MRS and MRI-determined Hepatic Proton Density Fat Fraction: Comparison of ROI Sampling Methods in Patients with Type 2 Diabetes

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Intended audience: Physicians (radiologists, endocrinologists, hepatologists), image analysts, and physicists with an interest in MR-based fat quantification.

Purpose: Magnetic resonance spectroscopy (MRS) is widely accepted as the noninvasive reference standard for liver fat quantification. MRI-proton density fat fraction (PDFF) is an emerging biomarker of liver fat that offers the possibility to cover the entire liver volume.[1,2] Conventionally, MRI-PDFF is calculated by sampling regions of interest (ROI). However, it is unclear how various ROI sampling methods reported in the literature would agree with the liver mean PDFF. In this study, we assessed the fat distribution heterogeneity across segments. We also examined the agreement between various ROI sampling methods reported in the literature.

Methods: In this substudy of the LIRAINS Trial, 34 patients with type 2 diabetes were evaluated.[3] This study was approved by our institutional review board. All subjects gave written informed consent. Patients were randomized to liraglutide or insulin therapy and evaluated by MRS and MRI at baseline and after 12 weeks of treatment. All studies were performed on a 3.0T clinical MRI system (Achieva TX, Philips Healthcare, Best, The Netherlands). MRS used a single breath-hold STEAM sequence without fat and water saturation. For each patient, two 25 mm x 25 mm x 25 mm voxels were placed in the right hepatic lobe, avoiding large vessels. The following parameters were used: TR = 3500 ms; TE = 10, 15, 20, 25, 30 ms; TM = 15 ms; spectral width = 1250 Hz. The TR was chosen to be sufficiently long to minimize T1-weighting effects and multi-echo data was acquired for correction of T2-weighting effects. Multi-echo spoiled gradient-recalled echo sequence with seven-echo readout were acquired during a single breath-hold to cover the entire liver. The following parameters were used: repetition time (TR), 235 msec; the first echo time (TE) was 1.15 msec, with a ΔTE of 1.15 msec (therefore, the 7 TEs were: 1.15, 2.30, 3.45, 4.60, 5.75, 6.90, and 8.05 msec); flip angle, 10°; field of view, 400 mm; section thickness, 9 mm; 1 mm gap; acquired voxel size, 2.5 x 2.5 x 9 mm; receiver bandwidth, 1215 Hz/pixel; SENSE acceleration factor, 2.6; and number of averages, 1. An image analyst reproduced the ROI methods described in publications relying on MRI for liver fat quantification. The image analyst was blinded to the MRS results and liver mean PDFF. The amount of steatosis heterogeneity by segment was analyzed by a repeated measures ANOVA using a linear mixed model to account for liver segments, time, treatment group, and their interaction. The agreement between fat quantification techniques (MRS and MRI-PDFF) was assessed by Bland-Altman. Comparison between mean liver fat MRI-PDFF and various ROI sampling methods was analyzed by intraclass correlation coefficient and Student's paired T-tests.

Results: There was no systematic variation on MRI-PDFF among the 9 liver segments on the repeated measures ANOVA analysis. There was also no effect of treatment group on MRI-PDFF. However, there was a significant effect of time on MRI-PDFF (p = 0.03). Furthermore, there was no significant interaction between liver segment, treatment group, and time. **Figure 1** shows a representative MR spectrum and co-localized MRI-PDFF measurement. Bland-Altman analysis showed good inter-method agreement between MRS and co-localized MRI, with a bias of -2.8 ± 3.6 % (bias ± SD) for voxel 1 and -1.5 ± 2.8% for voxel 2. **Table 1** summarizes the liver PDFF (mean ± SD) obtained by whole-liver segmentation and various ROI sampling methods at baseline. The agreement between liver mean PDFF and various ROI sampling methods was very good to excellent, ranging from 0.881 to 0.983. Paired T-tests revealed significant differences ($p < 0.05$) between mean liver fat fraction and ROI sampling methods that only sampled the right lobe (Yoshimitsu, JMRI 2008 and Yokoo, Radiology 2009) and those that predominantly sampled the right lobe (Qayyum, Radiology 2005 and Lee, J of Hepatology 2010).

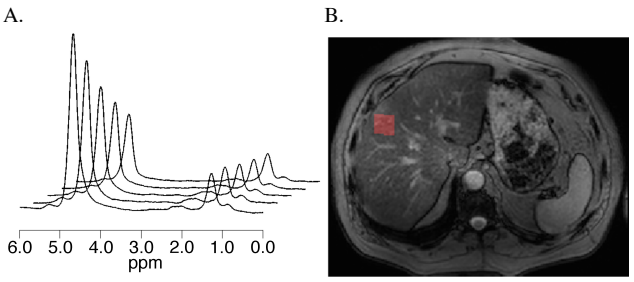

Figure 1. (A) Typical ^{1}H MR spectrum of liver in type 2 diabetes patient. **(B)** Co-localized MRI-PDFF measurement.

Table 1. ROI Sampling methods	Mean ± SD	*ICC* [a]	T-test[b] *p-value*
Mean liver fat fraction	13.8 ± 7.5	—	—
Single ROI			
Yoshimitsu, JMRI 2008	15.0 ± 9.1	0.947	0.028
O'Regan, Radiology 2008	14.5 ± 8.8	0.966	n.s.
Yokoo, Radiology 2009	15.0 ± 8.9	0.948	0.025
Guiu, Radiology 2009	14.2 ± 8.6	0.881	n.s.
Reeder, JMRI 2009	14.2 ± 8.4	0.970	n.s.
Lee, JMRI 2011	14.7 ± 8.8	0.961	n.s.
Meisamy, Radiology 2011	14.3 ± 8.3	0.975	n.s.
Yokoo, Radiology 2011	14.3 ± 8.3	0.963	n.s.
Two or more ROIs			
Qayyum, Radiology 2005	14.5 ± 8.5	0.981	0.032
Lee, J of Hepatology 2010	14.9 ± 8.7	0.970	0.009
Kang, JMRI 2011	14.6 ± 8.7	0.975	n.s.
Kang, Investigative Radiology 2012	14.5 ± 8.5	0.980	n.s.
Permutt, Alim Pharm Ther 2012	13.9 ± 8.3	0.982	n.s.
Tang, Radiology 2013	13.9 ± 8.4	0.983	n.s.

Note: [a] Intraclass correlation coefficient between mean liver fat fraction and ROI sampling methods. [b] Two-tailed paired T-tests between mean liver fat fraction and ROI sampling methods.

Conclusion: Numerous ROI sampling methods have been reported in the MRI-based fat quantification literature. In a population of type 2 diabetes patients, this study confirmed the high level of agreement between MRS and MRI-PDFF. This study also revealed small differences in mean fat fraction obtained by whole liver segmentation and some ROI sampling methods. Significant differences in fat fraction were observed for some ROI sampling methods that only included the right lobe or predominantly included the right lobe. These results suggest that liver MRI-PDFF estimation should include ROI sampling from all liver segments, including those of the left lobe, to reflect the mean liver fat fraction.

References: 1) Reeder SB, Cruite I, Hamilton G, Sirlin CB. *J Magn Reson Imaging*. 2011;34(4):729-49. 2) Yokoo T, Shiehmorteza M, Hamilton G, et al. *Radiology*. 2011;258(3):749-59. 3) NCT01399645 on http://clinicaltrials.gov/.