Value of 3 Tesla diffusion-weighted magnetic resonance imaging for assessing liver fibrosis

Lavrentios Papalavrentios\(^a\), Emmanouil Sinakos\(^a\), Danai Chourmouzi\(^b\), Prodromos Hytiroglou\(^c\), Konstantinos Drevelegas\(^b\), Manos Constantinides\(^b\), Antonios Drevelegas\(^b\), Jayant Talwalkar\(^d\), Evangelos Akriviadis\(^a\)

University of Thessaloniki, Greece; Interbalkan Medical Center, Thessaloniki, Greece; Mayo Clinic Rochester, Rochester, MN, USA

Abstract

Background Limited data are available regarding the role of magnetic resonance imaging (MRI), particularly the new generation 3 Tesla technology, and especially diffusion-weighted imaging (DWI) in predicting liver fibrosis. The aim of our pilot study was to assess the clinical performance of the apparent diffusion coefficient (ADC) of liver parenchyma for the assessment of liver fibrosis in patients with non-alcoholic fatty liver disease (NAFLD).

Methods 18 patients with biopsy-proven NAFLD underwent DWI with 3 Tesla MRI. DWI was performed with single-shot echo-planar technique at b values of 0-500 and 0-1000 s/mm\(^2\). ADC was measured in four locations in the liver and the mean ADC value was used for analysis. Staging of fibrosis was performed according to the METAVIR system.

Results The median age of patients was 52 years (range 23-73). The distribution of patients in different fibrosis stages was: 0 (n=1), 1 (n=7), 2 (n=1), 3 (n=5), 4 (n=4). Fibrosis stage was poorly associated with ADC at b value of 0-500 s/mm\(^2\) (r= -0.30, P=0.27). However it was significantly associated with ADC at b value of 0-1000 s/mm\(^2\) (r= -0.57, P=0.01). For this b value (0-1000 s/mm\(^2\)) the area under receiver-operating characteristic curve was 0.93 for fibrosis stage ≥3 and the optimal ADC cut-off value was 1.16 ×10\(^{-3}\) mm\(^2\)/s.

Conclusion 3 Tesla DWI can possibly predict the presence of advanced fibrosis in patients with NAFLD.

Keywords Liver fibrosis, non-alcoholic fatty liver, diffusion-weighted imaging, 3 Tesla

Ann Gastroenterol 2015; 28 (1): 118-123

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most prevalent cause of liver disease in Western countries. The development of non-alcoholic steatohepatitis (NASH) and fibrosis identifies a group with increased risk of liver-related deaths due to cirrhosis or hepatocellular carcinoma. The prevalence of NAFLD is estimated between 20% and 30% in Western countries [1,2], rising to 90% in the morbidly obese patients [3]. NASH, the more advanced and clinically important form of NAFLD, is less common, with an estimated prevalence of 2-3% in the general population [4], and 37% in the morbidly obese [3].

Liver biopsy is currently the gold standard to guide therapeutic decisions and assess prognosis in patients with NAFLD. The development of non-invasive methods for liver fibrosis evaluation aims to reduce biopsy-related risk and cost and to facilitate improved monitoring of disease progression. Serological assays, such as Fibrotest, and radiological methods like transient elastography (Fibroscan, Echosens, France) are used increasingly to evaluate liver fibrosis in NAFLD and other chronic liver diseases. Magnetic resonance imaging (MRI) is being evaluated as a non-invasive method of liver fibrosis assessment as well. Recently, MR elastography demonstrated excellent diagnostic accuracy with sensitivity and specificity of 98% and 99% respectively for detecting all grades of fibrosis [5].
Another MRI technique, diffusion-weighted imaging (DWI), has been lately used for liver fibrosis assessment. Diffusion is a physical property, which describes the microscopic random movement of (water) molecules driven by their internal thermal energy. Diffusion is quantitatively reflected in a diffusion coefficient, the *apparent diffusion coefficient* (ADC, expressed in mm$^2$/s). Conflicting results regarding the reliability of DWI and apparent diffusion coefficient (ADC) values in liver fibrosis staging for patients with chronic liver disease are reported [6,7], while several studies have shown a decrease in hepatic ADC in liver cirrhosis [8-10].

The aim of our study was to assess the clinical performance of DWI performed with 3 Tesla MRI scanners for the assessment of liver fibrosis in patients with NAFLD.

