Diffusion Weighted MRI for Hepatic Fibrosis: Impact of b-Value

Huseyin Ozkurt 1;*, Firat Keskiner 1; Ozan Karatag 2; Canan Alkim 3; Sukru Mehmet Erturk 1; Muzaffer Basak 1

1Department of Radiology, Sisli Etfal Education and Research Hospital, Istanbul, Turkey
2Department of Gastroenterology, Sisli Etfal Education and Research Hospital, Istanbul, Turkey
3Department of Radiology, Sisli Etfal Education and Research Hospital, Istanbul, Turkey
*Corresponding author: Huseyin Ozkurt, Department of Radiology, Sisli Etfal Education and Research Hospital, Istanbul, Turkey. Tel: +90-5325958625, Fax: +90-2122965407, E-mail: drhozkurt@yahoo.com

Received: June 6, 2012; Revised: April 28, 2013; Accepted: July 17, 2013

Background: Hepatic fibrosis is a typical complication of chronic liver diseases resulting in cirrhosis that remains a major public health problem worldwide. Liver biopsy is currently the gold standard for diagnosing and staging hepatic fibrosis. Percutaneous liver biopsy, however, is an invasive procedure with risks of complications. Therefore, there is need for alternative non-invasive techniques to assess liver fibrosis and chronic liver diseases. In recent years, MRI techniques, including diffusion weighted imaging (DWI), have been developed for in vivo quantification of liver fibrosis and to investigate the influence of b-value.

Patients and Methods: Twenty-four patients (13 males, 11 females), with a mean age of 46 years (36-73 years) diagnosed as chronic hepatitis and histopathologically proven liver fibrosis and 22 other patients (8 males, 14 females) with no clinical or biochemical findings of liver disease, with a mean age of 51.2 years (32-75 years) were included in the study. All patients with chronic hepatitis underwent percutaneous liver biopsy by an experienced hepatologist without sonographic guidance. The Knodell histology activity index (HAI) for grading of hepatic fibrosis and chronic liver diseases. In recent years, MRI techniques, including diffusion weighted imaging (DWI), have been developed for in vivo quantification of liver fibrosis and to investigate the influence of b-value.

Objectives: The purpose of this study is to evaluate the utility of diffusion weighted MRI in the diagnosis and quantification of the degree of hepatic fibrosis and to investigate the influence of b-value.

Methods: We detected decreased apparent diffusion coefficient values in patients with hepatic fibrosis compared to patients without chronic hepatitis and there was a trend toward decrease in hepatic apparent diffusion coefficient values with an increasing degree of fibrosis.

Conclusions: Our findings suggest that hepatic apparent diffusion coefficient measurement with a b-value of 750 sec/mm² or greater is useful in accurate quantification of liver fibrosis and necroinflammation.

Keywords: Liver Cirrhosis; Magnetic Resonance Imaging; Diffusion Magnetic Resonance Imaging

1. Background

Hepatic fibrosis is a typical complication of chronic liver diseases resulting in cirrhosis that remains a major public health problem worldwide (1, 2). Several factors have been described as being involved in the development of cirrhosis. These factors are mainly alcohol ingestion and hepatitis B and C infections that are stated as 80-90% of the cases in the literature. Other causes are hemochromatosis, primary biliary cirrhosis, primary sclerosing cholangititis, Wilson’s disease, autoimmune disease, Budd-Chiari syndrome and nonalcoholic steatohepatitis (3). Liver biopsy is currently the gold standard for diagnosing and staging hepatic fibrosis (1, 2, 4-6). Percutaneous liver biopsy; however, is an invasive procedure with risks of complications such as pain, hemorrhage, bile peritonitis, penetration to abdominal viscera, pneumothorax and death (6, 7). This procedure is also prone to interobserver variability and sampling error (1, 4, 8-11). In the literature, different morbidity and mortality rates have been mentioned for this invasive procedure. Tobkes et al. (7) stated that needle biopsy of the liver has a mortality rate between 0.009% and 0.12%; while in Wong et al.’s study (12), an 0.018% rate was declared. In addition, in a study conducted by Piccinino et al. (13), a morbidity of 3% and a mortality of 0.03% were pointed out for percutaneous liver biopsy (13). In another study, a 24% estimated false negative result was notified for percutaneous liver

Implication for health policy/practice/research/medical education: Diffusion weighted imaging can be used as an adjunct to the routine MRI protocol for accurate quantification of liver fibrosis and necroinflammation. We recommend reading this article to radiologists, infectious specialists and hepatologists.
biopsy due to inter-observer variability and sampling errors (14). Therefore, alternative non-invasive techniques have been developed to assess liver fibrosis and chronic liver diseases. Unfortunately, these approaches including routine biochemical and hematological tests, serum markers of connective tissue, and scoring systems using a combination of clinical and/or laboratory tests (4, 15-20) are not sensitive and specific enough to quantify liver fibrosis (2). Recently, measurement of liver stiffness with ultrasound transient elastography has been validated to detect significant fibrosis in patients with chronic hepatitis C. However, this method cannot be applied to patients with ascites, narrow intercostal spaces and over-weight status (4, 21).

