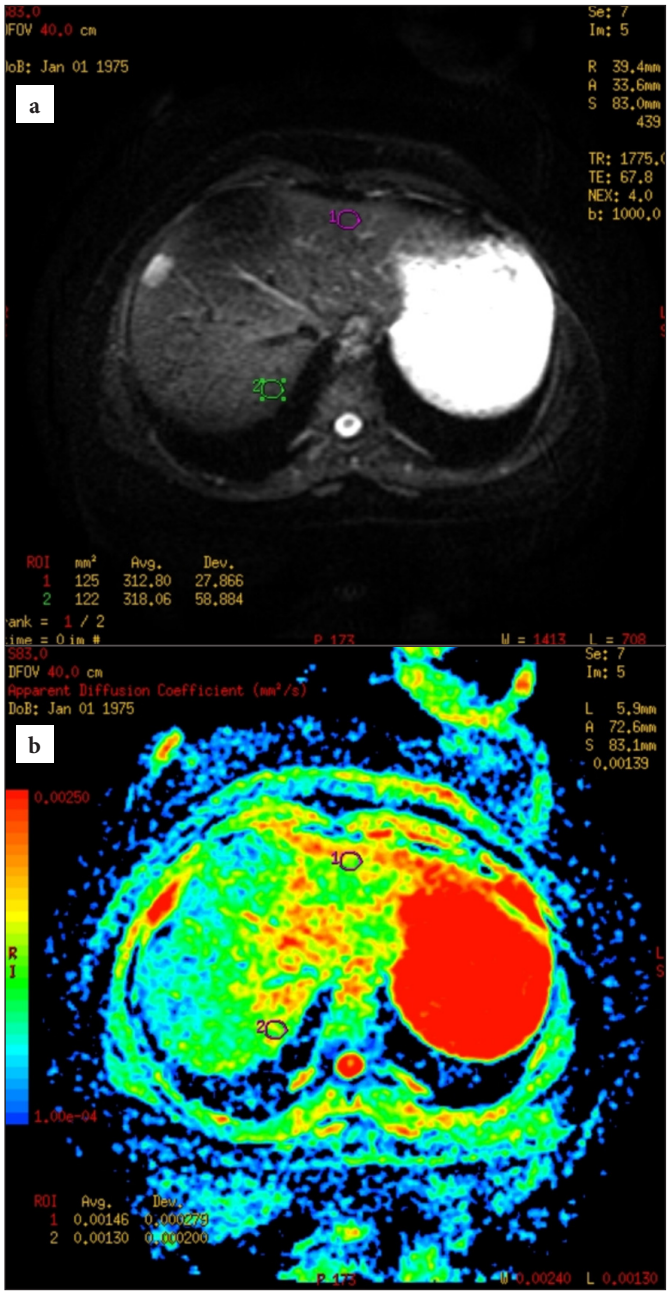

Figure 2. The diffusion-weighted images (a) and ADC map (b) of 32-year-old hepatitis B patient with stage 0 fibrosis. The mean ADC value was 1.38 x10-3.

Liver Biopsies

All our patients underwent percutaneous liver biopsy after MRI examination. A liver biopsy was carried out under ultrasound guidance using an 18-gauge needle by a hepatologist with five years of experience. Pathology slides from all patients were evaluated retrospectively by the same pathologist who then had eight years of experience. Fibrosis staging and inflammatory activity were interpreted according to the scoring system developed by the METAVIR group. The METAVIR stages F0, F1 was termed "no/minimal fibrosis," whereas the presence of METAVIR stages F2, F3, or F4 indicated "significant fibrosis," METAVIR stage F3 or F4 were termed "advanced fibrosis," and METAVIR stage F4 was termed "cirrhosis." For histological activity, grade 0 was termed "no histologic necroinflammatory activity," grade 1 was termed "minimal activity," grade 2 was termed "mild activity," grade 3 was termed "moderate activity," and grade 4 was termed "severe activity." The activity was assessed using a combination of severity and intensity of periportal and lobular necrosis (5).

Statistical Analysis

Statistical Analysis SPSS version 17.0 was used for analysis. A nonparametric Mann-Whitney test was used to compare hepatic ADC between patients stratified according to individual fibrosis stages and patients grouped as stage 1 or lower versus stage 2 or higher and stage 2 or lower versus stage 3 or higher, as well as between patients stratified by inflammation grade (grade 0 vs grade 1 or higher). The Spearman's rank correlation test was used to assess the correlation between hepatic ADC, stage of fibrosis, and grade of inflammation. Receiver operating characteristic (ROC) curve analyses were conducted to evaluate the utility of the ADC measures for prediction of stage 2 or higher and stage 3 or higher fibrosis and for prediction of grade 1 or higher inflammation. A value of $p<0.05$ was considered statistically significant.