**Patients and methods**

**Patients**

We included only patients with biopsy-proven NAFLD in this study. Patients with positive hepatitis B surface antigen, anti-hepatitis C virus antibody or histological evidence of concomitant liver disease were excluded from the study. Patients with alcohol consumption of more than 40 g/day were also excluded. All patients underwent percutaneous liver biopsy (LB) and then DWI within a 3-month interval. Anthropometric tests included body weight, body height, and waist circumference measurements. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. On the day of liver biopsy, a fasting venous blood sample was taken for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, albumin, glucose, total cholesterol, and triglycerides.

**DWI**

DWI was performed on a 3 Tesla MRI scanner (Sierra HDxt, General Electric, Milwaukee) with the aid of 8 channel Torso phased-array coil. Diffusion was in all cases acquired with respiratory gating with a Single Shot Echo Planar Imaging (DW-EPI) pulse sequence. Parallel imaging with Array Spatial Sensitivity Encoding Technique (ASSET) factor of 2 was used to improve image quality. DWI was performed in the axial plane with tri-directional diffusion gradients using three b values, namely, 0, 500, and 1000 s/mm$^2$. The repetition time (TR) was on the average 10,288 ms (between 8,571 and 13,330), echo time (TE) between 63.7 – 67.9 ms, slice thickness 6 mm, gap between slices 1 mm, matrix 128 × 128, field of view 400 mm, number of excitations 4. The total acquisition time was on the average 4-5 min. The ADC maps were calculated by commercial workstation software (GE Healthcare) over four random locations within the liver using 1-2 cm$^2$ regions of interest away from the intrahepatic vasculature. Mean ADC values were used for analysis (Fig. 1).

**Liver biopsy**

LB procedures were performed by experienced physicians using the intercostal approach with 1.6 and 1.8 mm diameter Menghini needles. All biopsies had at least 1.5 cm length and were evaluated by experienced liver pathologists using the METAVIR scoring system for staging fibrosis from 0 to 4: stage 0=absence of fibrosis; stage 1=perisinusoidal or portal; stage 2=perisinusoidal and portal/periportal; stage=3 septal or bridging fibrosis; and stage 4=cirrhosis. Grade of liver steatosis was defined according to Kleiner *et al* [11].

**Statistical analysis**

Continuous variables were presented as means ± standard deviation or median (range) and frequency data were presented as number and percentage. The correlations of ADC with different variables were explored using the Spearman’s $\rho$ correlation. The performance of ADC was assessed using the receiver operator characteristic (ROC) curve. Based on the ROC curve, a cutoff value was designated for ADC to maximize the sensitivity and specificity of the assay.

**Results**

Table 1 summarizes the baseline patients’ characteristics. 18 patients were included in our study. The median age of our patients was 52 years (range 23-73). The mean BMI was 28.1 kg/m$^2$ (range 20.3-38.2). 78% percent of subjects were male. The median values for AST, ALT, glucose, cholesterol, triglyceride, albumin, total bilirubin, and alkaline phosphatase levels were 37.5 IU/L (18-132); 58 IU/L (19-132); 98 mg/dL (86-176); 217 mg/dL (169-275); 150 mg/dL (77-305); 4.5 g/dL (4.1-4.9); 0.7 mg/dL (0.1-1.4); 108 IU/L (57-330), respectively. The distribution of patients in different fibrosis stages was: 0 (n=1), 1 (n=7), 2 (n=1), 3 (n=5), 4 (n=4). Degree of steatosis was: 0 (n=0), 1 (n=7), 2(n=3), 3(n=8).
ADC correlation with clinical variables

DWI examination was technically successful in all patients. Data processing was possible in all subjects. ADC at b value of 0-1000 s/mm² had a significant inverse correlation with age (r=-0.66, P=0.002). It was also correlated with anthropometric characters, like BMI and waist circumference (r=-0.47, P=0.04 and r=-0.46, P=0.05, respectively). Total cholesterol and AST levels were the only laboratory values that showed a relationship with ADC (r=-0.53, P=0.05 and r=-0.58, P=0.01, respectively). All these relationships were not found significant for ADC at b value of 0-500 s/mm².