In recent years, magnetic resonance imaging (MRI) techniques, including diffusion weighted imaging (DWI), have been developed for in vivo quantification of liver fibrosis (4, 22). This is an imaging method in which the severity of the disease is quantified by combined effects of capillary perfusion and diffusion using apparent diffusion coefficient (ADC) measurement (22-24). Several reports suggest that measures of DWI show lower ADC values in cirrhotic livers than in normal livers (2, 4, 22, 25, 26). This is due to accumulation of fibrosis leading to reduction in the amount of water proton diffusion in the affected liver tissue (1, 2, 27).

2. Objectives

The aim of our study is to evaluate the potential role of DWI in diagnosing the presence and quantifying the degree of hepatic fibrosis.

3. Patients and Methods

3.1. Patient Selection

The protocol for this study was approved by our ethics committee. Twenty-four patients (13 males, 11 females), with a mean age of 46 years (range: 36-73 years) diagnosed with chronic hepatitis and histopathologically proven liver fibrosis and 22 other patients with no clinical or biochemical findings for liver disease (8 males, 14 females), with a mean age of 51.2 years (range: 32-75 years) were included in the study. Liver disease was diagnosed on the basis of clinical history, liver function test results, and percutaneous liver biopsy that was clinically indicated. The causes of liver disease were chronic hepatitis C virus infection (n=15), chronic hepatitis B virus infection (n=8), and chronic hepatitis B+D virus infection (n=1). None of the patients had a diagnosis of hepatocellular carcinoma. Patients with focal malignant lesions of the liver visible on imaging procedures including ultrasound, computed tomography (CT) or MRI were excluded from the study. The patients without liver disease had neither a previous history of liver disease nor alcohol abuse.

3.2. Histopathologic Assessment

All patients underwent percutaneous liver biopsy by an experienced hepatologist using a 20-gauge needle without sonographic guidance. The biopsy was performed more than 1 month prior to MR imaging to avoid artifacts related to early post biopsy changes. Liver biopsies were performed in segments V and VI in order to correlate with DWI and to avoid sampling errors. Liver biopsy was not performed on patients without liver disease. The liver biopsy findings were retrospectively evaluated by an experienced pathologist. The Knodell histology activity index (HAI) for the grade of necroinflammatory changes and Metavir scoring system for the stage of liver fibrosis were used to record the severity of the disease. HAI system includes three subcategories: periportal necrosis and inflammation, scored from 0 to 10; intralobular necrosis and inflammation, scored from 0 to 4; and portal inflammation, scored from 0 to 4 (28). Fibrosis was staged on a 0-4 scale as follows: F0 – no fibrosis; F1– portal fibrosis without septa; F2–portal fibrosis and few septa; F3–numerous septa without cirrhosis; and F4 – cirrhosis (29, 30).

3.3. Imaging Protocol

All patients were examined with a 1.5 T MRI unit (Signa Excite; GE Medical Systems, Milwaukee, Wisconsin, USA) using the standard body coil. The patients underwent DWI with a routine hepatic MRI protocol. The hepatic protocol included axial T1-weighted spin-echo (160 ms/1.8 ms, repetition time [TR]/echo time [TE]; number of excitations [NEX], 1,0; 10 mm slice thickness; 34×48 cm field of view [FOV]; 256×128 matrix), coronal T1-weighted fast spoiled gradient-echo sequence (160ms/1.8ms, TR/TE; NEX, 1.0; flip angle, 80 o; 8 mm section thickness; 38×48 cm FOV; 256×128 matrix) with spectral fat saturation, axial T1-weighted fast spoiled gradient-echo sequence (160ms/1.8ms, TR/TE; NEX, 1.0; flip angle, 80 o; 10 mm section thickness; 34×48 cm FOV; 256×128 matrix) with spectral fat saturation, axial T1-weighted fast spoiled gradient-echo sequence (160ms/1.8ms, TR/TE; NEX, 2.0; 10 mm section thickness; 34×48 cm FOV; 512×256 matrix), coronal T2-weighted fast spin-echo sequence (6000 ms/93ms, TR/TE; NEX, 2.0; 7 mm section thickness; 38×48 cm FOV; 512×256 matrix). Spin echo echo-planar DWI was performed using the following acquisition parameters: TE=52-70 ms, TR=10000 ms, matrix=64×128, FOV=33×48, bandwidth=62-250kHz. Four different b-values were tested: 250, 500, 750 and 1000 sec/mm 2. A unidirectional (anterior-posterior) diffusion gradient was applied. Fat suppression was used to avoid image artifacts from subcutaneous fat. The patients and healthy volunteers held their breath for five seconds during expiration to avoid respiratory motion. Calculation of
ADC values was performed on a workstation using the GE software functool – ADC. Three region of interests (ROI) were placed over the liver within segments V and VI in order to avoid motion artifacts and artifacts from the great vessels. The ROIs were manually and carefully positioned in the same region between two corresponding DWIs of different b factors and care was taken to ensure that the ROIs did not encompass the main blood vessels (Figure 1). Insufficient measurements were available in the left lobe owing to the effects of cardiac motion. From these 3 ROIs, the software calculated 3 ADC values and the mean value was used for statistical analysis.

