Evaluation of Liver Iron Content in Non-alcoholic Fatty Liver Disease Using mDIXON-quant Magnetic Resonance Imaging

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Introduction

Increased iron deposition within the liver may contribute to liver disease via the production of reactive oxygen species, which may lead to lipid peroxidation, dysfunction of mitochondria and other organelles, cell injury, and death⁽¹⁾. Monitoring liver iron content (LIC) is crucial for clinical management of patients with β_2 -microglobulinemia. The aim of this study was to calibrate the R2* MRI technique for non-invasive LIC assessment and to compare the LIC in the liver biopsy-proven patients with nonalcoholic fatty liver disease (NAFLD) / nonalcoholic steatohepatitis (NASH).

Method and Materials

Patient population

This study protocol was approved by the IRB according to clinical practice guidelines. All the subjects divided to three groups, consisting of healthy controls ($n=10$; mean age 32.5 $\pm$ 6.1), simple steatosis (SS; $n=12$; mean 42.9 $\pm$ 11.1), and NASH ($n=10$; mean 35.7 $\pm$ 15.8). The 22 patients with NAFLD, which are histopathologically-proven, were admitted to our hospital for evaluation of hepatic fat and/or iron from January 2015 to December 2016. All subjects were examined for clinical indications⁽²⁾. Inclusion criteria were as follows: (a) age 18-70 years; (b) men consuming < 20 g of alcohol per day; and women consuming < 30 g alcohol per day for a two-year period; (c) no active malignancy; and no acute/chronic disease except obesity or type 2 diabetes; and (d) no contraindications to MRI. There were no cases for secondary hepatic fat accumulation according to the practice guidelines of NAFLD definition.

Magnetic resonance imaging (MRI)

All MRI examinations were performed on a 3.0 T MRI scanner (Achieva; Philips Medical Systems, Netherlands) with a 32-channel receiver body matrix coil. The T1WI (TR/TE= 4.2/1.97 ms) were acquired with 2-dimensional T1 high-resolution isotropic volume excitation pulse sequence: FOV= 38 $\times$ 38 $\times$ 14 cm; matrix size= 512 $\times$ 512, NEX= 2, slice thickness= 0.74 $\times$ 0.74 $\times$ 2.0 mm, no. of slices= 70 and scan time= 14 sec. Together with a single breath-hold technique, the imaging plane in the upper abdomen was axial and the sequence was triggered to expiration. Additional multislice T1- and T2-weighted sequences were obtained in sagittal, axial and coronal planes as a part of routine upper abdominal MRI protocol for inspection of the upper abdomen. Total examination time of the upper abdomen ranged from 25-45 min.

Image analysis for quantification of hepatic fat and iron

Quantitative T2* maps were calculated using customized mDIXON-Quant software (Philips Medical Systems) from the water-only, fat-only and fat fraction images. Ratios of fat contents in the liver were evaluated to confirm both SS and NASH groups⁽³⁻⁵⁾ as follows: fat fraction (%) = fat signal intensity (SI) / (water SI + fat SI) $\times$ 100.

In T2* map, SI drop was fitted on a pixel-by-pixel basis to a mono-exponential decay using a least-squares fit method. Truncated exponential fitting was used to reduce bias introduced by low signal-to-noise ratios. Regions of interest (ROIs) were drawn either in source images or T2* maps in a homogeneous area of the right hepatic lobe, avoiding blood vessels and obvious bile ducts. A monoexponential function of the form $S(TE) = S_0 \times \exp(-TE/R2^*) + C$ was assumed to describe the signal decay with echo time (TE), where $S(TE)$ is the SI at TE, S_0 is the signal amplitude at TE = 0, and C is a constant offset parameter added to compensate for background noise. T2* values were calculated on the scanner's console and T2* map images reconstructed for abdominal scans.

The measurements of hepatic fat contents in patients with simple steatosis (A, B) and NASH (C, D). Note that the white circles in the liver indicated the ROIs for quantification of hepatic fat contents.

Statistical analysis

All statistical analyses were performed using SPSS software (ver. 20, IL, USA). Variations in hepatic fat contents were analyzed by independent two sample t-test. Also, the variation in T2* values, which induced by the difference of hepatic iron contents, was evaluated with the ANOVA test. Two-sided p-values less than 0.05 were considered to indicate statistical significance in all tests.

Results

Hepatic fat contents in NAFLD

Twenty-two patients were pathologically-proven from liver biopsy. Hepatic fat contents (%) in both groups were summarized in Table 1. Hepatic fat fractions (%) were 3.35 $\pm$ 1.51% for healthy controls, 17.25 $\pm$ 9.52% for SS, and 25.13 $\pm$ 5.80% for NASH, respectively. Fat fractions of both patient groups were significantly different from healthy controls. However, there was no significant difference between two patient groups, SS and NASH.

Table 1. Hepatic fat fraction (%) in patients with SS and NASH

	Healthy controls (n=10)	Simple steatosis (n=12)	NASH (n=10)
Fat fraction (%) ^a	3.35 $\pm$ 1.51	17.25 $\pm$ 9.52	25.13 $\pm$ 5.80
p-value ^b			0.003

Data are presented as mean $\pm$ SD.

^a Note that fat fraction in healthy controls referred to a standard reference value.

^b Fat fraction was calculated as percentage = fat signal / (water signal + fat signal) $\times$ 100.

^c The difference between simple steatosis and NASH groups was analyzed by the independent two sample t-test.

Hepatic iron contents in NAFLD

Figure 3 shows the representative mDIXON-Quant images obtained from both patients with SS and NASH. In R2*-MRI examinations, T2* values in three different groups were summarized in Table 2. Mean R2* values were 45.12 $\pm$ 8.72 ms for healthy controls, 19.12 $\pm$ 4.52 ms for SS and 17.10 $\pm$ 6.05 ms for NASH. Mean T2* value in the NASH patients is shorter than that in patients with SS. There was a significant difference between both groups. The LICs in NASH patients are higher than that in SS patients. Therefore, it might be reflected the changes of intensity induced by hepatic inflammation. Especially, overproduction of reactive oxygen is to be a main factor of oxidative stress, causing insulin resistance in NASH as metabolic syndrome (MS). In NAFLD/NASH and MS, iron contents can be reflected their radical content and oxidative stress, which can exacerbate between NASH and SS.

Figure 3. Representative mDIXON-Quant images obtained from patients with simple steatosis (A-D) and NASH (E-H). Water images (A, E); Fat images (B, F); Fat fraction images (C, G); and T2* images (D, H).

Table 2. T2* values in patients with SS and NASH

	Healthy controls (n=10)	Simple steatosis (n=12)	NASH (n=10)
T2star (msec)	45.12 $\pm$ 8.72	19.12 $\pm$ 4.52	17.10 $\pm$ 6.05
R2star (s ⁻¹) ^a	2.216	5.230	5.848
Fe conc. ^b	0.77 mg/g	1.53 mg/g	1.68 mg/g
p-value ^c			0.016

Data are presented as mean $\pm$ SD.

^a R2star was calculated as $R2^* = 1/T2^* \times 100$.

^b Fe concentration in healthy subjects ranges from approx. 0.8 mg/g dry weight to 1.2 mg/g.

^c The difference among three groups was analyzed by the ANOVA test.

Conclusion

Our study demonstrates the feasibility for non-invasive subgroup differentiation of liver iron content in NAFLD and NASH instead of invasive liver biopsy and blood sampling methods. The R2*-MRI technique is a robust method with great repeatability in each examination.

Reference

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