T1 independent, T2* Corrected Chemical Shift Based Fat-Water Separation with Accurate Spectral Modeling is an Accurate and Precise Measure of Liver Fat

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Introduction: As the incidence of non-alcoholic fatty liver disease parallels the obesity and diabetes epidemic, accurate quantification of hepatic steatosis is urgently needed for early detection and treatment monitoring. T_1 independent, T_2* corrected chemical shift based fat-water separation methods with accurate spectral modeling of fat, such as quantitative IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least-squares estimation)[1,2,3,4] have been shown to provide accurate fat quantification over a range of fat-fractions[4,5]. The purpose of this work is to determine the precision and accuracy of quantitative IDEAL for quantifying fat in patients, using single voxel MR spectroscopy (MRS) as a reference standard.

Methods: Forty consecutive patients (20 male, 20 female) referred for liver MRI (all indications) were recruited for this study after obtaining informed consent and IRB approval. Mean age was 50.7 years (range, 23-78). Imaging was performed at 1.5T (Signa HDx, GE Healthcare, Waukesha, WI) using an eight-channel phased array cardiac coil.

Two repeated measurements with MRI and MRS were made to assess repeatability (precision). Between time points, patients sat up and then lied down, new localizers were acquired and the MRI and MRS sequences were re-prescribed. Breath-held MRI fat-fraction images were acquired over the entire liver using an investigational version of a 3D spoiled gradient echo (SPGR) IDEAL acquisition[6]. Single voxel breath-held MRS (STEAM) data were acquired without water suppression. The voxel was placed in the posterior segment of the right hepatic lobe while avoiding large vessels in the same attempted location for both acquisitions.

Imaging parameters for quantitative IDEAL were: TE_{min}=1.3ms, echo spacing=2.0ms, ETL=6, TR=13.7ms, BW=±125kHz, FOV=35x35cm, slice=10mm, 256x128 matrix, flip=5° to avoid T_1 bias[7], and 24 slices. A 2D parallel imaging acceleration method (ARC)[8] with effective acceleration of 2.2 was used to reduce total imaging time to a 21s breath-hold. Imaging parameters for MRS were: 2048 readout points, 2.5x2.5x2.5 cm^3 voxel, 1 average, TR = 3500ms, TE = 10, 20, 30, 40, 50ms, all acquired in a 21s breath-hold.

A modified quantitative IDEAL water/fat reconstruction was used to include correction for T_2* decay[1], noise bias[7], eddy currents[9], and multiple spectral peaks of fat using a pre-calibrated fat signal evolution model[2]. Blinded, off-site MRS post-processing was performed using the AMARES algorithm included in JMRUI to estimate a T_2-corrected MRS fat-fraction.

Two independent readers recorded the fat-fraction measured in 9 ROIs per volunteer at both time points, with one ROI in each of the 9 Couinaud segments. Precision of MRI fat-fraction measurements was assessed through Bland-Altman plots and calculation of concordance correlation coefficients between quantitative IDEAL ROIs from Time 1 and 2 for both readers and between readers.

Further, Reader 1 measured an ROI at the location of the MRS voxel. Accuracy was assessed through regression of MRI fat-fraction at the location of the MRS voxel compared with MRS. Using an average fat-fraction across the liver from the 9 ROI, sensitivity and specificity were calculated using 5.56%[10] as the threshold of a diagnostic indicator of steatosis.

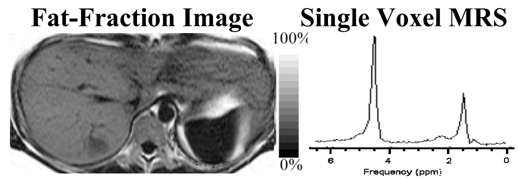

Figure 1: Representative fat-fraction image (left) and MRS spectrum (right) of a patient. At time 1 (time 2), readers reported 33% and 34% fat (33%, 34%), and MRS reported 34% fat (35%).

