Proton density fat fraction is a highly accurate biomarker of hepatic steatosis in adolescent girls and young women

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Target audience: Clinical radiologists and physicians who provide care to children, including specialists in pediatric endocrinology, gastroenterology and hepatology, and primary care providers in pediatrics and family medicine.

Purpose: The prevalence of non-alcoholic fatty liver disease (NAFLD) in children ranges from 1-10% worldwide and 28% to 38% in overweight children.[1] In fact, NAFLD is anticipated to be the leading cause of liver cirrhosis, failure, and transplant in the future - surpassing alcoholic liver disease, viral hepatitis and liver cancer.[2] Therefore, early identification of NAFLD is important for intervention and prevention of progression. Traditional methods of detecting fatty liver, such as ultrasound or serum aminotransferases, miss early changes. A rapid, clinically relevant, non-invasive method for early detection and staging of NAFLD is urgently needed.[3] The purpose of this work was to evaluate the accuracy of a novel quantitative MRI technique to quantify hepatic steatosis in adolescents.

Methods: ***Subjects:*** This is a cross-sectional study involving 132 females with BMI Z-scores ranging from -2.20 to 2.71 (mean 1.07 ± 1.12), aged 11 to 21 years (mean 13.30 ± 2.01), 27% Hispanic, 73% Non-Hispanic; 64% Caucasian, 31% African American and 5% Asian. Fifty-five percent of subjects were overweight or obese (BMI > 85%). Subjects were recruited through a local middle school and pediatric clinics.

Anthropometric and Laboratory Measures: Blood samples were collected within 1 month of imaging for assays including glucose, insulin, total and HDL cholesterol, and ALT after an overnight fast. All labs were performed in the same laboratory. Anthropometric measurements included height, weight, and waist circumference (WC). Homeostasis model of assessment- insulin resistance (HOMA-IR) was calculated as [fasting glucose (mg/dL) × fasting insulin (μU/ml)/405].

Imaging: Imaging was performed on a clinical 3T scanner (MR750, GE Healthcare, Waukesha, WI) using an investigational version of a chemical shift encoded water-fat separation method (IDEAL IQ) and a 32-channel phased array body coil. Single voxel STEAM spectroscopy and fat-water separation over the liver were acquired[4]. First, single voxel STEAM without water suppression was acquired in the posterior right lobe using the following parameters: TE = 10, 15, 20, 25, 30 ms acquired in a single TR of 3800ms, 2x2x2cm voxel, 1 signal average, 2048 points, and a spectral width of 5000, all acquired in a breath-hold of 23 seconds. Next, IDEAL IQ images were acquired over the entire liver using the following parameters: FOV = 44x40cm, first TE/TR = 1.2/8.6ms, echo spacing = 2.0ms, echo train length = 6 (2 shots of 3 echoes), BW = ±111kHz, flip = 3° to minimize T1 bias, 8mm slices, 28 slices, and 256x160 matrix. 2D parallel imaging (ARC) with R=2.86 was used to reduce imaging time to a 23 second breath-hold. An on-line reconstruction algorithm was used to perform T2* correction, spectral modeling and eddy current correction to create quantitative proton density fat-fraction (PDFF) maps over the entire liver. Fat-fraction measurements were made from PDFF maps determined by averaging PDFF value from regions of interested placed in the 9 Couinaud segments of the liver[5].. Hepatic Steatosis (HS) was defined as MRS-PDFF > 5.6%[6].

Statistics: Associations between fat fraction and other outcomes were examined using Spearman rank correlation analysis. Correlations were adjusted by BMI Z-score and age using nonparametric Spearman's analysis. Hepatic steatosis was identified by MRI-PDFF and MRS-PDFF and compared using a Kappa Index. A two-sided p-value of <0.05 was regarded as significant.

