Multi-Peak Spectral Modeling of Fat is Necessary for both Accurate Liver Fat and Iron Quantification: a Biopsy-MRI Correlation Study

Jens-Peter Kühn[1,2], Diego Hernando[1], Norbert Hosten[2], and Scott B Reeder[1,3]

[1]*Department of Diagnostic Radiology, Wisconsin Institutes for Medical Research USA, Madison, Wisconsin, United States,* [2]*Department of Diagnostic Radiology, University Greifswald, Greifswald, MV, Germany,* [3]*Medical Physics, Biomedical Engineering and Medicine, Wisconsin Institutes for Medical Research USA, Madison, Wisconsin, United States*

Introduction: Non-invasive chemical shift based multi-echo water-fat separation MR techniques, when corrected for confounding factors (T2* and T1 relaxation effects, noise bias, and spectral modeling of fat) are capable of measuring the proton density fat fraction (FF) as a biomarker of hepatic steatosis **(1-3)**. As part of the correction for T2* relaxation effects, an R2* map (R2*=1/T2*) is typically generated. In addition to being necessary for accurate fat quantification, the R2* map itself is of clinical interest, as R2* is an established biomarker of hepatic iron overload. However, it is unknown whether modeling of the spectral complexity of the fat signal is necessary for accurate iron quantification. The purpose of this study was to investigate the impact of the multi-peak spectral modeling of fat on the estimation of hepatic R2* values as a measure of hepatic iron overload, as well as its impact on the quantification of hepatic FF, using biopsy as reference standard.

Methods: A total of 95 patients (50 men, 45 women aged 57.2 ± 14.1 years) underwent a clinically indicated non-targeted liver biopsy, resulting in 97 liver core samples. The Couinaud segment, from which the image-guided biopsy was obtained, was recorded. Steatosis grade was evaluated by two board-certified pathologists using the method of Brunt et al **(1)** (percentage of hepatocytes containing intracellular fat droplets) on a scale of 0-100% in 5% steps and further classified: grade 0: < 5% cells affected; grade 1: 5-33% of cells affected; grade 2: 33-66% of cells affected; and grade 3: >66% of cells affected. Hepatic iron content was subjectively graded using Perl's Prussian blue staining by evaluating the relative number of hepatocytes containing iron granules as follows: grade 0: no iron 0-5%, grade 1: mild; 5-20%, grade 2: moderate; 21-50%, and grade 3: high iron content; >50%. Patients underwent abdominal MR imaging 24-72 hours after liver biopsy using a 1.5T MRI system (Magnetom Avanto, Siemens Healthcare). Multi-echo 3D gradient echo data for water and fat separation (TR/TE1/TE2/T3, FA: 11/2.4/4.8/9.6ms, 10º) was acquired in a single breath-hold over 19 seconds. Datasets were reconstructed offline and corrected for T1 and T2* effects (**4, 5**). FF and R2* maps were reconstructed with and without multi-peak spectral modeling of fat **(6).** One reader (radiologist with >5 years experience) reviewed the mean fat-fractions and R2* values according to single-peak and multi-peak reconstruction from operator-defined regions of interest (ROIs) in the biopsy segment location. R2* measurements were compared with the steatosis grade, and the histopathologically determined iron content. Additionally, FF maps with and without multi-peak fat modeling were compared with histologically observed steatosis grade.

Results: Mean steatosis grade from biopsy was 15.3% (range 0-95%). Hepatic iron was observed on biopsy in 26 cases (26.8%), with 15 mild, 6 moderate, and 5 high iron. In the 71 samples without iron (as confirmed by biopsy), a strong dependence (increase) in the apparent R2* was observed with increasing steatosis grade when multi-peak modeling of fat was not used (p=0.001) **(Figure 1a)**. When multi-peak modeling was used, there were no differences in the apparent R2* for different steatosis grading (p=0.645), and R2* values agreed closely with those reported in the literature **(Figure 1b)**. For all 97 samples, R2* values measured using both single-peak reconstruction and multi-peak reconstruction showed significant increases with increases in histological iron grade (p=0.001) **(Figure 2a-b)**. The sensitivity, specificity and accuracy of R2* mapping to distinguish normal (grade 0) from abnormal iron grades (grades 1-3) were 15%, 100% and 76%, respectively, for single-peak using a threshold of 93.5s^{-1} and 77%, 100%, and 93% for multi-peak using a threshold of 45.4s^{-1}. Good correlation between FF and steatosis grade (**Figure 3a**) was observed (Spearman`s correlation coefficient r_S=0.85) both without and with spectral modeling. However, a comparison of FFs using single-peak and multi-peak models demonstrates disagreement between the two methods (slope: 0.89±0.001, p≤0.001; intercept: -0.03±0.018, p=0.104) **(Figure 3b)**. The sensitivity, specificity and accuracy of MRI to distinguish normal (grade 0) from abnormal steatosis (grades 1-3) were 86%, 100% and 93%, respectively, using a threshold of 4.5% for single-peak and 5.1% for multi-peak modeling of fat.