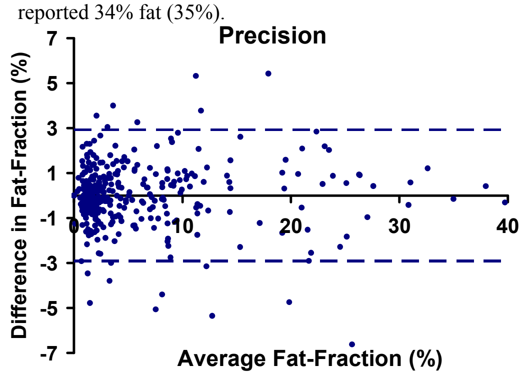

Figure 2: Bland-Altman plot comparing repeated measurements of MRI in 9 segments from 39 livers (351 points) for Reader 1 demonstrate excellent repeatability of fat-fraction measurements

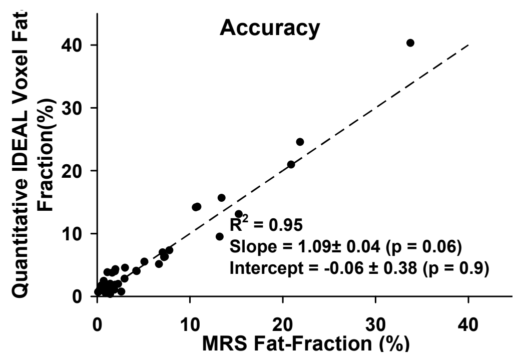

Figure 3: MRI vs MRS fat-fractions. MRI measures fat-fraction with high accuracy, using MRS as a reference standard. Excellent agreement is seen, and slope and intercept are statistically equivalent to 1.0 and 0.0, resp., for Reader 1, Time 1.

Results: Figure 1 contains a representative MRI fat-fraction image and the corresponding MRS spectrum of a patient referred for evaluation of a focal nodular hyperplasia (benign lesion). Average MRI fat-fraction for both readers and time points was 33.5±0.7% for this patient, and for both time points MRS gave 34.2±0.5%. All exams were of high image quality except for two patients, whose data were excluded due to severe breathing artifact and partial voluming effects on reconstructed images.

Using MRS as a reference, MRI provides very precise fat-fractions as shown by the Bland-Altman plot (Figure 2); the difference between Time 1 and 2 are shown for the 9 ROI across all 39 patients (359 points) for Reader 1. Further, precision is verified by the correlations, where values of 1.0 correspond to perfect agreement. Correlation for STEAM fat-fractions is 0.99, between readers for MRI at Time 1 (Time 2) is 0.93 (0.95), and between times for Reader 1 (Reader 2) is 0.97 (0.96), indicating that readers agree with each other and MRI shows high agreement for repeated measurements. The 95% confidence interval (CI) for differences in MRI measurements made by Reader 1, which encompass 95% of the data, is [-2.90, 2.92] and for MRS is [-1.64, 2.02]; differences in fat-fractions outside of the CI are true change in fat-fraction.

MRI provides highly accurate measures of fat-fraction using MRS as a reference standard, as seen by the regression between MRI measured at the MRS voxel location and MRS (Figure 3); excellent agreement was seen for Reader 1 for both time points, where r^2 >0.95, slopes were not significantly different than 1.0, and the intercept for Time 1 was not significantly different than 0.0 (p-values are Bonferroni-corrected since two readers were tested). Using 5.56% as a diagnostic cutoff, the sensitivity and specificity of quantitative IDEAL was 92% and 96%, respectively.

Discussion: Fat-fraction, when measured with T_1 independent, T_2* corrected quantitative IDEAL with accurate spectral modeling is a highly precise and accurate method of quantifying liver fat, when using T_2 corrected MRS as a reference standard. This method provides reliable in vivo fat quantification in patients and is highly promising as a quantitative biomarker of liver fat.

References: [1] Yu *et al*. JMRI 2007 [2] Yu *et al*. MRM 2008 [3] Bydder, *et al* MRM 2008 [4] Hines, *et al* JMRI 2009 [5] Hines *et al.* Radiology, in press [6] Reeder *et al*. JMRI 2007 [7] Liu, *et al* MRM 2007 [8] Beatty *et al*, ISMRM 2007 (#1749) [9] Yu, *et al* ISMRM 2009 (#461) [10] Szczepaniak *et al*. AJPEM 2004

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