ORIGINAL ARTICLE

Diffusion-weighted MRI and fibroscan vs. histopathology for assessment of liver fibrosis in chronic HCV patients: (Pilot study)

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Abstract *Introduction:* HCV infection is responsible for liver fibrosis. Fibroscan and diffusion MRI have been proposed for non-invasive diagnosis and staging of hepatic fibrosis.
Aim of the work: To assess the accuracy of diffusion MRI and/or fibroscan in the diagnosis of liver fibrosis as compared to histopathology. Patients and methods pre-treatment laboratory work up, fibroscan, diffusion MRI of the liver and liver biopsy were done for 52 chronic HCV patients for assessment of liver fibrosis.
Results: There was a significant difference between ADC values of F0 vs. F1, F3 and F4 ($P = 0.008$, 0.033 and 0.015) respectively, however no significant differences were seen in the ADC values between the other different fibrosis stages. As regard the liver stiffness values, there was a significant difference between F1 and F3 ($P = 0.001$), F1 and F4 ($P = 0.024$) and between F2 and F3 ($P = 0.014$). There was no significant difference in the ADC values between (F0, F1, F2) on one hand and (F3, F4) on the other hand ($P = 0.387$), while there was a highly significant difference in the liver stiffness values between both groups ($p < 0.001$).
Conclusions: Diffusion MRI can distinguish non-fibrotic liver (F0) from advanced fibrosis (F3 and F4) but cannot be used to distinguish between the intermediate stages of fibrosis-fibroscan can differentiate between (F0, F1, F2) and (F3, F4).
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1. Introduction

Chronic hepatitis C virus (HCV) infection is responsible for liver fibrosis and may lead to potential long-term complications such as liver cirrhosis and hepatocellular carcinoma (1).

Liver biopsy (LB) has traditionally been considered the gold standard for pretreatment evaluation of liver fibrosis in patients with chronic hepatitis C (CHC). However, LB is an invasive procedure with several shortcomings (intra- and interobserver variability of histo-pathological interpretation, sampling errors, high cost) and the risk of rare but potentially life-threatening complications. In addition, LB is poorly accepted by patients and it is not suitable for repeated evaluation. Furthermore, the prevalence of CHC makes LB unrealistic to be performed in all patients with this disease who are candidates for antiviral therapy (2).

These limitations have stimulated the search for new non-invasive approaches (3). Conventional cross-sectional imaging techniques have limited capability to demonstrate liver fibrosis. Ultrasound and CT-based modalities can demonstrate the morphologic alterations of cirrhosis, but they are limited in evaluating patients with earlier stages of liver disease (4,5).

In response to the rising prevalence of chronic liver diseases, a number of imaging based methods including ultrasonography-based transient elastography (fibroscan), computed tomography-based texture analysis and diverse magnetic resonance (MR) imaging-based techniques have been proposed for non-invasive diagnosis and grading of hepatic fibrosis across its entire spectrum of severity. MR imaging-based techniques in current practice and in development for noninvasive assessment of liver fibrosis include conventional contrast material-enhanced MR imaging, double contrast-enhanced MR imaging, MR elastography, diffusion weighted imaging and MR perfusion imaging (4).

There are several publications indicating the efficacy of quantitative apparent diffusion coefficient (ADC) measurement with diffusion weighted magnetic resonance imaging (DW-MRI) in proving liver fibrosis. Diffusion weighted imaging is an advanced application of MRI used in evaluating the microscopic structure of tissues. This imaging method relies on quantification of the diffusion of water molecules inside tissues. Combined with other methods, this imaging modality might be used in evaluating parenchymal tissue that has no proven abnormalities with routine imaging modalities (6).

Liver fibrosis results in extracellular accumulation of collagen, glycosaminoglycans and proteoglycans that may restrict the molecular diffusion of water, thus suggesting that diffusion-weighted imaging (DWI) may be useful for assessing fibrosis (6).

The aim of the study was to assess the accuracy of diffusion-weighted MRI and fibroscan in the diagnosis of liver fibrosis as compared to histopathology of liver.