3.4. Statistical Analysis

Statistical analyses were performed with SPSS 19.0 program. The nonparametric Mann Whitney U-test was used in order to analyze the differences in skewed continuous variables, while differences in normally distributed continuous variables were compared by unpaired Student’s t-test. Multiple comparisons were assessed by analysis of variance (ANOVA) followed by Bonferroni’s correction and Kruskall-Wallis test followed by the Mann-Whitney U-test. Spearman correlation coefficients were used to test the correlation between fibrosis score (F1, F2, and F3) and b-values (250, 500, 750, 1000). A p-value less than 0.05 was considered significant. Data are presented as mean ± standard deviation.

4. Results

The histopathological characteristics of our 24 patients are summarized in Table 1. No patient had grade 4 inflammation, nor stage 4 fibrosis. All of the patients without liver disease assumed to have stage 0 fibrosis and grade 0 inflammation. There was a decrease in calculated ADC values for the patients diagnosed with hepatic fibrosis compared to patients without liver disease. There was a trend toward decrease in hepatic ADC values with an increasing degree of fibrosis. For each b-value employed in this study (250, 500, 750, and 1000 sec/mm²), the mean hepatic ADC values of patients with hepatic fibrosis were significantly lower than those of patients without hepatic fibrosis (Table 2).

Table 1. Histopathological Characteristics of 24 Patients

| Characteristics | Frequency (Total Number of Patients=24) |
|-----------------|----------------------------------------|
| Cause of liver disease |                                      |
| HCV             | 15 (62.5%)                              |
| HBV             | 8 (33.3%)                               |
| HBV+HDV         | 1 (4.16%)                               |
| Histologic activity index (Knodell) |            |
| 0               | 0                                      |
| 1               | 1 (4.16%)                               |
| 2               | 11 (45.8%)                              |
| 3               | 12 (50.0%)                              |
| 4               | 0                                      |
| Fibrosis score (Metavir) |                   |
| F0              | 0                                      |
| F1              | 10 (41.6%)                              |
| F2              | 9 (37.5%)                               |
| F3              | 5 (20.8%)                               |
| F4              | 0                                      |

Table 2. Comparison of Mean ADC Values of Liver Parenchyma in Patients With and Without Hepatic Fibrosis in Different b-Values

| b-Value | ADC in Patients With Hepatic Fibrosis (mean±SD)(mm²/sec) | ADC in Patients without Hepatic Fibrosis (mean±SD)(mm²/sec) | P-Value |
|---------|----------------------------------------------------------|-----------------------------------------------------------|---------|
| 250     | 0.58±10⁻³±0.14±10⁻³                                       | 1.44±10⁻³±0.19±10⁻³                                       | <0.01   |
| 500     | 0.77±10⁻³±0.16±10⁻³                                       | 1.33±10⁻³±0.16±10⁻³                                       | <0.01   |
| 750     | 0.61±10⁻³±0.14±10⁻³                                       | 1.27±10⁻³±0.12±10⁻³                                       | <0.01   |
| 1000    | 0.83±10⁻³±0.52±10⁻³                                       | 1.19±10⁻³±0.12±10⁻³                                       | <0.01   |

Figure 1. A 38-year-old patient with hepatic fibrosis. Sequence parameters: TR: 5000 ms, TE: 52 ms, b-value: 500 sec/mm². Measurement technique of ADC with 3 ROI is seen.
As we mentioned above, we also evaluated the stage of hepatic fibrosis with Metavir scoring system. There were three subgroups of liver fibrosis stage according to Metavir scoring system (Table 1). We had no patient with stage 4 fibrosis (F4). We also compared the ADC values for all $b$-values between different hepatic fibrosis stages according to Metavir scoring (F1, F2, and F3). First, we found significant statistical difference in multivariate analysis among the whole group ($P=0.025$). Subsequently, we compared each ADC value at each $b$-value between F1, F2, and F3 with appropriate post-hoc tests (Table 3) to find out the difference between fibrosis score groups. In the post-hoc analysis, there were statistically significant differences between F1 and F2 ($68.1\times10^{-3}\pm12.14\times10^{-3}$ vs. $58.44\times10^{-3}\pm13.92\times10^{-3}$, $P=0.045$) and F1 and F3 ($68.1\times10^{-3}\pm12.14\times10^{-3}$ vs. $52.6\times10^{-3}\pm10.26\times10^{-3}$, $P=0.027$) at a $b$-value of 750 (Figure 2), and also in the $b$-value of 1000, there were statistically significant differences between F1 and F2 ($116.2\times10^{-3}\pm57.14\times10^{-3}$ vs. $69.0\times10^{-3}\pm39.06\times10^{-3}$, $P=0.023$) and F1 and F3 ($116.2\times10^{-3}\pm57.14\times10^{-3}$ vs. $43.4\times10^{-3}\pm14.13\times10^{-3}$, $P=0.02$) (Table 3) (Figure 3).

