Simultaneous Measurement of Hepatic Lipid and Iron with High-Speed T2-Corrected Single-Voxel Spectroscopy (HISTO): Analysis of Water-Lipid Compartments

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Introduction: Fatty liver disease is common, while superior non-invasive measures of hepatic lipid (HL) are an important clinical unmet need. Single-voxel magnetic resonance spectroscopy (MRS) is widely viewed as an accurate measurement of HL fraction. However, broad clinical use has been limited due to acquisition speed and sensitivity to susceptibility effects, such as from hepatic iron. High speed T2 corrected (HISTO) MRS has been introduced for T2-corrected hepatic lipid measurements within a single breath hold acquisition [1]. In addition to corrected HL measurement, HISTO may concurrently quantify intracellular iron content using the separately measured R2 (1/T2) of water and lipid. Since multi-echo imaging methods provide measurement of bulk R2 or R2*, iron quantification may be compromised in the presence of variable lipid content. Spectroscopy allows separation of water and lipid peaks for individual R2 measurement, allowing insight into compartmental dependence of iron susceptibility effects.

Purpose: To determine the role of physiological range liver iron content on the separateT2 relaxation rate of water and lipid using the HISTO MRS technique in phantoms and in a human fatty liver model with the objective of improving our techniques for accurate HL and iron measurements.

Methods: This investigation was IRB approved and HIPPA compliant. Imaging was performed on a 1.5T Siemens Avanto system with phased array body coils. ***Phantoms-*** Nine 200ml homogenous lipid-iron phantoms were created with varying lipid (5, 15 and 30% vegetable oil by volume) and increasing molar amounts of iron (0, 0.1, 0.3mM Ferridex, Berlex, NJ) in solution. Water motion and T2 was constrained using 2% agar. Fat was constrained in micelles produced by the addition of lecithin (2% wt/vol) to reproduce the intracellular morphology seen in fatty liver disease. The HISTO MRS pulse sequence has been described previously [1]. The adjustable TE set was fixed to {12, 24, 36, 48, 72}ms, with TR=3000ms, voxel=3x3x3cm^3, 1024 points, and 1200 Hz bandwidth. The acquisition duration was 15 sec and repeated three times. For comparison, phantom R2* were also measured using fast multi-echo gradient echo imaging, with TE=4.8 and 9.5ms, TR=50ms, and flip=5 degrees. ***Patients-*** 3 patients with known hepatic steatosis underwent HISTO MRS before and following two administrations (t=0, 30min) of 0.5ml Feridex diluted in 50ml of 5% dextrose. Each administration was 25 ml over 5mins, and acquisition commenced +15mins following infusion. HISTO data was exported off-line for processing with Matlab (Mathworks, Natick, MA), where spectra at each TE were analyzed automatically by determining peak area over a user-defined frequency range (water peak: 4.6ppm; lipid peak: 1.3, 2.0ppm). The integrated spectrum signals of water and lipid at each TE allowed analysis of exponential T2 decay, whereby the equilibrium signal (M_0) and the relaxation rate (R2=1/T2) were determined by least-squares approximation. Using M_0 for water and lipid, the T2-corrected lipid content was calculated from: %lipid = M_{0lipid} / (M_{0lipid} + M_{0water}). Iron content was compared to measures of water and lipid R2 using linear regression.

Results: ***Phantoms-*** Using the measured R2 of water and lipid, HISTO phantom lipid% was measured to be 4.7% ± 0.3, 15.3% ± 1.5, and 29.9% ± 4.6 across the three iron levels. T2 curve fitting in all phantom experiments using HISTO exceeded rsq= 0.95. Figure 1 depicts the relationship between measured R2 and iron content for both water and lipid spectra, along with corresponding R2* measures obtained from gradient echo imaging. As shown with HISTO, there is a strong positive linear relationship with R2-water (y=136.9x+14.7), which is not evident for R2-lipid (y=7.4x+19.7) (p<0.0001 for iron > 0mM). Conversely, R2* reveals an overall positive linear trend with iron content (y=164.8x+33.4), but dependence on lipid content is evident, suggesting combined water-lipid susceptibility effects on bulk R2*, which may cause erroneous iron estimations.

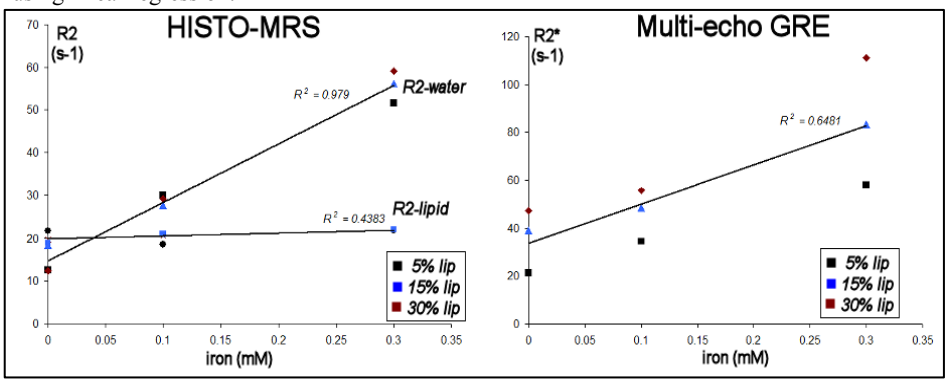

Table 1. In vivo HISTO measures of HL% and R2 following Feridex

	Pt1			Pt2			Pt3		
	HL%	R2wat	R2lip	HL%	R2wat	R2lip	HL%	R2wat	R2lip
Pre	11.6	26.3	19.1	14.1	27.6	21.6	26.7	30.8	17.1
Post1*	11.3	34.3	22.0	13.8	30.6	22.8	28.3	37.0	18.8
Post2*	12.5	43.9	21.3	14.4	38.9	18.5	28.4	40.0	18.4

*Mean values shown, SD of 3measures <10%; *Post1: +15mins 1st inj; Post2: +15mins 2nd inj*

Patients- Results from three patients are presented in Table 1. A similar trend exists in vivo, as shown in phantoms; liver R2-water exhibits increased values with Feridex dose for each subject, while R2-lipid remains constant across all measures. Additionally, HISTO T2-correction yielded stable HL% measurements, insensitive to Feridex-induced susceptibility changes.

Conclusions: **1)** Accurate HL% measurement requires correction for susceptibility effects; **2)** HISTO-MRS provides accurate corrected lipid% in phantoms, corrects for liver iron effects in patients, and can simultaneously provide a measure of the iron content within the water fraction; **3)** Susceptibility effects of iron are mediated primarily on the water fraction within phantoms and in patient livers; **4)** While uncorrected susceptibility effects render measurement of HL% inaccurate in imaging methods, varying lipid content may also obscure iron measures due to integrated R2* measures of the lipid averaged with water – a phenomenon obviated by using spectroscopy to separately evaluate R2-water and R2-lipid.

References: [1] Pineda N, et al. Radiology 2009: 252(2):568-76