2. Patients and methods

2.1. Patients

This pilot study included 52 chronic HCV patients as diagnosed by seropositivity for HCV antibodies and HCV RNA by PCR. They were referred for assessment prior to antiviral therapy.

Patients included were naïve to antiviral therapy, their ages ranged from 18 to 60 years. Patients with other liver diseases, decompensated liver cirrhosis, hepatocellular carcinoma, liver biopsy contraindication, those who were not fit for combined interferon and ribavirin treatment due to persistent hematological abnormalities and those with BMI > 35 were excluded.

Patients were subjected to thorough history taking, clinical examination, pre-treatment laboratory work, abdominal ultrasound, fibroscan, MR diffusion and liver biopsy. The study protocol was approved by the institutional review board and written informed consent was given by each patient.

2.2. Liver stiffness measurement using fibroscan

Liver stiffness was measured using the ultrasound TE fibroscan device (Echosens, Paris, France), which consists of a 5-MHz ultrasound transducer probe mounted on the axis of a vibrator. TE measures liver stiffness in a volume that approximates a cylinder 1 cm wide and 4 cm long, between 25 and 65 mm below the skin surface.

The patient was lying in the dorsal decubitus with the right arm in maximal abduction. The tip of the transducer was covered with a drop of gel and measurements were taken in the right lobe of the liver by placing the tip of the transducer perpendicularly in the intercostal space.

The median value of ten successful acquisitions expressed in kilopascal (kpa) and was kept as representative of liver stiffness measurement.

– The clinical interpretation of TE depends on two important parameters for results to be considered reliable:

(1) The interquartile range, which reflects the variability of the validated measures, should not exceed 30% of the median value.
(2) The success rate (the ratio of the number of successful measurements to the total number of acquisitions) should be at least 60%.

Liver stiffness measurements can be difficult in obese patients or with narrow intercostal space and impossible in patients with ascites (7)

2.3. Ultrasound guided liver biopsy

It was performed after fibroscan examination, using a semi-automatic true-cut needle (16 G). Liver biopsy was fixed in formalin and embedded in paraffin and all biopsy specimens were analyzed by an experienced pathologist blinded to the result of fibroscan. All biopsy specimens were at least 15 mm lengths and contain 6 portal tracts. Liver fibrosis staging was evaluated according to the METAVIR scoring system (8).

2.4. Diffusion-weighted MRI of the liver

MRI was performed using 1.5-T MRI scanner (Philips Intera) equipped with phased-array torso surface coil.

Examination included axial T1 and T2 weighted images and Diffusion MRI. Acquisition parameters were TR 4.4 ms, TE 2.1 ms, flip angle 10°, matrix size, 172 × 163, field of view

300–350 mm and slice thickness 2–3 mm. DWI was performed using respiratory triggered fat suppressed single-shot echoplanar sequence that combined the two diffusion (motion-probing) gradients before and after the 180° pulse along with the three directions of section-select, phase-encoding, and frequency-encoding and data acquisition with EPI readout. Five increasing b values were applied as follows: 0, 200, 500, 700 and 1000 s/mm^2.

ADC derives from linear regression analysis of the signal intensity measured at each gradient application following the equation: $ADC = \ln S/S_0/(b_0 - b)$ where b is the gradient factor, S is the signal intensity after application of the diffusion gradient, and S_0 is the signal intensity at $b = 0$ s/mm^2.

Parallel imaging with generalized auto-calibrating partially parallel acquisition (GRAPPA) with an acceleration factor of two was applied to reduce the acquisition time.

2.4.1. Image analysis

After application of the DW sequence, we obtained a set of images corresponding to each b value applied and an ADC map, automatically calculated by special software. Quantitative analysis of the ADCs of liver parenchyma was performed by placing a circular region of interest (ROI) of standard dimensions (1 cm^2) on the ADC map in right liver segments to avoid artifacts from abdominal wall and vascular motion. ADC was automatically calculated. The ROI was placed far from visible vascular and biliary structures and at least 1 cm far from the liver capsule and then transported on corresponding ADC maps with a copy-paste operation. Measurement was repeated three times, calculating mean ADC value. It was decided to measure ADCs only on good-quality images and in homogeneous areas of parenchyma not affected by major artifacts due to chemical shift, magnetic susceptibility, abdominal wall or vascular motion (Fig. 1).

