

Quantitative comparison of hepatic fat fraction in type 2 diabetes with triple-echo MRI and proton MRS

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Target Audience: MR researchers and clinical investigators interested in quantitative assessment of hepatic fat in type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD).

Introduction: Approximately 70% of persons with T2DM have a fatty liver and the disease follows a more aggressive course with necroinflammation and nonalcoholic steato-hepatitis in diabetes. NAFLD is a chronic liver condition characterized by insulin resistance and hepatic fat accumulation, in the absence of other causes such as alcohol abuse, viral hepatitis, auto-immune hepatitis(1). NAFLD is most commonly diagnosed by liver biopsies, ultrasound, CT and MRI. At present, non-invasive ¹H-MRS, although time consuming and limited availability, is the most reliable imaging technique for hepatic fat steatosis, providing a close correlation with fat estimated from liver biopsies in patients (2). There is an active search for more practical ways to study the large numbers of patients with NAFLD and T2DM. Breath-hold triple-echo spoiled gradient-echo (MRI-TRE) sequence at low flip angle with consecutive first in phase [IP₁], opp phase [OP], and second in phase [IP₂] acquisitions at varying [TEs] enables estimation of signal intensity loss between IP and OP, corrected for T₁ and T₂* decay makes an effective method to estimate quantitative fat fraction(3). The purpose of this study was to compare and validate the triple-echo sequence method for liver fat measurement in T2DM subjects with breath-hold short TR non-water suppressed MRS, long TR non-water suppressed and water-suppressed MRS.

Methods: Eight T2DM subjects (6 male, 2 female, 45-70years, BMI: 23.8~36.3kg/m²) underwent MR imaging and spectroscopy examinations of the liver on Siemens 3T Magnetom TIM Trio system using an abdominal surface array coil along with spine-array coil. Correct positioning was achieved by breath-hold localizing sequences in axial, coronal and sagittal planes. MR imaging of the full volume of the liver was performed with two separate breath-holds (17s each) using a T₁-weighted transversal 2D triple-echo spoiled gradient-echo sequence (MRI-TRE): TR / TE = 175 / 2.46 ms [IP₁], 3.69 [OP], 4.93 [IP₂], α = 20°, 6 mm slice, matrix = 256 x 192, GRAPPA acc. factor = 2. Single-voxel MR spectroscopy (¹H-MRS) was obtained using PRESS with a 20 x 20 x 20 mm voxel positioning on Couinaud segment VII of liver. MRS was obtained using three different acquisitions **a.** (MRS-2s) single breath-hold non-water suppressed: TR/TE = 2000 / 30 ms, 4 avg, 2000 Hz, **b.** (MRS-4s) non-water suppressed: TR / TE = 4000 / 30 ms, 32 avg, 1250 Hz, **c.** (MRS-WS-4s) water-suppressed TR / TE = 4000 / 30 ms, 32 avg, 1250 Hz. Automated optimization of gradient shimming followed by manual adjustment of central frequency (H₂O FWHM: 30~45 Hz) was performed.

Data Analysis: All ¹H-MRS data were processed using the AMARES fitting algorithm in the jMRUI 5.0 software package. Signal intensities from water (H₂O: 4.7 ppm) and fat (methylene - (CH₂)_n- lipid :1.3 ppm) were quantified by lorentzian function fitting and baseline correction. T₁ & T₂ corrections were performed using previous reported values (3) for water (T₁ = 809 ms, T₂ = 26.3 ms) and lipid (T₁ = 382 ms, T₂ = 59.1 ms). Hepatic fat fraction with MRS was calculated as FF_{MRS} (%) = [S_{fat} / (S_{fat} + S_{water})]. MR in phase (IP) and opp phase (OP) image analysis was performed using MANGO where ROI (8cm³) was drawn in segment VII at the same site as MRS Voxel. T₂* relaxation time of the liver was calculated as T₂* (ms) = -ΔTE / ln (S_{IP2} / S_{IP1}) where ΔTE = 2.46 ms. Signal intensities for S_{IP1}, S_{OP} were corrected for T₂* and T₁ was assumed negligible at low flip angle. Fat fraction was calculated as FF_{MRI-TRE} (%) = [(S_{IP} - S_{OP}) / (2.S_{IP})]. Relationship between FF_{MRI-TRE} vs. FF_{MRS} was assessed using a scatter plot and Pearson correlation coefficients. Agreement between methods was assessed using limit-of agreement Bland-Altman analysis. All statistical analyses were performed by using R 3.0.2 statistical software. P < 0.05 were considered to indicate a significant difference.