Regarding patients with hepatic fibrosis, the correlation

Table 3. Comparison of Each ADC Value at All $b$-Values Between Fibrosis Stages F1, F2, and F3

| Fibrosis Score | 250  | 500  | 750  | 1000 |
|---------------|------|------|------|------|
| $b$-Value     | F1   | F2   | F3   | F1   | F2   | F3   | F1   | F2   | F3   |
| 250           | 52.8\times10^{-3}\pm10.71\times10^{-3} | 66.66\times10^{-3}\pm14.72\times10^{-3} | 52.8\times10^{-3}\pm14.73\times10^{-3} |
| 500           | 73.2\times10^{-3}\pm10.84\times10^{-3} | 87.55\times10^{-3}\pm15.02\times10^{-3} | 67\times10^{-3}\pm18.49\times10^{-3} |
| 750           | 68.1\times10^{-3}\pm12.14\times10^{-3} | 58.44\times10^{-3}\pm13.92\times10^{-3} | 52.6\times10^{-3}\pm10.26\times10^{-3} |
| 1000          | 116.2\times10^{-3}\pm57.14\times10^{-3} | 69\times10^{-3}\pm39.06\times10^{-3} | 43.4\times10^{-3}\pm14.13\times10^{-3} |

| Post hoc analysis $P$-Values |
|-----------------------------|
| 250 | F1 vs F2; $p=0.1$ |
|     | F1 vs F3; $p=0.9$ |
|     | F2 vs F3; $p=0.2$ |
| 500 | F1 vs F2; $p=0.5$ |
|     | F1 vs F3; $p=0.2$ |
|     | F2 vs F3; $p=0.6$ |
| 750 | F1 vs F2; $p=0.045$ |
|     | F1 vs F3; $p=0.027$ |
|     | F2 vs F3; $p=0.3$ |
| 1000 | F1 vs F2; $p=0.023$ |
|     | F1 vs F3; $p=0.02$ |
|     | F2 vs F3; $p=0.1$ |

Figure 2. Differences of ADC values between F1, F2, and F3 groups at a $b$-value of 750 ($^*P=0.045$ and $^{**}P=0.027$)

Figure 3. Differences of ADC values between F1, F2, and F3 groups at a $b$-value of 1000 ($^*P=0.023$ and $^{**}P=0.02$)
between HAI values and ADC values in a $b$-value of 750 sec/mm$^2$ was significant, negative and moderate ($r=-0.512; P=0.01$) (Figure 4). For other $b$-values, the correlation with the HAI value was not significant. The correlations between the fibrosis score and ADC values in $b$-values of 750 and 1000 sec/mm$^2$ were significant, negative, and moderate ($r=-0.510; P=0.01$ and $r=-0.567; P=0.004$, respectively) (Table 4).

5. Discussion
Clinical examinations and laboratory results are unreliable for differentiating the stages of hepatic fibrosis (22). The diagnosis of fibrosis stage 2 or greater is clinically important because owing to cost, risk of toxicity, and limited efficacy, only patients with fibrosis stage 2 or greater should receive antiviral treatment (31). MRI has become an important modality for assessing chronic liver disease. In a study carried out by Semelka et al. (32), two parenchymal enhancement patterns of chronic hepatitis were described using contrast enhanced dynamic MRI: early patchy enhancement indicating inflammatory changes in the liver and late linear enhancement indicating the presence of fibrosis (32). Cross-sectional imaging findings of advanced chronic hepatitis and cirrhosis are generally capable of detecting advanced diseases on the basis of signs of portal hypertension with good sensitivity and specificity (33). However, these findings have limited value in the detection of fibrosis (4). DWI has become possible in the abdomen with the advent of echoplanar MRI technique because it allows fast imaging and could minimize the effect of gross physiologic motion from respiration and cardiac movement (4, 6, 34). DWI is related to the diffusion of protons within tissues (35). Collagen fiber is the main component of hepatic fibrosis. The protons contained in this tissue are less abundant than those in water and are tightly bound (36). Therefore, diffusion in hepatic fibrosis should be restricted and the ADC values decreased compared to normal liver parenchyma (1). This statement was also confirmed by our results since we have demonstrated that ADC values within fibrotic liver parenchyma were reduced compared to ADC values within the normal parenchyma of patients without liver disease. Several studies have shown that the ADC of cirrhotic liver is lower than that of the normal liver, possibly due to the presence of a larger amount of connective tissue in the liver, narrowed sinusoids, and decreased blood flow (8, 37). There are limited data, however, on the correlation between hepatic ADC and the histologic stage of fibrosis. Muller et al. (38) were the first to observe a reduced ADC in cirrhosis (using $b$-values up to 400 sec/mm$^2$) (38). Amano et al. (39) reported that the difference of ADC values between cirrhotic and normal livers was greater in higher $b$-values (up to 400 sec/mm$^2$) (40). Aube et al. (1) measured significant differences between healthy and cirrhotic livers (at a $b$-value of 200 sec/mm$^2$) (1). DWI sequences using a low $b$-value were mostly sensitive to parenchymal microperfusion (41). A higher $b$-value must be used to increase the sensitivity to diffusion and to lessen the impact of perfusion. It therefore seems logical that improved results may be obtained by using higher $b$-values (250 to 1000 sec/mm$^2$ in our study). However, increasing the $b$-value results in a decreased signal. Therefore, calculated ADC values are decreased proportionally by the increase in $b$-value (42). In this respect, the choice of $b$-value plays a critical role. This value is a function of the amplitude and duration of the diffusion gradient and of the time allowed for the proton to diffuse between the 2 successive gradient pulses. Therefore, its choice is a compromise between adequate diffusion strength and image quality (4, 25, 42, 43).