RESULTS

Seventeen of our patients were male (56.6%) and 13 were female (43.3%). The mean age of our patients was 50.9±8.5 (35-72). The patients distribution according to stages of fibrosis and activity grade is summarized in **Table 1**. At all b-values, the hepatic fibrosis stages were negatively correlated with ADC values ($p<0.001$). At stage 0 the mean ADC value was 2.17±0.25; at stage 1 it was 1.96±0.37; at stage 2 it was 1.72±0.39; at stage 3 it was 1.48±0.14; and at stage 4 it was 1.13± 0.21 $x10^{-3}mm^2/s$. The distribution of liver ADC values according to the stage of fibrosis is shown in **Table 2**. When patient group whose liver fibrosis stages were 2 or higher (significant fibrosis) were compared with patient groups whose fibrosis stages were 1 or lower (no / minimal fibrosis), the ADC values were significantly lower in patients with significant fibrosis at all b-values. Moreover, when patient groups whose liver fibrosis stages were 3 or higher (advanced fibrosis) were compared with patient groups whose fibrosis stages were 2 or lower (significant fibrosis), the ADC values of advanced fibrosis patients were significantly lower at all b-values ($p<0.001$, for all b-values) (**Table 3**). The evaluation of receiver operating characteristic (ROC) analysis revealed that hepatic ADC values were statistically significant in determining significant and advanced fibrosis (**Table 4**). Furthermore, we detected a negative correlation between ADC values and activity

index. At b-values 300 and 1000, the ADC values were significantly lower in the groups whose histological activity indexes were 1 or higher when compared to the group whose activity index was 0 (at b-value 300 p<0.034, and at b-value 1000 p<0.027) (**Table 5**). ROC analysis revealed that ADC values might be used as an important marker in patients with activity indexes of grade 1 or higher (**Table 6**). In addition, Spearman's correlation test showed that there was a moderate positive correlation between ADC values, inflammation, and stages of fibrosis (r=0.418, p=0.021)

Table 1. Distribution of Fibrosis Stage and Inflammation Grade Among Patients with Chronic Hepatitis B(n: 30)

State or Grade	Fibrosis	Inflammation
0	5	2
1	6	7
2	5	7
3	8	7
4	6	7
Total	30	30

*Fibrosis staging and inflammatory activity were interpreted according to scoring system developed by the METAVIR group

Table 2. Distribution of liver apparent diffusion coefficients (value × 10^{-3} mm²/s) stratified by fibrosis stage (n = 30)

Fibrosis Stage	b Value (s/mm²)				
	50	300	500	700	1,000
0	3.35±0.35	2.62±0.29	1.96±0.17	1.55±0.26	1.38±0.18
1	3.10±0.55	2.24±0.25	1.82±0.14	1.40±0.55	1.23±0.40
2	2.50±0.24	2.04 ±0.11	1.59±0.74	1.36±0.65	1.13±0.21
3	2.23±0.14	1.62±0.12	1.35±0.12	1.20±0.17	1.00±0.16
4	1.57±0.23	1.22±0.26	1.06±0.28	0.95±0.16	0.86±0.12

Table 3. Comparison of liver apparent diffusion coefficients (value × 10–^{3} mm²/s) stratified by fibrosis stage ≤ 1 versus ≥ 2 and fibrosis stage ≤ 2 versus ≥ 3 (n = 30)

Fibrosis Stage	b Value (s/mm²)				
	50	300	500	700	1,000
≤ 1	3.21±0.46	2.41±0.25	1.88±0.16	1.47±0.10	1.30±0.10
≥ 2	2.09±0.42	1.60±0.35	1.32±0.26	1.16±0.19	0.99±0.12
p	<0.001	<0.001	<0.001	<0.001	<0.001
≤ 2	2.99±0.52	2.29±0.27	1.79±0.19	1.43±0.10	1.24±0.11
≥ 3	1.95±0.38	1.45±0.27	1.22±0.24	1.09±0.18	0.94±0.10
p	<0.001	<0.001	<0.001	<0.001	<0.001

Note—Liver apparent diffusion coefficient is significantly decreased in patients with moderate and advanced fibrosis at b values of 500 s/mm² or greater or a combination of all b values (0, 50, 300, 500, 700, and 1,000 s/mm²).
Statistically significant values are displayed in boldface.