The time interval between MRI and histopathology ranges from 27 to 42 days (mean 33.4 days).
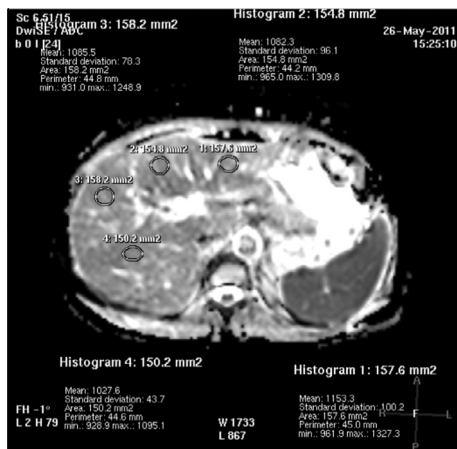
Fig. 1 44 years old female with chronic HCV cirrhosis (stage F4 on liver biopsy). Breath hold axial single shot echo-planar DWI obtained with increasing b values. ADC map shows placement of ROI in liver parenchyma. Calculated hepatic ADC was 1.08×10^{-3} mm^2/s.

3. Statistical analysis

Analysis of data was performed using SPSS 17 for Windows. Description of quantitative variables was in the form of mean, standard deviation (SD), median, 25th and 75th percentiles. Description of qualitative variables was in the form of numbers (no.) and percents (%).

Data were explored for normality using Shapiro–Wilk test of normality. The results indicated that some data were normally distributed (parametric data) and some were not normally distributed (nonparametric data), so suitable tests were used accordingly.

Binary correlation was carried out by Pearson correlation test or Spearman correlation test in case of nonparametric or categorical ordinal variables.

A receiver operating characteristic (ROC) curve was graphed to determine an appropriate fibroscan score in predicting stage of liver fibrosis that gives optimal sensitivity and specificity.

The significance of the results was assessed in the form of P-value which is Significant when P-value $\leqslant 0.05$.

4. Results

Our study included fifty-two patients, 37 (71.2%) were males and 15 (28.8%) were females with mean age of (38.2 ± 8.37) years.

Histopathological analysis and fibrosis staging according to the METAVIR scoring system revealed F0 in one patient (1.9%), F1 in 17 patients (32.7%), F2 in 25 patients (48%), F3 in 7 patients (13.5%) and F4 in 2 patients (3.8%).
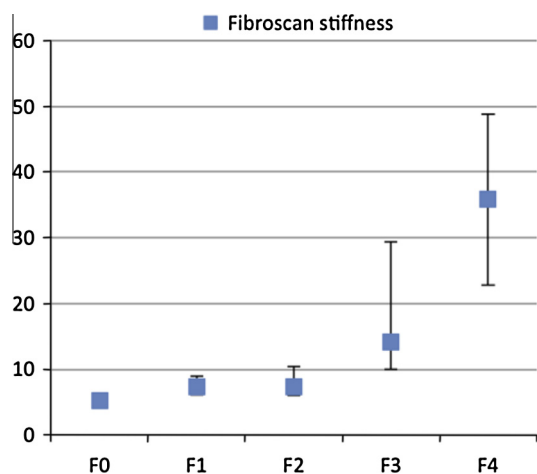
There are statistically significant differences in the mean ADC values between F0 and F4, F0 and F3, F0 and F1 fibrosis stages (p value 0.015, 0.033 and 0.008 respectively), however no significant differences were seen in the ADC values between other fibrosis stages (Fig. 2).

Taking all fibrosis groups, there was no significant difference in the ADC values between the groups (p value 0.215).