![Figure 4. Correlation between HAI values and ADC values in a $b$-value of 750 sec/mm$^2$](image-url)

Table 4. Correlation Between ADC Values and HAI Scores or Fibrosis Scores for Different $b$-Values

| $b$-Value | HAI Score (Correlation Coefficient, P-value) | Fibrosis Score (Correlation Coefficient, P-Value) |
|-----------|--------------------------------------------|--------------------------------------------------|
| 250       | 0.03; $P>0.05$                             | 0.16; $P>0.05$                                   |
| 500       | -0.45; $P>0.05$                            | -0.02; $P>0.05$                                 |
| 750       | -0.512; $P=0.01$                           | -0.51; $P=0.01$                                 |
| 1000      | -0.32; $P>0.05$                            | -0.567; $P=0.004$                               |
A study by Boulanger et al. (6) using 5 different \( b \)-values ranging from 50-250 sec/mm\(^2\), reported a lack of a significant difference between the control subjects and HCV patients (6). In another study performed by Koinuma et al. (22), \( b \)-values of 0 and 128 sec/mm\(^2\) were used and a correlation between ADC values and fibrosis scores were detected while no correlation between ADC and inflammation grade was found (22). Both studies involved relatively small \( b \)-values that could not detect the differences between fibrotic and nonfibrotic liver; because the diffusion signal intensity was contaminated by perfusion (22, 42, 43). The study conducted by Hollingsworth et al. (5) suggested that in order to limit the influence of perfusion changes, breath-hold diffusion weighted studies of the liver should be performed at high \( b \)-values (750 and 500 sec/mm\(^2\)) (5).

In our study, we used 4 different \( b \)-values (250, 500, 750 and 1000 sec/mm\(^2\)) in order to obtain a more precise calculation of ADC with less perfusion contamination and less regional ADC variation. The results showed that ADC values decreased as the stage of liver disease progressed from normal function to chronic hepatitis. The relationship between ADC values and the fibrosis score was significant with the use of higher \( b \)-values (750 and 1000 sec/mm\(^2\)). We also found a significant relationship between ADC values and necroinflammation scores with the use of a 750 sec/mm\(^2\) \( b \)-value.

Transient elastography, real-time elastography and MR elastography are other new techniques that can be used in non-invasive evaluation of liver fibrosis. Transient elastography is a rapid and reproducible technique equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator (44, 45). The liver stiffness is automatically calculated from the velocity of propagation of an elastic shear wave through the liver parenchyma that is induced by vibrations transmitted toward the tissue. The stiffness of the liver is recorded in kilopascal (kPa) (45-47). Assessment of different blood markers using transient elastography measurement of tissue elasticity has shown hopeful results in determining the degree of liver fibrosis (48). In a previous study by Lewin et al. (4), out 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, aspartate aminotransferase to platelets ratio index (APRI), Forns index, and hyaluronate results. Consequently, it was stated in this study that in cases where liver fibrosis is evident, DWI is more useful than other non-invasive techniques in detecting the degree of fibrosis. It is also stated that the combination of ADC and transient elastography resulted in the best diagnostic performance for significant fibrosis (F\(\geq\)2) (4). Transient elastography can be an ineffective method in case of obesity, narrow intercostal space and ascites. In a study by Fraquelly et al. (49) an overall 2.4% rate of indeterminate results of transient elastography was noted that was due to high body mass index (BMI $>$ 28 kg/m\(^2\)) in four patients and narrow intercostal space in one patient (49). Real-time elastography is an ultrasound-based method to measure tissue elasticity and it is technically different from transient elastography. With conventional ultrasound probes, echo signals before and under slight compression are compared and analyzed (48, 50). In contrast to transient elastography, this method can also be used effectively in case of unfavorable conditions such as patient obesity and ascites.