Results: Mean fat fraction with MRI triple-echo sequence exhibited considerable inter-individual variability FF_{MRI-TRE} = 8.685% (SD: 5.05, range: 2.10-18.26). T₂* relaxation time of the liver was 14.607 ± 2.45ms. Mean fat fraction observed with MRS: FF_{MRS-2s} = 7.499% (SD: 4.80, range: 3.43-18.57); FF_{MRS-4s} = 4.842% (SD: 4.69, range: 1.38-15.72); FF_{MRS-WS-4s} = 8.042% (SD: 4.90, range: 1.25-17.90). Strong significant correlations were observed between fat fractions with Pearson correlation coefficients: MRI-TRE vs. MRS-2s (r = 0.872, p = 0.004); MRI-TRE vs. MRS-4s (r = 0.931, p = 0.0007); MRI-TRE vs. MRS-WS-4s (r = 0.963, p = 0.0001). Bland Altman plots between fat fractions produced good agreement and all the data points are within the 95% limits of agreement suggesting these methods can be used interchangeably. Bias estimate was moderately low for MRI-TRE vs. MRS-2s (1.1863) and MRI-TRE vs. MRS-WS-4s (0.6438) but was considerably higher for MRI-TRE vs. MRS-4s (3.8425).

Discussion: Our results indicate that strong concordance can be observed between the fat fractions calculated from breath-hold MRI-TRE, single breath-hold short TR non-water suppressed MRS and long TR water-suppressed MRS but not with long TR non-water suppressed MRS that underestimated the fat fraction due to motion artifacts resulting in broadened water resonance linewidth and reducing signal intensities of lipid peak. The breath-hold Triple-echo GRE sequence can be used to measure the heterogeneous fat distribution throughout the liver without any discrepancies in spatial registration, as the images can be acquired simultaneously by three echoes. Image acquisition and post-processing are typically faster in MRI-TRE and the extent of potential problems of shimming, longer scan times, adequate SNR, increasing line width due to patient motion, contamination by surrounding tissues observed in MRS can be completely avoided. Limitations of this study include small number of subjects, comparing fat fraction from the signal obtained from protons in fatty acids with two MR-based methods (MRI-TRE and MRS) as opposed to weight of lipids per unit of liver volume measured in histology findings of biopsies, and neglecting the heterogeneity of liver fat fraction in various segments due to single voxel limitations in MRS.

Conclusion: This study provides a reliable comparison of non-invasive liver fat quantification using MRI triple echo and MRS. Breath-hold Triple-echo gradient echo MRI sequence is fast, accurate and provides excellent concordance and correlation with MRS and can be used to replace time-consuming MRS for longitudinal and large cohort studies.

References: [1] Cusi K. et al. Curr Opin Endocrinol Diabetes Obes. 2009; 16(2):141-149 [2] Reeder SB. et al JMRI 2011; 34(4). [3] Guiu B. et al Radiology 2009; 250(1):95-102 [4] Hyeonjin Kim et al. MRM 2008; 59:521-527 [5] Guiu B. et al. Eur Radiol 2009 19:1786-1793.

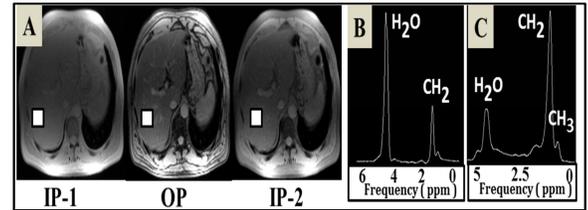


Fig 1: A. MR images triple-echo spoiled gradient-echo (2.46 [IP₁], 3.69 [OP], 4.92 [IP₂]). ROI was placed in segment VII of liver B. ¹H MRS PRESS (TR/TE = 2s/30ms, 8mL, 8avg) C. ¹H MRS water suppressed (TR/TE = 4s/30ms, 32avg).

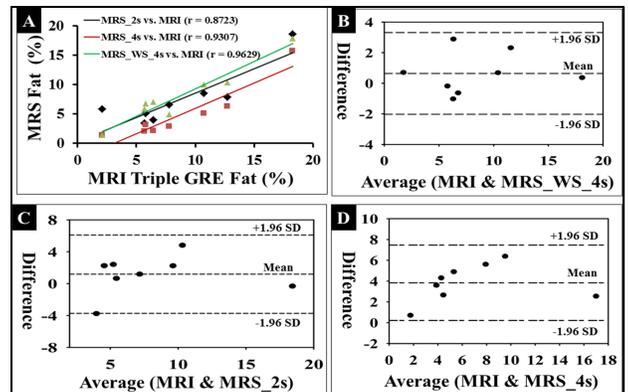


Fig 2: A. Scatterplot and regression line show close correlation between liver fat content calculated with FF_{MRS} (%) and FF_{MRI-TRE}(%). B-D. Bland-Altman plot: Differences between liver fat fraction estimated by various MRS methods and triple-echo MRI plotted against means, with 95% confidence intervals. All data points were within limits of agreement.