Quantitative MR Imaging of Hepatic Steatosis: Validation in Ex Vivo Human Livers

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Target Audience: Physicists and clinicians interested in MRI based quantification of hepatic steatosis.

Purpose: To validate MRI based proton density fat-fraction (PDFF) as an imaging biomarker of hepatic steatosis through a direct comparison of MRI-PDFF with histology, MR spectroscopy (MRS) and biochemical triglyceride extraction as three independent reference standards.

Methods: Thirteen isolated human livers authorized for medical research were obtained for this prospective *ex vivo* study. Each of the nine liver segments was labeled on the liver surface (*Figure 1A*) with an MR visible marker for precise co-localization of MRI regions of interest (ROIs), MRS voxels, core biopsies for histology and tissue wedges for triglyceride analyses. MR imaging was performed at 1.5 T (Signa HDx, GE Healthcare) using a 3D multi-echo spoiled gradient echo (SPGR) sequence [1] with a 44x44cm field of view, 256x160 matrix, 8mm slice thickness, 32 slices, 5° flip angle, ±125kHz receiver bandwidth, TR=13.6ms, and 6 echoes (TE_{init}=1.20ms, ΔTE=1.98ms). Separated fat and water images were reconstructed using a graph-cut algorithm to avoid water-fat swapping [2], as well as spectral modeling of fat and T2* correction [3,4] Eddy current-related phase errors were addressed by using a mixed magnitude/complex fitting technique [5]. PDFF maps were calculated using the separated water and fat images (F/(W+F)) to remove the effects of B_1 coil-sensitivity. For MRS (STEAM, Stimulated Echo Acquisition Mode) [6] a 2x2x2cm^3 voxel was placed in each of the nine liver segments. Multi-TE STEAM data were automatically processed to provide T2-corrected MRS-PDFF [7]. After the imaging, a 16-gauge core biopsy for histologic analyses and a ~1.5x1.5x1cm^3 tissue wedge for biochemical triglyceride analyses were obtained from each of the nine liver segments. MRI-PDFF was plotted against MRS-PDFF, histological grading (the current non-invasive and invasive reference standards), and tissue triglyceride concentration. Histological analysis was also compared to TG content. Pearson's correlation coefficients (**r**) with 95% confidence intervals (CI) were computed.

Results: *Figure 1* illustrates three examples of livers without, with moderate and with severe steatosis. Results of MRI, MRS, histology, and triglyceride extraction from all 117 liver segments are included in *Figure 2*. *Figure 2A, B* demonstrates excellent agreement between MRI-PDFF and MRS-PDFF (**r = 0.984**; CI: 0.978-0.989) and good correlation between MRI-PDFF and histology (**r = 0.850**; CI: 0.791-0.894). *Figure 2C, D* demonstrates good correlation between MRI-PDFF and triglyceride concentration (**r = 0.871**; CI: 0.818-0.909) and good correlation between histology and triglyceride concentration (**r = 0.870**; CI, 0.817-0.908).

Discussion: As in previous *in vivo* studies, this *ex vivo* study confirmed that MRI-PDFF shows only good to moderate correlation with histology, and excellent correlation and agreement with MRS-PDFF. Moreover, our *ex vivo* results revealed good correlation between hepatic triglyceride content, which was comparable to the correlation between histological steatosis grading and hepatic triglyceride content.

Conclusion: MRI-PDFF is an accurate imaging biomarker of liver triglyceride content, with the advantage of non-invasive quantification over the entire liver.

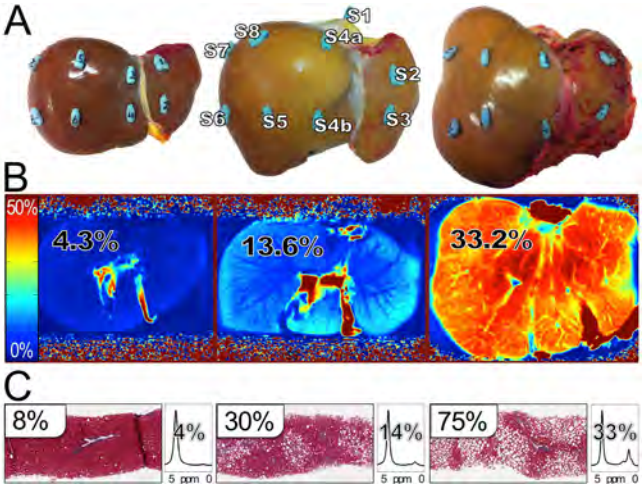

Figure 1: Examples of a healthy liver vs. moderate and severe steatosis. *(A) Photographs demonstrate increase in size and yellowish color with increasing steatosis. (B) Volumetric PDFF maps, and representative results of (C) histology and (D) MRS spectra from liver segment VIII. Results of triglyceride analyses from liver segment VIII were 8%, 14% and 39%, respectively.*

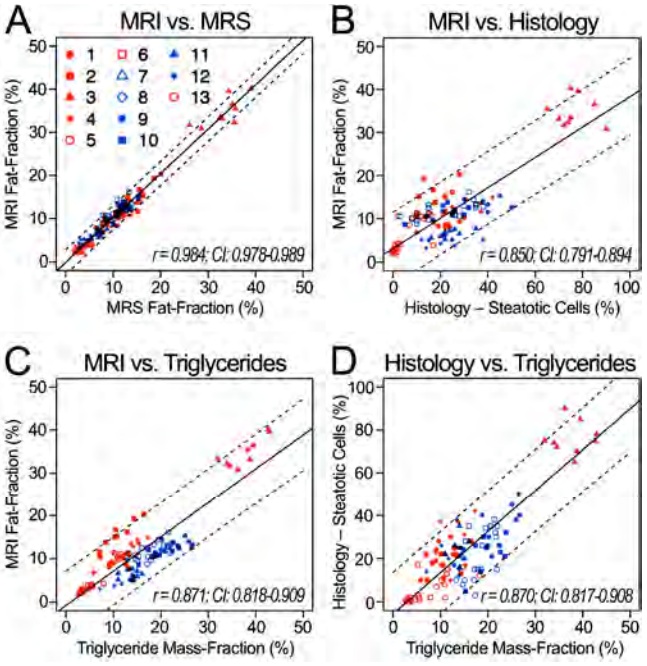

Figure 2: Excellent agreement of MRI-PDFF with (A) MRS and good correlation with (B) histology and (C) extracted triglycerides. (D) *Histology also shows good correlation with extracted triglycerides. Each of the 13 livers is indicated by nine symbols representing sampling from each of the liver segments.*

References: [1] Meisamy et al Radiology 2011; [2] Hernando et al MRM Jan 2012; [3] Yu et MRM 2008 [4] Yu et al JMRI 2007; [5] Hernando et al MRM Mar 2012; [6] Hamilton et al JMRI 2009; [7] Hernando et al ISMRM 2014

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