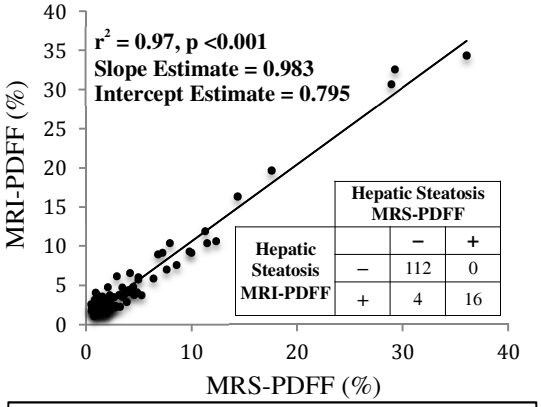

Figure 1: Quantitative MRI methods are equivalent to MRS for measuring hepatic fat fraction and identifying HS (PDFF > 5.6%). Sensitivity=100%, Specificity=97%, Kappa index=0.87 (SE 0.063, CI 0.749-0.994)

Table 1: All Study Subjects (n=132)

	r	p
BMI	**0.46**	**<0.001**
WC	**0.46**	**<0.001**
ALT	**0.25**	**0.004**
HOMA-IR	**0.41**	**<0.001**
HDL	**-0.30**	**<0.001**
TC	-0.60	NS

Table 2: Overweight and Obese Subjects (n=74)

	r	p
BMI	0.23	NS
WC	**0.26**	**0.03**
ALT	**0.41**	**<0.001**
HOMA-IR	**0.47**	**<0.001**
HDL	**-0.25**	**0.03**
TC	0.16	NS

Table 3: Subjects with Hepatic Steatosis (n=20)

	r	p
BMI	0.39	NS
WC	0.3	NS
ALT	**0.81**	**<0.001**
HOMA-IR	**0.75**	**<0.001**
HDL	-0.4	NS
TC	0.19	NS

Tables 1, 2 & 3: Spearman rank correlation (r) with liver PDFF shows association with biomarkers of metabolic disease. Strong correlation of ALT with PDFF in HS subjects suggests hepatocellular damage prior elevation of ALT beyond the accepted normal range.

Results: Figure 1 demonstrates excellent agreement between PDFF measured with MRS and MRI and a high degree of reliability between MRI and MRS for determining hepatic steatosis (PDFF > 5.6%). In overweight and obese subjects 21% had HS by MRS and 25% by MRI. Tables 1-3 show correlations of PDFF with metabolic makers. Mean ALT was 25.91± 23.39. 129 (98%) of subjects had ALTs within the normal range (≤60 U/L). When serum and anthropomorphic biomarkers were adjusted for age and BMI Z-score they did not correlate significantly with MRS-PDFF or MRI-PDFF.

Discussion: Quantitative MRI is a feasible and accurate measure of hepatic triglyceride content in a diverse group of adolescents and young women. It is highly reliable for identifying early hepatic steatosis and correlates with metabolic risk factors (insulin resistance, low HDL). In contrast, BMI was not predictive of HS in the overweight girls. The strong correlation of ALT with PDFF in HS subjects is evidence of hepatocellular injury[3]; however 18 of these subjects had an ALT within the accepted normal range and would be missed by current pediatric HS screening guidelines. Thus, ALT is not a sensitive screening tool for early HS. The ability to use PDFF as an accurate biomarker for hepatic steatosis offers a strong advantage over traditional measures in identifying NAFLD risk and following the effectiveness of interventions for NAFLD in obese adolescents. Future work will include the use of MR elastography to measure liver stiffness and identify progression of fatty liver disease in children and adolescents.

Conclusion: Liver PDFF measured with quantitative MRI is a rapid, clinically relevant, non-invasive method for early detection and quantitative staging of hepatic steatosis in adolescent girls and young women. This novel quantitative MRI technique holds promise as a method for early identification of NAFLD, thus allowing intervention prior to development of irreversible hepatic injury and progression of metabolic disease.

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