ADC correlation with histological parameters

Steatosis was not associated with ADC, neither for b value of 0-500 s/mm² (P=0.64), or for b value of 0-1000 s/mm² (P=0.09). Fibrosis stage was poorly associated with ADC at b value of 0-500 s/mm² (r=-0.30, P=0.27) yet it was significantly associated with ADC at b value of 0-1000 s/mm² (r=-0.57, P=0.01) for this b value (0-1000 s/mm²) the area under ROC curve was 0.93 for fibrosis stage ≥3 and the optimal ADC cut-off value was 1.16 × 10⁻³ mm²/s by maximizing the sum of sensitivity and specificity (positive predictive value: 100%, negative predictive value: 90%) (Fig. 2, 3). Namely, no patient with fibrosis stage <3 had ADC value lower than 1.16 × 10⁻³ mm²/s, whereas only 1 patient with fibrosis stage ≥3 had ADC value greater than 1.16 × 10⁻³ mm²/s. Significant decrease in ADC values was seen in patients with fibrosis stage ≥3 versus fibrosis stage ≤2, especially for b value of 0-1000 s/mm² (Table 2).

The ability to discriminate fibrosis stage ≥2 at b value of 0-1000 s/mm² was also very good (area under ROC curve 0.88). As the sample of patients was very similar (only one patient had fibrosis stage 2) between the groups with fibrosis stage ≥3 and ≥2, the optimal ADC cut-off value for this group of patients was the same (1.16 × 10⁻³ mm²/s), but with different predictive values (positive predictive value: 100%, negative predictive value: 80%). However, the ability to diagnose cirrhosis (fibrosis stage 4) was poor (area under ROC curve 0.64, positive predictive value: 43%) and only exclusion of this condition could be safely predicted (negative predictive value: 91%).

Discussion

The diagnosis and treatment of patients with NAFLD depends significantly on liver fibrosis staging. Liver biopsy is still considered the “gold standard” for the assessment of liver fibrosis and is currently recommended by professional society practice guidelines. Although generally safe, this procedure is invasive and has a minor possibility of serious adverse events (hemorrhage, death) [12]. In addition, the accuracy of liver biopsy varies significantly depending on inter-observer variability and sampling error. This results in up to 30% false-negative results and underestimation of cirrhosis, especially in small (<1.5cm) or fragmented specimens [13-16].

During the last decade a number of non invasive methods for liver fibrosis assessment have been introduced. MRI methods like MR elastography, spectroscopy and DWI are being evaluated as non invasive methods of liver fibrosis assessment. Advantages of MRI methods include the ability...
Diffusion-weighted MRI in liver fibrosis

Table 2 Comparison of liver apparent diffusion coefficient (ADC) (value×10⁻³ mm²/s) for fibrosis stage ≤2 and ≥3 (n=18)

| Fibrosis stage | b value 0-500 | b value 0-1000 |
|---------------|--------------|---------------|
| ≤2            | 1.61±0.16    | 1.30±0.08     |
| ≥3            | 1.39±0.18    | 1.06±0.14     |
| P             | 0.05         | 0.001         |

N.B. Liver ADC decrease is statistically significant in patients with advanced fibrosis at b values of 1000 s/mm².
of patients with NAFLD and to correlate 3 Tesla DWI findings with liver fibrosis. These new technology scanners may provide a useful tool for the treatment and follow up of this subset of patients.