Table 5: Distribution of Liver Apparent Diffusion Coefficients (value × 10^{-3}mm²/s) Stratified by Inflammation Grade (n = 30)

Inflamation grade	b Value (s/mm²)				
	50	300	500	700	1,000
0	3.32±0.24	2.62±0.03	1.95±0.07	1.50±0.14	1.43±0.02
≥ 1	2.45±0.68	1.85±0.48	1.50±0.35	1.26±0.22	1.08±0.17
p	0.088	0.034	0.067	0.133	0.027

Note—Statistically significant values are displayed in boldface.

Table 6: The Performance of ADC for Determining of Liver Inflammation in Different b-values (n = 30)

b value (s/mm²)	ADC (Value x 10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)
50	≤ 3.07	0.866	100	85.7
300	≤ 2.55	0.955	100	92.9
500	≤ 1.85	0.893	100	89.3
700	≤ 1.37	0.821	100	60.7
1,000	≤ 1.38	0.973	100	93.4

Note—Sensitivity and specificity are calculated when hepatic apparent diffusion coefficient is used to diagnose grade 1 or greater inflammation. AUC: Area under the receiver operating characteristics curve, ADC: Apparent Diffusion Coefficient

DISCUSSION

In our study, we determined a significant negative correlation between hepatic ADC values and stages of fibrosis in patients with chronic hepatitis B. Liver diffusion ADC values were highly sensitive and specific in predicting stages of liver fibrosis.

Most of the studies in the literature were based on hepatitis C patients and cirrhosis patients with different etiologies. Our study is based on patients with hepatitis B disease. In our study, sensitivity and the specificity of the ADC values to determine the fibrosis was found to be much higher than in most of the other studies.

Histopathological data is needed to determine the prognosis in patients with chronic viral hepatitis B in order to start antiviral therapy and to evaluate the efficacy of treatment. However, due to possible complications and limitation of sampling sizes of biopsy, there is a need for a more non-invasive examination method (6,7). Basar et al. (8) investigated the relationship of pre-treatment aspartate aminotransferase to platelet ratio index (APRI), Forn's index, FIB-4, S-index, Shanghai Liver Fibrosis Group's index (SLFG), and

Table 4: The Performance of ADC for Determining Liver Fibrosis in Different b-values (n = 30)

b- values (s/mm²)	Prediction of Stage 2 or Greater Fibrosis				Prediction of Stage 3 or Greater Fibrosis			
	ADC (Value ×10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)	ADC (Value × 10^{-3}mm²/s)	AUC	Sensitivity (%)	Specifity (%)
50	≤ 2.72	0.967	90.9	94.7	≤ 2.47	0.962	81.3	100
300	≤ 2.20	0.974	81.8	100	≤ 1.85	1.000	94.1	100
500	≤ 1.65	0.995	100	94.7	≤ 1.52	0.998	93.8	100
700	≤ 1.37	0.959	90.9	84.2	≤ 1.37	0.980	81.3	100
1,000	≤ 1.17	1.000	100	96.1	≤ 1.11	1.000	96.4	100

HepascoreR with fibrosis in patients with chronic hepatitis B. The authors emphasized that non-invasive serum tests might be useful in indicating the stages of liver fibrosis, monitoring the effectiveness of treatment, and may reducing the need for biopsy. The specificity and sensitivity values of conventional MRI in patients with chronic liver disease and liver fibrosis are low (9). Currently, diffusion-weighted imaging, MR elastography and sonoelastography are used for the detection of fibrosis (10).

Fujimato et al. (11) evaluated 43 patients with hepatitis C, compared the mean and entropy ADC values with fibrosis and activity indices, and reported that mean ADC values decreased with increasing fibrosis stage and activity index, while entropy ADC values increased with increasing fibrosis stage and activity index. In addition, they reported that the combined evaluation of mean ADC and entropy ADC values was more accurate and more successful in indicating the early stages of fibrosis and inflammation compared to the evaluation of ADC values alone. Their ROC analysis determined that sensitivity and specificity for prediction of the activity of stage 1 and higher were 81% and 83%, respectively, and that the cut-off ADC value was 1.35 x 10^{-3}. Bozorg et al. (12) in their study with 33 patients with chronic hepatitis B used three different b-values and reported that the specificity and sensitivity of ADC values at b500 were higher. In our study, the ADC values at b500 and b1000 had higher sensitivity in indicating fibrosis. The reason for this might be that at high b values the influence of perfusion on ADC values is reduced. With the development of fibrosis, the levels of extracellular collagen, glycosaminoglycan, and proteoglycan increase and the diffusion of water molecules become limited. This situation is more prominent at high b-values. Some studies reported that the ADC measurements at low b-values were not indicative of fibrosis (3, 13). In an experimental study, Annet et al. (14) showed that in live mice decreased ADC values were consistent with increased liver fibrosis. However, once the mice were sacrificed the relationship between ADC values and fibrosis was not detectable. As a result, they reported that rather than reflecting restricted diffusion, which developed secondary to fibrosis, the ADC values reflect changes in the perfusion associated with fibrosis. Extracellular collagen deposition and changes in perfusion are seen in liver fibrosis. Changes in body temperature and the location of ROI may affect the ADC values (3, 4, 14). In our study the ROIs were placed away from the vascular areas and the average of three different measurements was taken.