MR elastography is a promising new non-invasive MR imaging technique that quantifies the stiffness of the tissues. In this technique, MR images are obtained with a gradient-echo sequence as the waves propagate through the liver. Liver stiffness measured with MR elastography increases as the stage of fibrosis advances (36).

There are several studies about the potential applications of these non-invasive methods; in particular, transient elastography, for evaluation of liver fibrosis. In a study by Kim et al. (51), transient elastography was performed in patients with chronic hepatitis B infection during long-term antiviral treatment. They aimed to assess liver fibrosis regression in these patients (51). Furthermore, there are studies in which liver stiffness measurements are found to be effective in predicting clinical decompensation and portal hypertension-related complications such as esophageal varices in patients with chronic liver disease (52-55). Transient elastography has also been used to assess the degree of liver fibrosis and the risk of hepatocellular carcinoma development in patients with chronic hepatitis (56, 57).

Our study had several limitations. One of which was the inability to use a surface coil for the acquisition of DWI data. The use of body coil significantly decreases the acquired signal and signal-to-noise ratio (SNR) (1, 39). The use of surface coils, by increasing the amount of acquired signal, should provide significant results using higher \( b \)-values (>400 sec/mm\(^2\)) (1). Other limitations to our study include the small number of subjects and intermediate levels of hepatic fibrosis and necroinflammation, limiting the ability to achieve statistically significant results. Future work is needed to assess larger numbers of patients and to correlate DWI findings with findings obtained with newer methods of perfusion MRI (58, 59), MR elastography (60, 61) and serologic markers of fibrosis.

In conclusion, our findings suggest that hepatic ADC measurement with DWI with a \( b \)-value of 750 sec/mm\(^2\) or greater can be used in accurate quantification of liver fibrosis and necroinflammation. DWI can be used as an adjunct to the routine MRI protocol. It may be possible to use DWI findings for follow up of patients with chronic hepatitis.

**Acknowledgments**

We would like to thank Associate Professor Kubilay Ukinc, Department of Endocrinology and Metabolism, Canakkale Onsekiz Mart University Faculty of Medicine,
Canakkale, Turkey for his expertise in statistical analysis.

Authors’ Contribution

Study concept and design: Ozkurt and Keskiner; analysis and interpretation of data: Ozkurt, Keskiner, Alkim and Karatag; drafting of the manuscript: Karatag; critical revision of the manuscript for important intellectual content: Ozkurt, Karatag, Alkim, Basak; statistical analysis: Erturk.

Financial Disclosure
There is no conflict of interest.

Funding/Support
The study was self-funded.

