Hepatic Fat Quantification by Low Flip-angle Multi-echo Gradient-echo MR Imaging: A Clinical Study with Validation with MR Spectroscopy

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INTRODUCTION: Non-alcoholic fatty liver disease (NAFLD) is an emerging epidemic, affecting 17-33% of the United States population[1]. NAFLD can be associated with steatohepatitis, which can over time progress to fibrosis, cirrhosis, end-stage liver disease, and death. Early diagnosis and intervention is critical for prevention of the long-term sequelae. Although liver biopsy remains the gold standard for diagnosis and staging, noninvasive techniques would be preferred for routine screening, active monitoring of disease progression, and assessment of treatment response in therapeutic trials.

MR spectroscopy (MRS) is generally considered the most accurate noninvasive method to quantify intrahepatic triglyceride[2], but it tends to be time-consuming, technically demanding, and restricted in availability; moreover, it provides limited spatial coverage and may be prone to sampling errors. MR imaging, on the other hand, offers greater speed and spatial coverage, is simpler to perform, has wider availability, and is suitable for routine use. Recently, several gradient-echo-based MR strategies have been proposed that address potentially confounding T1 and T2* relaxation effects and thereby aim to quantify hepatic fat by proton density[3-5]. Although these techniques show promise, they have not been validated in large-scale clinical studies.

The goal of this study was to assess the fat quantification accuracy of a T1-independent, T2*-corrected gradient-echo technique in human subjects with confirmed or suspected NAFLD. The technique uses a low flip angle (FA) to minimize T1 effects and acquires three echoes to measure and account for T2* relaxation. For comparison, gradient echo techniques with high FA (not T1 independent) and/or with only two echoes (not T2* corrected) were also assessed. MRS measures of "fat proton fraction" (ratio of fat proton density to total [fat+water] proton density) served as a non-invasive surrogate reference standard for tissue triglyceride concentration.

METHODS: This prospective cross-sectional clinical study was approved by institutional IRB and was compliant with HIPAA. Seventy-four subjects, 52 adult (male/female 28/24) and 22 pediatric (male/female 16/6), with known or suspected NAFLD gave consent and participated in research MR exams. Axial 2D 3-echo spoiled gradient echo images (TR 120ms, FA 10° and 90°, TE 2.3, 4.6, and 9.2ms, 8-mm slice thickness; ~16s breath-hold) and 5-echo single-voxel stimulated echo spectra (TR 3000ms, TE 20, 30, … 60ms, 2x2x2 cm; 15s breath-hold) of the liver were performed at 1.5T. On the MR images, a region of interest (ROI) was selected that corresponded in location to the MRS voxel. Assuming a fat-water signal phase interference period of 4.6 msec, the fat signal fraction was calculated at each flip angle (10° and 90°) from the first two echoes (2.3 and 4.6 msec) as the ratio of the fat signal to the total (fat + water) signal. T2* was estimated from the two in-phase echoes (4.6 and 9.2 msec) assuming mono-exponential decay, and the calculated fat signal fraction was corrected for T2*. Spectral quantification was performed in the time domain using the AMARES algorithm included in MRUI[6,7]; the spectroscopic fat proton fraction was measured as the T2-corrected integrals of the water (~4.0-5.0 ppm) and fat (~0.5-3.0 ppm) peaks.

RESULTS: An illustrative example of a 56 year-old man with NAFLD is provided in **Figure 1**. Fat signal fraction maps without and with T2* correction obtained at high and low FA are shown. In the co-localized imaging-spectroscopy ROI, the low FA, T2* corrected technique provides the closest agreement with the T2-corrected spectroscopic fat fraction. The imaging fat signal fraction values are plotted against the reference spectroscopic fat proton fraction in **Figure 2**; for the low-FA, T2*-corrected technique (blue circles, right panel), data points tightly cluster around the diagonal line, indicating high accuracy. The sensitivity and specificity values calculated at diagnostic classification thresholds of 2, 4, .., and 12% spectroscopic fat fraction are summarized in **Tables 1 and 2**. Regression analysis of the subset of individuals with spectroscopic evidence of NAFLD (nominally defined as > 6%)[2] shows that the low-FA, T2*-corrected method provides the highest total accuracy (**Table 3**). On high-FA data, T1 effects tilt the regression slope away from 1 and lead to overestimation. On T2*-uncorrected data, T2* effects shift the regression intercept away from 0 and lead to underestimation.

CONCLUSION: The low-FA, T2*-corrected three-echo gradient-echo imaging technique offers high diagnostic sensitivity and specificity for classification of subjects as normal or abnormal and permits accurate quantification of liver fat proton density over a wide range of severity.

Table 1: Sensitivity / Specificity (Low FA)

Dx threshold	2%	4%	6%	8%	10%	12%
Without T2* Correction	0.83 0.94	0.83 1.00	0.82 1.00	0.79 1.00	0.95 1.00	1.00 1.00
With T2* Correction	1.00 0.12	1.00 0.12	1.00 0.77	0.96 0.90	1.00 0.94	1.00 0.97

Table 2: Sensitivity / Specificity (High FA)

Dx threshold	2%	4%	6%	8%	10%	12%
Without T2* Correction	0.70 0.47	0.68 0.52	0.57 0.61	0.50 0.60	0.32 0.54	0.35 0.56
With T2* Correction	1.00 0.00	0.87 0.17	0.71 0.42	0.66 0.46	0.47 0.49	0.47 0.54

Table 3: Regression Slope / Intercept

1.28*/ -0.04*	1.41*/ -0.01	FA 90°
1.00 / -0.03*	0.97 / 0.02	FA 10°
No T2* Correction	T2* Correction	* p < 0.05

Figure 1

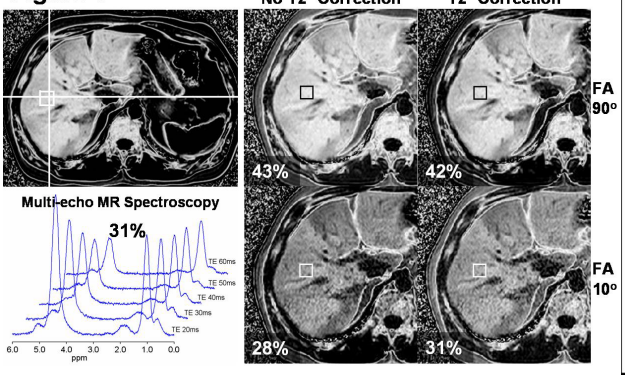
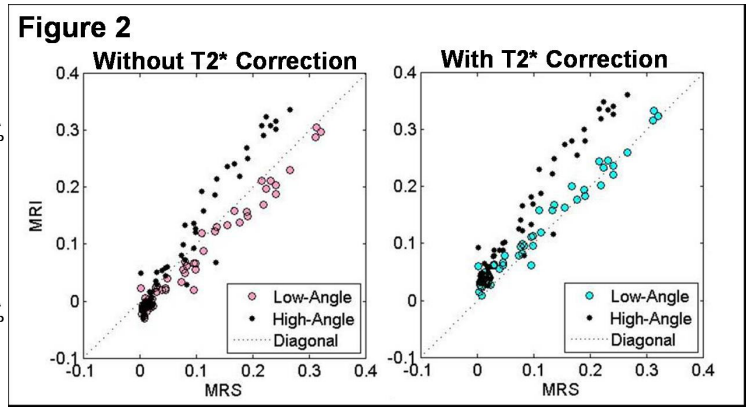


Figure 2



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