As regards the fibroscan (Fig. 3), the median (interquartile range) stiffness values were 5.2 (5.2–5.2), 7.3 (6.10–8.90), 7.3 (6.0–10.35), 14.1 (10.0–29.30) and 35.8 (22.8–48.8) Kpa in fibrosis stages F0, F1, F2, F3, and F4 respectively. There was a statistically significant difference in the median stiffness
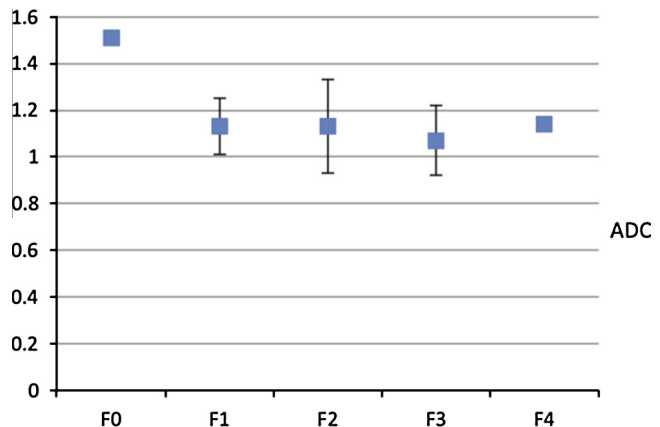
Fig. 2 ADC values for different fibrosis stages as detected by biopsy.

Fig. 3 Fibroscan stiffness values for different fibrosis stages as detected by biopsy.

between F1 and F4 ($P = 0.024$), F1and F3 ($P = 0.001$), F2 and F3 ($P = 0.014$) and F2 and F4 (p value = 0.033) and by comparing all fibrosis groups, there was a statistically significant difference in the median stiffness of fibroscan between groups (p value 0.004) (Table 1).

When grouping the patients into those ⩽F2 and those >F2 the mean ± SD of ADC values was 1.14 ± 0.18, 1.09 ± 0.13 respectively and there was no significant difference in the ADC values between both groups ($P = 0.387$), while there was a highly significant difference in the median (interquartile range) fibroscan stiffness between both groups 7.3 (6.1–9.30), 17.5 (11.3–31.15) respectively ($p < 0.001$) (Table 2).

ROC curves were used to analyze the usefulness of both ADC values and liver stiffness measurements in predicting >F2 fibrosis stages.

Table 1 *P* value between different fibrosis stages (as regards ADC by MRI diffusion and fibroscan stiffness values).

	P value	
	ADC by MRI diffusion	Fibroscan stiffness
F0 vs. F4	.015[*]	.221
F1 vs. F4	.924	.024[*]
F2 vs. F4	.994	.033[*]
F3 vs. F4	.579	.143
F0 vs. F3	.033[*]	.127
F1 vs. F3	.351	.001
F2 vs. F3	.441	.014[*]
F0 vs. F2	.076	.257
F1 vs. F2	.889	.473
F0 vs. F1	.008	.147

5. Discussion

Diffusion-weighted imaging is an imaging modality implemented to be used in abdominal diseases including diffuse liver diseases. This modality takes approximately 3 min in addition to a routine abdominal MRI and is a non-invasive procedure, which does not require contrast material injection. Its advantages include application without breath holding, repeatability and relative cheapness. This modality may also be used in the follow up of patients by making quantitative measurements on ADC map constituted from diffusion images. Diffusion includes movement behaviors of molecules in microscopic random pattern and this movement is measured from mean diffusion coefficient. DW-MRI is sensitive to this movement that is measured with ADC and water diffusion is measured with ADC [9].

Huseyin et al., 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 [10].

Our results, in common with those of most studies, revealed that there was a significant difference in ADC values between F0 and F4, F0 and F3, F0 and F1 fibrosis stages, however, there was substantial overlap in the ADC values of F1–F4 especially in the intermediate fibrosis stages.

The ADC values of cirrhotic patients or patients with advanced fibrosis are lower than healthy persons as liver fibrosis results in extracellular accumulation of collagen, glycosaminoglycans, and proteoglycans that may restrict the molecular diffusion of water and this could explain lower ADC values in those patients [6].

Moreover we could not specify a cutoff ADC value to differentiate between patients ⩽F2 and patients >F2 or predict advanced stage of fibrosis.

In this respect it was found that diffusion weighted MRI did not add information to conventional imaging methods or that could replace core liver biopsy, which is the reference standard for liver fibrosis staging [11].