References

1. Aube C, Racineux PX, Lebigot J, Oberti F, Croquet V, Argaud C, et al. Diagnostic et quantification de la fibrose hépatique par IRM de diffusion : résultats préliminaires. J Radiol. 2004;85(1):301-306.
2. Talwalkar JA, Yin M, Filidor JL, Sanderson SO, Kamath PS, Eham RN. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. Hepatology. 2008;47(3):332-42.
3. Ito K, Mitchell DG. Imaging diagnosis of cirrhosis and chronic hepatitis. Interimwrology. 2004;47(5):334-43.
4. Lewin M, Poujoil-Robert A, Boelle PY, Wendum D, Lasiner E, Viallon M, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology. 2007;46(1):63-70.
5. Hollingsworth KG, Lomas DJ. Influence of perfusion on hepatic MR diffusion measurement. NMR Biomed. 2006;19(2):229-35.
6. Boulanger Y, Amara M, Lepanto L, Beaudoin G, Nguyen BN, Allaire Y, et al. Measurement of liver hepatocellular carcinoma detection: application of a numerical scoring system. NMR Biomed. 2000;13(5):172-7.
7. Taouli B, Vilgrain V, Dumont E, Daire JL, Fan B, Menu Y, et al. Diffusion-weighted imaging of liver: technical challenges and prospects for the future. Magn Reson Med Sci. 2005;4(1):375-86.
8. Koinuma M, Ohashi I, Hanafusa K, Shibusawa H. Apparent diffusion coefficient measurement with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. J Magn Reson Imaging. 2002;15(6):1615-30.
9. Adams LA, Bulsara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem. 2005;51(10):1867-73.
10. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos N, et al. Complications following percutaneous liver biopsy: A multicentre retrospective study on 68 276 biopsies. J Hepatol. 2003;39(5):726-31.
11. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in patients with chronic hepatitis C. J Hepatol. 1997;26(1):26-40.
12. Boulanger Y, Amara M, Lepanto L, Beaudoin G, Nguyen BN, Allaire Y, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 2005;41(4):1031-8.
13. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1994;20(2):107-15.
14. Kim AI, Saab S. Treatment of hepatitis C. Am J Med. 2005;118(8):808-15.
15. Semelka RC, Chung JH, Hussain SM, Marcos HB, Woosley JT. Chronic hepatitis: correlation of early patchy and late linear enhancement patterns on gadolinium-enhanced MR images with histopathological findings. Radiographics. 2002;22(4):889-904.
16. Ikeda T, Kato N, Kishida K, Nakazawa Y, Ohnishi Y, Kodama T. Accuracy of liver stiffness measurement by transient elastography for detecting liver fibrosis in patients with chronic hepatitis C infection: a prospective study. J Hepatol. 2006;45(2):255-61.
17. Patel K, Gordon SC, Jacobson I, Hezode C, Oh E, Smith KM, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. J Hepatol. 2004;41(4):435-42.
18. Guechot J, Lautad A, Loria A, Serfaty I, Poupon R, Giboudeau J. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. Clin Chem. 1996;42(4):558-63.
19. Forns X, Ampurdanes S, Llovet JM, Aponte J, Quinto L, Martinez-Bauer E, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. Hepatology. 2002;36(4 Pt 1):986-92.
20. Adams LA, Bulsara M, Rossi E, DeBoer B, Speers D, George J, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem. 2005;51(10):1867-73.
21. Ziol M, Mandala-Lucia A, Rettanaei C, Christidis C, Mal F, Kazemi F, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology. 2005;41(4):48-54.
22. Aube C, Racineux PX, Lebigot J, Oberti F, Croquet V, Argaud C, et al. Diagnostic et quantification de la fibrose hépatique par IRM de diffusion : résultats préliminaires. J Radiol. 2004;85(1):301-306.
23. Talwalkar JA, Yin M, Filidor JL, Sanderson SO, Kamath PS, Eham RN. Magnetic resonance imaging of hepatic fibrosis: emerging clinical applications. Hepatology. 2008;47(3):332-42.
24. Ito K, Mitchell DG. Imaging diagnosis of cirrhosis and chronic hepatitis. Interimwrology. 2004;47(5):334-43.
25. Lewin M, Poujoil-Robert A, Boelle PY, Wendum D, Lasiner E, Viallon M, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology. 2007;46(1):63-70.
26. Hollingsworth KG, Lomas DJ. Influence of perfusion on hepatic MR diffusion measurement. NMR Biomed. 2006;19(2):229-35.
27. Boulanger Y, Amara M, Lepanto L, Beaudoin G, Nguyen BN, Allaire Y, et al. Diffusion-weighted MR imaging of the liver of hepatitis C patients. NMR Biomed. 2003;16(3):322-6.
28. Tobler AI, Nord HW. Liver biopsy: Review of Methodology and Complications. Dig Dis. 1995;13(5):267-274.
29. Taouli B, Tolia AJ, Losada M, Babb JS, Chan ES, Bannan MA, et al. Diffusion-weighted MRI for quantification of liver fibrosis: preliminary experience. AJR Am J Roentgenol. 1997;169(4):979-86.
30. Maharaj B, Leary WP, Naran AD, Maharaj RJ, Coopman RM, Pirie D, et al. Sampling Variability and its Influence on the Diagnostic Yield of Percutaneous Needle Biopsy of the I-liver. The Lancet. 1986;327(8480):523-525.
31. Regev A, Berho M, Jeffers IJ, Milikowski C, Molina EG, Pyrsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002;97(9):2644-8.
32. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003;38(3):985-90.
33. Wong JB, Bennett WG, Koff RS, Faulk RS. Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs. JAMA. 1998;280(24):2088-93.