In a study with 54 chronic HCV-infected patients, Lewin et al. (15) compared non-invasive tests such as diffusion-weighted MRI and transient elastography in terms of hepatic fibrosis prediction values and reported that diffusion-weighted MR imaging was as effective as other non-invasive tests in predicting fibrosis in patients with chronic HCV infection.

Taouli et al. (3) used five different b-values in evaluating 23 patients with chronic liver disease and reported that b-values of b500 and higher are more sensitive in showing fibrosis at stages 3 and above. The necroinflammatory activity evaluation in the same study indicated that the hepatic ADC values were lower in the group with mild-to-moderate inflammation (grades 1 and above) compared to the group without inflammation (at b700 the cutoff of ADC=1.35 x 10^{-3}, the sensitivity and specificity of this cutoff value at stages 1 and above was 85.7% and 75%, respectively). We found hepatic ADC in all b values to have high sensitivity and specificity of hepatic fibrosis. The sensitivity and specificity of ADC cutoff value 1.38 at b1000 in determining inflammatory activity of grades 1 or higher were 100% and 93.4%, respectively. In the literature, there is no correlation or low correlation between inflammatory activity score and ADC. ADC was found to be more successful in predicting the stage of fibrosis.(3, 16) In the comparison of inflammatory activity with ADC, we found low ADC in all b values, but b500 and b700 ADC were not statistically significant. Differences in the accompanying fibrosis stage, parenchymal heterogeneous distribution of fibrosis, technical and patient-related factors may cause this statistical difference. Our findings are consistent with the findings of both aforementioned studies.

For chronic active hepatitis B, pegylated interferon and the oral antiviral agents such as entecavir, tenofovir are the choice of treatment. Especially for the oral antiviral agents, apart from the resistance development and different side effect profiles, none of them is superior to the other, in terms of their effects on the liver parenchyma. In chronic active hepatitis B patients, the histopathological analysis which is used for the determination of the efficacy of the antiviral treatment cannot be performed due to ethical issues and invasive procedure complications. Few studies (17, 18) have shown the histopathological recovery of the liver fibrosis in chronic hepatitis B with oral antiviral agents. As the diffusion ADC can detect the stage of the liver fibrosis in chronic hepatitis B patients with a reliability closed to histopathological analysis, studies related to diffusion ADC can be guide the clinicians about evaluating the efficacy of oral antiviral agents and their superiority to each other.

The examinations with diffusion-weighted imaging for assessment of fibrosis have been frequently conducted in patients with chronic hepatitis C, but there are only few reports of this kind of study in patients with chronic hepatitis B (10, 19).

Biexponential, and stretched-exponential diffusion-weighted imaging models, fat and iron corrected ADC evaluation, diffusion curtosis, MR elastography and whole liver histogram diffusion analysis have performed for staging hepatic fibrosis and grading inflammatory activity in patients with chronic hepatitis and recently studies showed that these diffusion methods have good diagnostic performance (20-26).

The limitations of our study are small sample size, lack of ADC values in the post-treatment follow-up. Current diffusion ADC techniques were not used in our study because of the time period in which the patient group is selected.