The results of several studies have shown that the ADC values of cirrhotic patients are lower than those of noncirrhotic patients or of healthy volunteers [12], but the usefulness of the ADC in evaluating the intermediate stages of fibrosis remains questionable.

Taouli et al. [13] assessed seven control subjects and 23 patients with hepatitis related liver disease. Although there was a significant difference in the ADC of the F0 and F1 groups compared with the ADC of the F2–F4 groups, there was much overlap in the ADC values of individual patients in each group.

Table 2 Comparison between ADC values and fibroscan stiffness values in patients ⩽F2 and patients >F2.

	Histopathology		*P* value
	⩽F2	>F2	
ADC (s/mm²) mean ± SD	1.14 ± 0.18	1.09 ± 0.13	0.387
Fibroscan (Kpa) stiffness median (IQR)	7.30 (6.1–9.30)	17.50(11.3–31.15)	<0.001[*]

ADC: apparent diffusion coefficient, SD: standard deviation, IQR: interquartile range.
[*] *p* value significant <0.05.

Boulanger et al. (14) could not find a difference between ADC values and fibrosis scores in 18 patients with hepatitis C and 10 healthy volunteers.

Sandrasegaran et al. (11) showed a significant difference in the ADC values of nonfibrotic (F0) and cirrhotic (F4) patients. However, it could not be used to reliably distinguish among the intermediate stages of fibrosis.

Regarding fibroscan, our results showed that the median stiffness values increased as the fibrosis stage increased, with some overlap between F0 and F1 fibrosis stages.

There was a statistically significant difference in the median stiffness between F1 and F4 ($P = 0.024$), F1 and F3 ($P = 0.001$), F2 and F3 ($P = 0.014$) and F2 and F4 (p value = 0.033). No statistically significant difference was seen between F0 and F4 in our study as one patient only was diagnosed as F0 by histopathology.

The difference between patients $\leqslant$F2 and patients $>$F2 was highly statistically significant ($P < 0.001$).

Consistent with the study by Castera et al. (15), our results reported a cutoff value of 9.95 kpa for the prediction of advanced fibrosis $>$F2 with Area under the ROC curve (AUC = 0.889), $P(< 0.001)$ sensitivity = 89%, and specificity = 79%.

Lewin et al. (6) was able to discriminate F0–F1–F2 vs. F3–F4, the best cut points were less than 1.21 s/mm^2 for ADC and greater than 12.9 kpa for transient elastography. Moreover they compared DW MRI with ultrasound elastography (Fibro-Scan, EchoSens) and Surrogate Serum Fibrosis Markers (FibroTest, APRI, Forns index and Hyaluronate). They found that DW MRI was equivalent to these tests in detecting high stages (F3 and F4) of fibrosis. On the other hand, our results showed that fibroscan can differentiate between different fibrosis stages with significant difference between patients $\leqslant$F2 and patients $>$F2 while diffusion-weighted MRI cannot be used to differentiate between both groups of patients.

The disagreement between our study and the study done by Lewin et al. (6) as regards the cutoff value of ADC values between patients $\leqslant$F2 and patients $>$F2 could be explained by several factors. It was found that there was a significant relationship between the ADC values and necro-inflammation scores. Besides fibrosis, it seems that ADC values might also reflect the intensity of inflammation or necrosis and decrease with the alteration of the tissue structure. Steatosis could also affect the ADC value. The disagreements sometimes found between the DW MRI and liver biopsy results for fibrosis assessment could be explained by biopsy sampling errors. Lastly, the small number of patients involved in our study could have a role in the disagreement of results.

6. Conclusions

– MRI diffusion can be used to distinguish nonfibrotic liver (F0) from cirrhotic liver (or from liver with advanced fibrosis F3 and F4) but it cannot be used to distinguish between the intermediate stages of fibrosis.
– Fibroscan stiffness can differentiate between (F0, F1, F2) and (F3, F4), and that fibroscan remains one of the best and reliable methods for assessment of fibrosis in chronic HCV patients.

Conflict of interest

The authors declare that there are no conflicts of interest.

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