34. Piccinni PM, Sagnelli E, Pasquale G, Giusti G, Bottoncini A, Bernardi M, et al. Complications following percutaneous liver biopsy: A multicentre retrospective study on 68 276 biopsies. J Hepatol. 1986;22(3):155-171.
35. Juergen Nord H. Biopsy diagnosis of cirrhosis: blind percutaneous versus guided direct vision techniques—a review. Gastrointest Endosc. 1982;28(2):102-104.
36. Ikeda T, Kato N, Kishida K, Nakazawa Y, Ohnishi Y, Kodama T. Accuracy of liver stiffness measurement by transient elastography for detecting liver fibrosis in patients with chronic hepatitis C virus infection: a prospective study. J Hepatol. 2001;37(5):962-969,1075.
37. Wai CT, Greenson JK, Fontana RJ, Kalbfeisch JD, Marrero JA, Conjevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):558-56.
fibrosis. *J Magn Reson Imaging*. 2007;25(1):322-8.
38. Muller MF, Prasad P, Siebert W, Nissenbaum MA, Raptopoulos V, Edelman RR. Abdominal diffusion mapping with use of a whole-body echo-planar system. *Radiology*. 1994;190(2):475-8.
39. Amano Y, Kumaizaki T, Ishihara M. Single-shot diffusion-weighted echo-planar imaging of normal and cirrhotic livers using a phased-array multicoil. *Acta Radiol*. 1998;39(4):440-2.
40. Oberti F, Valsesia E, Pilette C, Rousselet MC, Bedossa P, Aube C, et al. Noninvasive diagnosis of hepatic fibrosis or cirrhosis. *Gastroenterology*. 1997;113(5):3669-16.
41. Ichikawa T, Haradome H, Hachiy J, Nitatori T, Araki T. Diffusion-weighted MR imaging with single-shot echo-planar imaging in the upper abdomen: preliminary clinical experience in 61 patients. *Abdom Imaging*. 1999;24(5):456-61.
42. Kim T, Murakami T, Takahashi S, Hori M, Tsuda K, Nakamura H. Diffusion-weighted single-shot echo-planar MR imaging for liver disease. *AJR Am J Roentgenol*. 1999;173(2):393-8.
43. Yamada I, Aung W, Himeno Y, Nakagawa T, Shibuya H. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. *Radiology*. 1999;210(1):567-23.
44. Foucher J, Chanteloup E, Vergnol J, Castéra I, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut*. 2006;55(3):401-8.
45. Laharie D, Seneschal J, Schaeverbeke T, Doutre MS, Longy-Boursier M, Pellegrin JL, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: a case-control study. *J Hepatol*. 2003;38(6):393-40.
46. Yoshioka K, Kawaue N, Hashimoto S. Transient elastography: Applications and limitations. *Hepatol Res*. 2006;38(3):106-13.
47. Guo YZ, Liu B, Jiang W, Yu HT, Bai XF. The diagnostic value of ultrasound elastography in patients with hepatitis B virus infection: a prospective study. *J Int Med Res*. 2010;38(6):2477-25.
48. Friedrich-Rust M, Onf MF, Herrmann F, Dries V, Samaras P, Zeezem S, et al. Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. *AJR Am J Roentgenol*. 2007;188(3):758-64.
49. Fraquelli M, Rigamonti C, Cassasza G, Conte D, Donato MF, Ronchi G, et al. Reproducibility of transient elastography in the evaluation of liver fibrosis in patients with chronic liver disease. *Gut*. 2007;56(7):968-73.
50. Wang J, Guo L, Shi X, Pan W, Bai Y, Ah L. Real-time elastography with a novel quantitative technology for assessment of liver fibrosis in chronic hepatitis B. *Eur J Radiol*. 2012;81(1):31-6.
51. Kim SU, Park JY, Kim do Y, Ahn SH, Choi EH, Seok JY, et al. Non-invasive assessment of changes in liver fibrosis via liver stiffness measurement in patients with chronic hepatitis B: impact of antiviral treatment on fibrosis regression. *Hepatol Int*. 2010;4(4):567-80.
52. Kazemi F, Kettaneh A, N’Kontchou G, Pinto E, Game-Carrie N, Trimch JC, et al. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. *J Hepatol*. 2006;45(2):230-5.
53. Vizzutti F, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology*. 2007;45(5):1290-7.
54. Bureau C, Metvier S, Peron JM, Selves J, Robic MA, Gourraud PA, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. *Aliment Pharmacol Ther*. 2008;27(12):3261-8.
55. Castera L, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *Hepatol*. 2009;50(1):59-68.
56. Jung KS, Kim SU, Ahn SH, Park YN, Kim do Y, Park JY, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). *Hepatology*. 2011;53(3):885-94.
57. Kuo YH, Lu SN, Hung CH, Kee KM, Chen CH, Hu TH, et al. Liver stiffness measurement in the risk assessment of hepatocellular carcinoma for patients with chronic hepatitis. *Hepatol Int*. 2010;4(4):700-6.
58. Annet L, Materne R, Danse E, Jamart J, Horsmans Y, Van Beers BE. Hepatic flow parameters measured with MR imaging and Doppler US: correlations with degree of cirrhosis and portal hypertension. *Radiology*. 2003;229(2):409-14.
59. Huwart I, Peeters F, Smits K, Annet L, Salameh N, ter Beek IC, et al. Liver fibrosis: non-invasive assessment with MR elastography. *NMR Biomed*. 2006;19(2):173-9.
60. Rouviere O, Yin M, Desner MA, Rossman PJ, Burgess LJ, Fidler JR, et al. MR elastography of the liver: preliminary results. *Radiology*. 2006;240(2):440-8.
61. Hagiwara M, Rusinek H, Lee VS, Losada M, Bannan MA, Krimsky GA, et al. Advanced liver fibrosis: diagnosis with 3D whole-liver perfusion MR imaging-initial experience. *Radiology*. 2008;246(3):926-34.