

Quantification of Hepatic Steatosis with MRI: Histological Validation

T. D. Reed¹, R. Agni², C. Hines¹, R. Bruce¹, M. Ranade¹, B. Soriano², K. Mohajer¹, and S. B. Reeder¹

¹Radiology, University of Wisconsin, Madison, WI, United States, ²Pathology, University of Wisconsin, Madison, WI, United States

Introduction: Non-alcoholic fatty liver disease (NAFLD) affects an estimated 20-80 million people in the US alone and is expected to increase as the epidemics of obesity and diabetes continues¹⁻³. Over the last several years, quantitative MR methods developed for accurate measurement of hepatic steatosis have been described. The majority of these studies have been validated through comparison with single voxel MRS as the reference standard. These methods have demonstrated excellent correlation and agreement between proton density fat-fraction ("fat-fraction" for brevity) and MRS so long as all confounding factors are addressed including: T1 related bias, T2* correction, spectral complexity of fat, noise related bias, and eddy currents⁴⁻⁸. However, there is a paucity of tissue validation of these methods. The purpose of this work is to compare quantitative fat-measurements with MRI to histology, obtained through non-targeted biopsy or surgical resection.

Methods: After obtaining IRB approval, a retrospective study was performed in 26 patients scanned between July, 2007 and November 2010. All imaging exams were performed within four months of biopsy. There were 11 females and 15 males with an age range of 10-74 (average=48.3). Imaging was performed on 1.5T clinical scanners (Signa HDxt, GE Healthcare, Waukesha, WI) using an 8 channel phased torso or cardiac coil, with the following parameters: TR=12.5-13.6ms, TE_{min}=1.3ms, ΔTE=2.0-2.2ms, BW=±125-142kHz, FOV=35cm, 8-10mm slice, 24-32 slices, and 256 x 128-160 matrix. 2D parallel imaging acceleration using ARC (R≈2.2) was used, and total scan time=20-22 seconds. Image reconstruction was performed with an online algorithm that corrects for T₂* decay, eddy currents, and noise bias, and uses spectral modeling of fat⁴⁻⁸. A flip angle of 5° was used to minimize T1 related bias. MRI fat-fraction was measured from the weighted average of ROI's from all nine Couinaud segments.

All histological slides were stained with H&E and/or Masson's tri-chrome stain, and were re-evaluated for this study. Histology was graded using the Brunt classification⁹ that assesses the number of cells affected with macrosteatosis (grade 0-3): 0 is < 5%, 1 is 5-32%, 2 is 33-66%, 3 is >66%. Linear regression was performed comparing MRI fat-fraction with steatosis grading performed to the nearest 5% of cells affected by steatosis.

Sensitivity, specificity, and area under the ROC curve (AROC) were calculated comparing fat-fractions positive for steatosis, according to Szczepaniak et al¹⁰ and grades of steatosis greater than or equal to 1.

Results: Figure 1 shows examples of fat-fraction images obtained in patients with mild, moderate and severe steatosis, respectively. Corresponding micrographs from biopsy cores demonstrates excellent subjective agreement.

Figure 2 plots the measured fat-fractions from the left lobe of the liver compared with histological. Statistical analysis demonstrates excellent correlation with $r^2=0.77$. Note that the slope (0.40±0.04) and intercept (3.43±1.26) are different than 1.0 and 0.0, respectively. This occurs because there is not a one to one correspondence because fat-fraction, which reflects tissue triglyceride concentration, and histological grading which reflects the number of cells affected by steatosis. Using a fat-fraction threshold of 5.56%¹⁰ the sensitivity and specificity for detection of grade 1 (or higher) steatosis was calculated and found to be 0.73 and 0.53.

Discussion: These results demonstrate good correlation of the MR proton density fat-fraction and histological grading, validating the use of quantitative MRI as an accurate non-invasive biomarker of hepatic steatosis. Further, these results provide a preliminary "calibration curve" that translates MRI measures of proton density fat-fraction and histological grading. The moderate sensitivity and specificity for detection of steatosis using MRI may be related to the relatively long interval between biopsy and imaging (≤4 months) or the high sampling variability of biopsy¹¹.

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Acknowledgements: This work was supported by GE Healthcare, the NIH (NIH R01-DK083380, R01-DK088925, RC1-EB010384), and the Coulter Foundation.

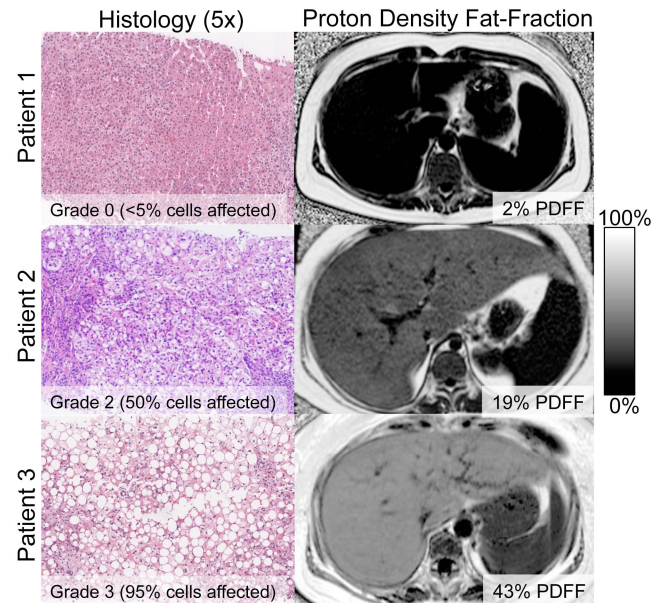


Figure 1: Three examples demonstrating good subjective correlation between MRI and histological grading of steatosis. Patient 1 demonstrates grade 0 (<5%) steatosis on histology with corresponding low PDFF (2%), while patient 2 demonstrates grade 2 (50%) histological grading with 19% PDFF, and patient 3 demonstrates grade 3 (95%) steatosis with 43% PDFF.

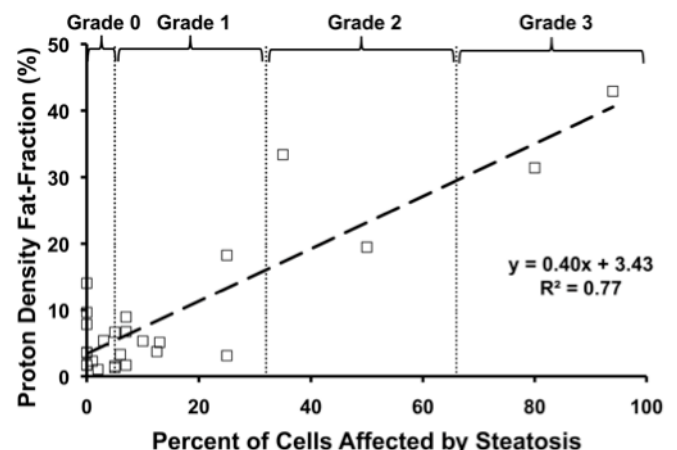


Figure 2: Proton density fat-fraction measured with MRI demonstrates good correlation ($r^2=0.77$) with histology, validating PDFF as a quantitative biomarker of steatosis. Note that the slope and intercept of this regression differ from 1.0 and 0.0, respectively, because PDFF and histology grading, while related, are fundamentally different metrics of liver fat content.