Relationship between Proton-Density Fat-Fraction and True Fat Concentration for In Vivo Fat Quantification with Magnetic Resonance Imaging

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Introduction: Proton density fat-fraction (PDFF) is emerging as a useful metric for fat tissue quantification using MRI. After addressing known confounding factors (T2* decay, T1 bias, spectral complexity of fat, eddy currents, noise bias)[1-5], PDFF provides a platform- and protocol-independent metric of tissue fat concentration, and is a fundamental property of tissue, making it a useful biomarker of fat content. PDFF is the ratio of unconfounded signal from mobile fat protons (primarily triglycerides) normalized by the total unconfounded signal from fat protons and mobile water protons. Unfortunately, gold standard reference assays that measure triglyceride content do not account for NMR invisible species, and therefore may not correspond directly with PDFF measured with MRI. The purpose of this work is to expand on past work[6,7] that describes the relationship between true fat concentration and PDFF measured with MRI, and to validate this relationship in a fat-water-deuterium oxide phantom.

Theory and Methods: In this work, we assume that all confounding factors have been addressed and that MRI has accurately measured the PDFF. In this case, the PDFF of triglycerides in tissue is:

$$\eta_{PDFF} = \frac{m_f}{m_f + m_w} \quad [1]$$

where m_f and m_w are the masses of fat and water, respectively. Importantly, it has been previously shown that the proton densities of protons in triglycerides and water are effectively identical[7], and therefore mass and volume are interchangeable in Eq. 1. The true tissue fat-fraction measured with chemical extraction assays can be written:

$$\eta_{Tissue} = \frac{m_f}{m_f + m_w + m_o} \quad [2]$$

where m_o is the mass of "other", NMR invisible material. Comparison of Eqs. 1 and 2 show important similarities and differences. If the NMR invisible component is non-trivial then PDFF will overestimate the true concentration of fat. For example, in normal liver, the quantity of free water relative to total tissue is approximately 71%[6]. If this value is known, a conversion between η_{Tissue} and η_{PDFF} can be constructed. Specifically:

$$\eta_{Tissue} = \frac{k\eta_{PDFF}}{1 - \eta_{PDFF}(1-k)} \quad [3] \quad \text{and} \quad \eta_{PDFF} = \frac{\eta_{Tissue}}{\eta_{Tissue} - (1-k)\eta_{Tissue}} \quad [4] \quad \text{where} \quad k = \frac{m_w}{m_o + m_w} \quad [5]$$

is the fraction of free water, relative to NMR invisible material. Using Eqs. 3 and 4, direct conversion between true fat-fraction and PDFF can be determined, if the fraction of water relative to NMR invisible material (k) is known.

Phantom: A fat-water-deuterium oxide phantom was constructed to validate Eqs. 3 and 4. Three sets of eight 20ml vials were constructed, each with varying concentration of peanut oil: 0, 2.5, 5, 10, 20, 30, 40, and 50% using previously reported methods[8,9]. For each set of vials, the "water" component was altered by using different concentrations of deuterium oxide (D_2O, Fisher Scientific) mixed in distilled water. Deuterium is NMR invisible on clinical MRI scanners and is a convenient way to create known fractions of NMR invisible material. Water and D_2O were mixed in the following volume fractions: 1) 75% H_2O: 25% D_2O (k=75%) ; 2) 50% H_2O: 50% D_2O (k=50%) ; 3) 25% H_2O: 75% D_2O (k=25%).

Imaging: Imaging was performed on a 1.5T clinical scanner (Signa HDxt, GE Healthcare, Waukesha, WI) using a quadrature head coil and an investigational version of the multi-echo IDEAL (3D-IDEAL-SPGR) sequence. Imaging parameters included: FOV=35cm, 256x256 matrix, 1 average, 24 slices, slice=8mm, BW=±141kHz. TR=45ms with a 5° flip angle to avoid T_1 related bias[2,3]. Scan time was 5:23min. 6 echoes / TR were acquired using a flyback readout with TE_{min}=1.3ms, ΔTE=2.1ms. PDFF images were reconstructed with an on-line reconstruction algorithm that uses T_2* correction[1,2], spectral modeling of fat[2,4], and a hybrid magnitude reconstruction algorithm to avoid the effects of eddy currents[5]. PDFF was measured and subsequently corrected using Eq. 3, and results should correspond to the true tissue fat-fraction.

Results: Figure 1 plots PDFF before and after correction for the presence of D_2O. As the concentration of D_2O increases, large increases in the PDFF are observed, because the concentration of NMR visible protons from water is reduced. Knowing the relative concentrations of water and D_2O, allows the use of Eq. 3 to correct PDFF to estimate the true fat-fraction. Excellent agreement and correlation was observed in all cases after correction, with r^2>0.995 and slope and intercept statistically equivalent to 1.0 and 0.0, respectively in all three cases.

Discussion: PDFF measured with MRI and tissue triglyceride concentration measured through lipid extraction are fundamentally different metrics of tissue fat content. Understanding the correspondence between these metrics is important when performing validation studies that compare PDFF to extracted tissue triglyceride concentration. Further, if the relative amount of NMR invisible material is known, PDFF can be corrected to generate an equivalent value to tissue triglyceride concentration. Finally, the use of D_2O may be a useful way to increase the PDFF beyond 50%, which previously has been challenging due to the difficulty of creating a stable complex of water, fat and agar at high fat concentrations.

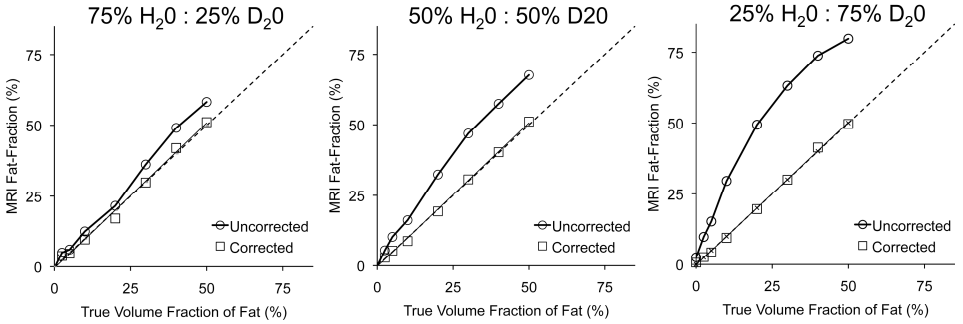

Figure 1: *PDFF fat-fraction measured with MRI vs. true volume fraction of fat, at increasing concentrations of* D_2O *(25%, 50%, 75%) in the "water" component of the fat-water mixture. As the concentration of* D_2O *increases, the apparent PDFF increases deviates further from unity, because the signal from water protons decreases. With these known concentrations and Eq. 3, the PDFF can be corrected to correspond to the true tissue concentration. Excellent correlation (r^2>0.995) and agreement (slope and intercept statistically equivalent to 1.0 and 0.0, respectively) was seen in all cases. Note also, that very high PDFF values can be achieved using* D_2O *at high concentrations.*

References: **1.** Yu et al, JMRI, 2007 60(1): 198-209, **2.** Bydder et al MRI, 2008 26(3):347-59, **3.** Liu et al, MRM, 2007 58(2):354-64, **4.** Yu et al, MRM 2008 60(5):1122-34, **5.** Yu et al ISMRM 2009 pg. 461, **6.** Longo et al JMRI, 2005 5:281-5, **7.** Reeder et al ISMRM 2009 pg. 211, **8.** Bernard et al, JMRI 2008, 27(1):192-7. **9**. Hines et al, JMRI, 2009 30(5):1215-22.

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