CONCLUSION

ADC in all b values have high sensitivity in demonstrating liver fibrosis in patients with chronic hepatitis B. We suggest that the addition of diffusion-weighted MR images into liver MRI examination might reduce the requirement for liver biopsies in patients with chronic hepatitis B.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of the Non-invasive Clinical Researches Ethics Committee of Ankara Atatürk Sanatorium Training and Research Hospital (Date: 09.01.2014, Decision No: 2014/352).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Zeng MD, Lu LG, Mao YM, et al. Prediction of significant fibrosis in HBeAg-positive patients with chronic hepatitis B by a noninvasive model. Hepatology 2005; 42: 1437- 45.
2. Afdhal NH, Nunes D. Evaluation of liver fibrosis: a concise review. Am J Gastroenterol 2004; 99: 1160-74.
3. Taouli B, Tolia AJ, Losada M, et al. Diffusion weighted MRI for quantification of liver fibrosis: preliminary experience. AJR 2007; 189: 799-806
4. Taouli B, Koh DM. Diffusion-weighted MR imaging of the liver. Radiology 2010; 254: 47-66.
5. The French METAVIR Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretion in patients with chronic hepatitis c. Hepatology 1994; 20: 15-20
6. Rockey DC, Bissell DM. Noninvasive measures of liver fibrosis. Hepatology 2006; 43:113-20
7. Rockey DC. Current and future anti-fibrotic therapies for chronic liver disease. Clin Liver Dis 2008; 12: 939-62.
8. Başar O, Yimaz B, Ekiz F, et al. Non-invasive tests in prediction of liver fibrosis in chronic hepatitis B and comparison with post-antiviral treatment results. Clin Res Hepatol Gastroenterol 2013; 37: 152-8.
9. Awaya H, Mitchell DG, Kamishima T, Holland G, Ito K, Matsumoto T. Cirrhosis: modified caudate-right lobe ratio. Radiology 2002; 224: 769-74.
10. Manning DS, Afdhal NH. Diagnosis and quantitation of fibrosis. Gastroenterology 2008; 134: 1670-81.
11. Fujimoto K, Tonan T, Azuma S, et al. Evaluation of the mean and entropy ofapparent diffusion coefficient values in chronic hepatitis C: correlation with pathologic fibrosis stage and inflammatory activity grade. Radiology 2011; 258: 739-48.
12. Vaziri-Bozorg SM, Ghasemi-Esfe AR, Khalilzadeh O, et al. Diffusion-weighted magnetic resonance imaging for diagnosis of liver fibrosis and inflammation in chronic viral hepatitis: the performance of low or high B values and small or large regions of interest. Can Assoc Radiol J 2012; 63: 304-11.
13. Boulanger Y, Amara M, Lepanto L, et al. Diffusion-weighted MR imaging of the liver of hepatitis C patients. NMR Biomed 2003; 16: 132-6.
14. Annet L, Peeters F, Abarca-Quinones J, Leclercq I, Moulin P, Van Beers BE. Assessment of diffusion-weighted MR imaging in liver fibrosis. J Magn Reson Imaging 2007; 25: 122-8.
15. Lewin M, Poujol-Robert A, Boëlle PY, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology 2007; 46: 658- 65 .
16. Koinuma M, Ohashi I, Hanafusa K, Shibuya H. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. J Magn Reson Imaging 2005;22: 80-85
17. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010; 52: 886-893.
18. Kim JK, Ma DW, Lee KS, Paik YH. Assessment of hepatic fibrosis regression by transient elastography in patients with chronic hepatitis B treated with oral antiviral agents. J Korean Med Sci 2014; 29: 570-5.
19. Hsu FO, Chiou YY, Chen CY, et al. Diffusion-weighted magnetic resonance imaging of the liver in hepatitis B patients with Child-Pugh a cirrhosis. Kaohsiung J Med Sci 2007; 23: 442-6.
20. Pan Z, Meng F, Hu Y, Zhang X, Chen Y. Fat- and iron-corrected ADC to assess liver fibrosis in patients with chronic hepatitis B. Diagn Interv Radiol 2022; 28: 5-11.
21. Fu F, Li X, Chen C, et al. Non-invasive assessment of hepatic fibrosis: comparison of MR elastography to transient elastography and intravoxel incoherent motion diffusion-weighted MRI. Abdom Radiol (NY) 2020; 45: 73-82.

22. Sheng RF, Jin KP, Yang L, et al. Histogram Analysis of Diffusion Kurtosis Magnetic Resonance Imaging for Diagnosis of Hepatic Fibrosis. Korean J Radiol 2018; 19: 916-922.
23. Kromrey ML, Le Bihan D, Ichikawa S, Motosugi U. Diffusion-weighted MRI-based Virtual Elastography for the Assessment of Liver Fibrosis. Radiology 2020; 295: 127-135.
24. Fu F, Li X, Liu Q, et al. Noninvasive DW-MRI metrics for staging hepatic fibrosis and grading inflammatory activity inpatients with chronic hepatitis B. Abdom Radiol 2021; 46: 1864-75.
25. Zheng Y, Xu YS, Liu Z, et al. Whole-liver apparent diffusion coefficient histogram analysis for the diagnosis and staging of liver fibrosis. J Magn Reson Imaging 2020; 51: 1745-54.
26. Jiang H, Chen J, Gao R, Huang Z, Wu M, Song B. Liver fibrosis staging with diffusion-weighted imaging: a systematic review and meta-analysis. Abdom Radiol 2017; 42: 490-501.