MR-liver fat volume fraction quantification using a magnitude-based technique with independent fat and water T2* estimations, T1-related bias correction and accounting for fat multiple resonances

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INTRODUCTION

In Western countries, Non Alcoholic Fatty Liver Disease (NAFLD) is the most common cause of chronic liver disease. In about 20% of cases, NAFLD leads to steato-hepatitis with liver fibrosis then to cirrhosis whose complications are an important cause of morbidity and mortality. While the histology after liver biopsy is the gold standard for liver steatosis assessment, inherent risk, interobserver variability and sampling errors of this method are inappropriate for clinical follow-up. Several accurate and non-invasive MR quantification methods have been proposed for liver fat fraction quantification including ^{1}H MRS, low flip angle and single T_2*-IDEAL, or low flip angle multiple gradient echoes (1-5). The aims of this work were to validate a magnitude-based technique for liver fat volume fraction (FVF) quantification with independent fat and water T_2* estimations, a T_1-related bias correction and accounting for the fat multiple resonances using a two-angles multiple gradient-echo acquisition. Validations were performed on an in-vivo prospective study at 1.5T, an in-vivo study on healthy volunteers at 3.0T and a fat-water emulsion phantom study at 3.0T where the presented method is compared with MRS FVF quantification.

MATERIAL and METHOD

Subjects: ***At 1.5T***: Fifteen subjects (4 women and 11 men; mean age: 55.0 ± 11.4 years; mean weight: 79 ± 11.7 kg) with biopsy-confirmed chronic liver diseases with NAFLD or at risk for NAFLD were enrolled prospectively. Steatosis was quantified as the proportion of hepatocytes containing intracellular vacuoles of fat, then stratified as follow: grade 0 (*normal*): < 5% of cells affected; grade 1 (*mild*) : 5-33%; grade 2 (*moderate*) : 34-66% and grade 3 (*severe*) > 66%. ***At 3.0T***: Eight healthy volunteers (2 women and 6 men; mean age: 25.7 ± 1.8 years; mean weight: 68.2 ± 8.0 kg) with no risk for liver steatosis were enrolled.

MR acquisition: ***At 1.5T***: Acquisitions were performed on a Magnetom Symphony *(Siemens Medical Solutions, Erlangen, Germany)*. FLASH 2D sequence was repeated twice on the liver with two flip angles: 15° and 70°. Acquisition parameters were: 6 first Out-of-Phase (OP) echoes and 6 first In-Phase (IP) echoes; TR/TE, 219/n × 2.38 ms with n = 1,…,12; 208 × 256 matrix; 244 × 400 mm^2 FOV; 500 Hz.pixel^{-1} bandwidth and 8 mm slice thickness in the axial plane. ***At 3.0T*** : Acquisitions were performed on a GE Discovery MR 750 *(GEHC, Milwaukee, WI, USA)* using a 8-channels torso coil. FSPGR sequence was repeated twice on the liver with two flip angle: 5° and 45°. Acquisition parameters were: 2 first Out-of-Phase (OP) echoes and 2 first In-Phase (IP) echoes; TR/TE, 100/n × 1.2 ms with n = 4,…,8; 256² matrix; 410 × 410 mm^2 FOV; 976 Hz.pixel^{-1} bandwidth, 2 NEX and 8 mm slice thickness in the axial plane. All acquisitions were performed in breath-holding.

Phantom study: Nine lipid individual emulsions with increasing fat concentration with Gd^{3+} doped water (between 1.6 to 3.2 mL), olive oil, surfactant and agar gel (between 0.25 to 0.5 %) were scanned at 3.0T by MRS and MRI. MRS acquisition parameters were: PROBE STEAM sequence with TR/TE, 3000/14 ms; $(1.5)^3$ cm^3 voxel, 2048 readout points and 8 NEX. MRI parameters were the same as *in-vivo*.