Conclusions: In the presence of fat, accurate measurement of R2* values requires multi-peak spectral modeling of fat. Errors in R2* estimation are clinically significant and would lead to misdiagnosis of iron overload when fat is present. In patients with liver fat, the fat-fraction is systematically underestimated using the single-peak model compared to the multi-peak fat model. Accounting for the spectral complexity of the fat signal removes both errors in R2* estimation and the underestimation of fat-fraction and is necessary for accurate quantification of both liver fat and iron.

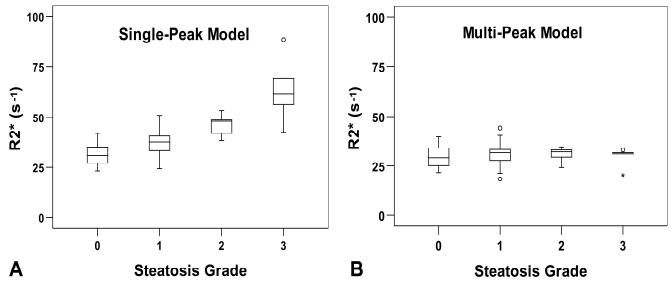

Figure 1: Apparent R2* measured in 71 patients with no iron overload. **A)** Single-peak model shows a clear increase of R2* with increasing steatosis grade (p≤0.001), **B)** Using multi-peak modeling no differences in the R2* values are observed (p=0.645). Without multi-peak spectral modeling of fat (A), the apparent increase in R2* at high steatosis grades could lead to an inaccurate diagnosis of iron overload.

References:

1-Yokoo T et al. Radiology 2009; **2**-Yokoo T et al. Radiology 2011; **3**-Meisamy S et al. Radiology 2011; **4**-Brunt EM et al. Am J Gastroenterol 1999; **5**-Hines CD et al. JMRI 2011; **6**-Yu H et al. JMRI 2007, **7**-Yu H et al. MRM 2008

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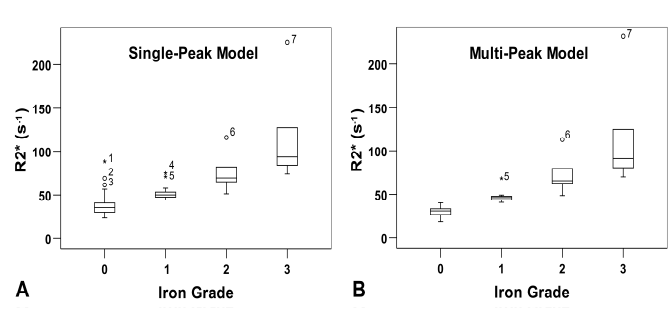

Figure 2: Apparent R2* measured in all 97 biopsy samples compared to histological iron grade, for single-peak modeling of fat **(A)** and multi-peak modeling of fat **(B)**. There are several outlier cases when single-peak modeling of fat is used (case with large liver content 1-4).

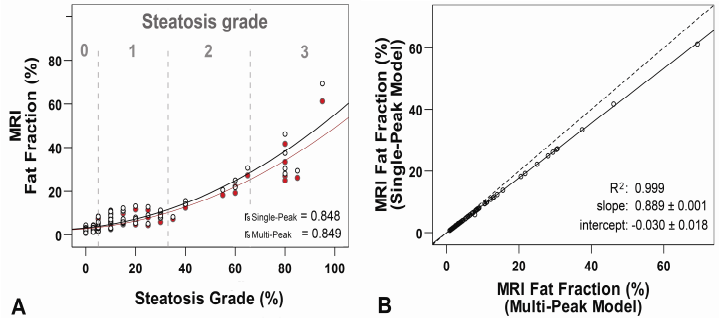

Figure 3: A) Fat-fractions from single- (red circles) and multi-peak modeling (black circles) show excellent correlation compared to steatosis grading from biopsy. **B)** Comparision of fat-fraction from single- and multi-peak modeling shows disagreement between methods, indicating that at least one method is incorrect.