References

1. Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. Hepatology 2004;40:1387-1395.
2. Bedogni G, Miglioli L, Masotti F, et al. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. Hepatology 2005;42:44-52.
3. Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histology in obese patients undergoing bariatric surgery. J Hepatol 2006;45:600-606.
4. Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. J Hepatol 2003;37:1202-1219.
5. Yin M, Talwalkar JA, Glaser KJ, et al. Assessment of hepatic fibrosis with magnetic resonance elastography. Clin Gastroenterol Hepatol 2007;5:1207-1213.
6. Taouli B, Ehmam RL, Reeder SB. Advanced MRI Methods for Assessment of Chronic Liver Disease. AJR 2009;193:14-27.
7. Taouli B, Tolis A, Losada M, et al. Diffusion-Weighted MRI for Quantification of Liver Fibrosis: Preliminary Experience. AJR 2007;189:799-806.
8. Namimoto T, Yamashita Y, Sumi S, et al. Focal liver masses: characterization with diffusion-weighted echo-planar MR imaging. Radiology 1997;204:739-744.
9. Ichikawa T, Haradome H, Hachiya J, et al. Diffusion-weighted MR imaging with a single-shot echoplanar sequence: detection and characterization of focal hepatic lesions. AJR 1998;170:397-402.
10. Amano Y, Kumazaki T, Ishihara M. Single-shot diffusion-weighted echo-planar imaging of normal and cirrhotic livers using a phased-array multicoil. Acta Radiol 1998;39:440-442.
11. Kleiner DE, Brunt EM, Van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41:1313-1321.
12. Bravoo AA, Sheth S, Chopra S. Liver biopsy. N Engl J Med 2001;344:495-500.
13. Castéra L, Négre I, Samii K, et al. Pain experienced during percutaneous liver biopsy. Hepatology 1999;30:1529-1530.
14. Colloredo G, Guido M, Sonzogni A, et al. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: the smaller the sample, the milder the disease. J Hepatol 2003;39:239-244.
15. Regav A, Berho M, Jeffers LJ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
16. Siddique I, El-Naga HA, Madda JP, et al. Sampling variability on percutaneous liver biopsy in patients with chronic hepatitis C virus infection. Scand J Gastroenterol 2003;38:427-432.
17. Kele PG, van der Jagt EF. Diffusion weighted imaging in the liver. World J Gastroenterol 2010;16:1567-1576.
18. Charles-Edwards EM, deSouza NM. Diffusion-weighted magnetic resonance imaging and its application to cancer. Cancer Imaging 2006;6:135-143.
19. Thoeny HC, De Keyzer F. Extracranial applications of diffusion-weighted magnetic resonance imaging. Eur Radiol 2007;17:1385-1393.
20. Kwee TC, Takahara T, Ochiai R, et al. Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS): features and potential applications in oncology. Eur Radiol 2008;18:1937-1952.
21. Sandrasegaran K, Akisik FM, Lin C, et al. Value of Diffusion-Weighted MRI for Assessing Liver Fibrosis and Cirrhosis. AJR 2009;193:1556-1560.
22. Taouli B, Martin AI, Qayyum A, et al. Parallel imaging and diffusion tensor imaging for diffusion-weighted MRI of the liver: preliminary experience in healthy volunteers. AJR 2004;183:677-680.
23. Chang K, Kamei I, Macura K, Belmer D. 3.0-T MR Imaging of the Abdomen: Comparison with 1.5 T. Radiographics 2008;28:1983-1998.
24. Erturk SM, Alberich-Bayarri A, Herrmann KA, Martin-Bonnati L, Ros PR. Use of 3.0-T MR imaging for evaluation of the abdomen. Radiographics 2009;29:1547-1563.
25. Tosun M, Inan N, Sarisoy HT, et al. Diagnostic performance of conventional diffusion weighted imaging and diffusion tensor imaging for the liver fibrosis and inflammation. Eur J Radiol 2013;82:203-207.
26. Yoon JH, Lee JM, Baek JH, et al. Evaluation of hepatic fibrosis using intravoxel incoherent motion in diffusion-weighted liver MRI. J Comput Assist Tomogr 2014;38:110-116.
27. Koimura M, Ohashi I, Hanafusa K, et al. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. J Magn Reson Imaging 2005;22:80-85.
28. Lewin M, Poujol-Robert A, Boelle PY, et al. Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology 2007;46:658-665.
29. Bakan AA, Inci E, Bakan S, Gokturk S, Cimilli T. Utility of diffusion-weighted imaging in the evaluation of liver fibrosis. Eur Radiol 2012;22:682-687.
30. Bonekamp S, Torbensson MS, Kamel IR. Diffusion-weighted magnetic resonance imaging for the staging of liver fibrosis. J Clin Gastroenterol 2011;45:885-892.
31. Woodhams, Ramadan S, Stanwell P, et al. Diffusion-weighted
32. Boulanger Y, Amara M, Lepanto L, et al. Diffusion weighted MR imaging of the liver of hepatitis C patients. NMR Biomed 2003;16:132-136.

33. Yamada I, Aung W, Himeno Y, et al. Diffusion coefficients in abdominal organs and hepatic lesions: evaluation with intravoxel incoherent motion echo-planar MR imaging. Radiology 1999;210:617-623.

34. Ozkurt H, Keskiner F, Karatag O, Alkim C, Erturk SM, Basak M. Diffusion weighted MRI for hepatic fibrosis: impact of b-value.

35. Girometti R, Furlan A, Esposito G, et al. Relevance of b-values in evaluating liver fibrosis: a study in healthy and cirrhotic subjects using two single-shot spin-echo echo-planar diffusion-weighted sequences. J Magn Reson Imaging 2008;28:411-419.

36. Wang QB, Zhu H, Liu HL, et al. Performance of magnetic resonance elastography and diffusion-weighted imaging for the staging of hepatic fibrosis: A meta-analysis. Hepatology 2012;56:239-47.

37. Papalavrentios L, Sinakos E, Chourmouzi D, et al. 3 Tesla diffusion-weighted MRI for assessing liver fibrosis in nonalcoholic fatty liver disease. Hepatology 2013;58:449-450.