Post-processing was performed using an in-house application on Matlab r2010a (*The MathWorks, Natick, MA, USA*). Initially, separation of fat and water signal magnetizations at t=0 (M_{0fat} and M_{0water}) was done from the T_1-weighted images using a 2-parameters interference bi-exponential model. Then, apparent T_1 (T_{1app}) assuming a mono exponential signal (single component) was estimated from the first IP images acquired with the two angles. Because T_1 of fat (T_{1fat}) is almost invariant, it was fixed at 340 and 390 ms at 1.5T and 3.0T respectively and then T_1 of water (T_{1water}) was calculated as: $T_{1water} = (T_{1app} - (M_{0fat}/(M_{0water} + M_{0fat})) \times T_{1fat}) / (1 - (M_{0fat}/(M_{0water} + M_{0fat})))$. This relation was verified from fat and doped water mixture phantoms with measurement of pure water T_1-values, pure fat T_1-values and equally-mixed fat-water T_1-values. Finally, quantification of proton density fat fraction (PDFF) was performed using a 4-parameters dual-T_2* bi-exponential model including a T_1 correction from previous estimated T_1-values and a five resonance fat modeling (at 0.9-1.3-2.1-4.2 and 5.3 ppm) as described by Hamilton *et al* (6). Fat volume fraction (FVF) was then computed with: $FVF = PD_f / (k \times PD_w + PD_f)$ were k is a scaling coefficient (k = 0.95) correcting for the relative difference between proton density of fat (PD_f) and water (PD_w) as described by Reeder *et al*. (7). All results were measured on 4 regions of interest (12.7 cm^3 each) and all fits were realized using the Levenberg-Marquardt algorithm and multi-start technique to improve fit robustness. Based on a pixel-by-pixel computing, 5 parametric maps (T_1 recombined, T_2* recombined, PD_f, PD_w and fat volume fraction) were generated. MRS post-processing consisted in correcting spectra of each coil for the zero order phase and in combining them using a sum of squares weighting function. Combined spectra were quantified using a nonlinear least-squares algorithm that fits the time-domain signal to a Voigt model function and uses multiple random starting values and bounds (8). Ten Voigt components were selected from 0.9ppm to 4.7ppm. The total fat signal was calculated by summing the amplitude from peaks located at identical locations as the multi-peak fat spectrum used for MRI. The water and fat amplitudes were then corrected for T_2 decay using a-priori knowledge of the emulsions T_2 values. As MRI, PDFF was calculated as $PDFF = PD_w / (PD_w + PD_f)$.

RESULTS

Histological results were as follows: 7 subjects scored grade 0; 4 scored grade 1 (mean: 27.5 ± 5%); 3 scored grade 2 (mean: 46.5 ± 5.8%) and 1 scored grade 3 (90%). ***Phantom study***: Regression coefficient (r) between MRI and MRS was r = 0.99; p<0.001 (*Fig.1)*. ***In-vivo study***: MR results were strongly correlated with histology (Pearson's coefficient = 0.99, p<0.001) (*Fig.1*). **1.5T**: FVF stratified according to the grade of steatosis were: 0.67 ± 0.3 %; 12.0 ± 1.54 %; 18.4 ± 2.90 % and 33.3% for grade 0 to 3 respectively when T_1 correction is performed. With any T_1 correction, FVF were systematically higher: 3.61 ± 4.09 %; 17.9 ± 3.1%; 27.3 ± 3.4 % and 46.5% for grade 0 to 3 respectively. Mann-Whitney test showed a significant difference between grade 0 vs. grade 1-3, between grade 1 vs. grade 2 and between grade 1 vs. grade 2-3 (p<0.001). **3.0T**: FVF MR results were 2.2 ± 1.1 % and 5.5 ± 0.9% with and without T_1 correction respectively. Mean water T_2* were: 21.9 ± 3.7 ms and 23.1 ± 5.7 ms at 1.5T and 3.0T respectively. Mean fat T_2* were: 20.5 ± 5.6 ms and 5.07 ± 1.1 ms at 1.5T and 3.0T respectively. Mean T_1 of water was 587 ± 105 ms and 793 ± 131 ms at 1.5T and 3.0T respectively.

DISCUSSION

Phantom study showed a very good agreement between MRI method and MRS. 1.5T *in-vivo* results showed that MR-estimated FVF and histological results were strongly correlated and FVF estimates allowed a good separation between steatosis stages. Nevertheless, these results were correlated but not in agreement because FVF and histological analysis do not measure the same parameter. Liver water T_1-values at 3.0T and 1.5T estimates were close to encountered in the literature (9). In-vivo results obtained at 3.0T were in accordance with results expected on healthy subjects. All these features demonstrate the good accuracy of this method and its versatility in being used on different MR platforms. Results obtained without any T_1 correction involve an overestimation of fat fraction compared to results obtained with T_1 correction. Hence, at 3.0T and without T_1 correction, grade 0 of steatosis could be erroneously scored as grade 1. This observation demonstrates the need to avoid T_1 effect or to correct for it especially at 3.0T. Due to magnitude approach, the amplitude of FVF quantifiable with this method is limited to 0-50%. This is a minor limitation since FVF greater than 50% are uncommon in liver. Moreover, post-processing step was simplified especially since noise and eddy-current bias encountered with complex-based method were avoided. In conclusion, this method allows FVF quantification, corrected for the different confounding factors of fat and water respectively. The estimated FVF could be a suitable biomarker for the clinical follow-up of patient with NAFLD or at risk. Moreover, this latter is not dependant on acquisition parameters and could be transposable on any clinical systems and fields. Nevertheless, this results need to be confirmed with furthers large scale prospective study.

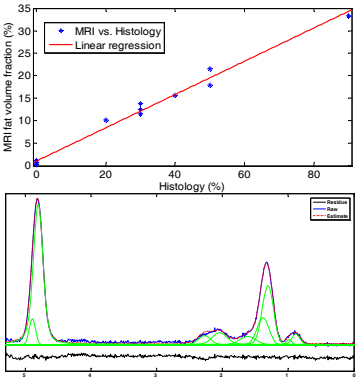

Fig.1: Linear regression between fat volume fraction quantified with the MRI method and histological results *(up)* and combined spectra quantified using a nonlinear least-squares algorithm that fits the time-domain signal to a Voigt model function *(down)*.

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