Chemical shift-based imaging to measure fat fractions in dystrophic skeletal muscle

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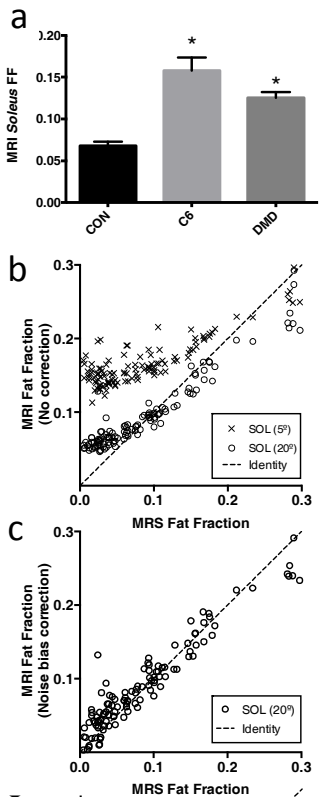
Introduction. Muscular dystrophies (MD) are a diverse set of muscle diseases characterized by progressive loss of muscle function, and early death. Currently, there is no cure for MD, but recent preclinical and early clinical trials have indicated that new therapies offer great promise. This exacerbates the need for reliable measures that can capture the disease progression and evaluate treatment efficacy. MR has great potential in providing objective and quantitative biomarkers for therapeutic intervention in MD. Localized ^{1}H-MRS can be used to measure muscle composition and relaxation properties of individual metabolites, but with low spatial resolution. Chemical shift-based water-fat separation [1] offers an alternative method, providing high resolution mapping of muscle fat content with excellent coverage, an important feature given the known heterogeneity in MD. Different models have been proposed to take into account the spectral complexity of fat and other confounding factors such as the difference in T_1 and T_2* for fat and muscle [2], and the effect of low signal to noise. This may be of particular importance in MD, as the pathophysiological changes might alter tissue relaxation properties. The goal of this work was to evaluate the combined influence of the model used for fat spectral decomposition, T_1 variations, and signal to noise on the calculated fat fraction (FF) in Duchenne muscular dystrophy (DMD), congenital muscular dystrophy (C6), and control muscles, using localized ^{1}H-MRS as a validation measure.



Methods. MR scans of the lower leg muscles were acquired in Control (n=18), C6 (n=17), and DMD subjects (n=63) on repeated visits using a 3T Philips Achieva system (Philips Medical Systems, R2.6.3-3.2) with an 8-channel receive only (upper leg) or transmit 16-channel receive knee volume coil (lower leg) (Invivo corp). ***Chemical shift-based imaging:*** Unipolar GRE images were acquired at 3 different echo times (TE=8.06, 9.21, 10.36 ms) over 16-25 axial slices (TR =430 ms, 5º or 20º flip angle). ***Relaxivity and muscle composition:*** single voxel ^{1}H-MRS data were acquired from the soleus (SOL; Fig. 1) using STEAM (TR 9s; 16 echoes: 10-288 ms, 6 inversion times: 100-9000 ms). ***Data Analysis***. FF was calculated as the phase corrected signal from the lipid region (0.5-1.9ppm) normalized to the (H_2O+lipid) signal, and individually corrected for T_1 and T_2 saturation. Water, fat and field maps were jointly estimated using a graph cut algorithm [3], applied to a single (1P) or multi peak (6P) [4] fat signal model and corrected for T_1 saturation, and noise bias [5]. FF was then assessed from the pixels corresponding to the spectroscopy voxel in the *soleus* and *vastus lateralis.*

Results. *Soleus* FF measured by chemical shift based MRI ranged from 4.8 to 58.6 % in DMD, 6.3 to 24.9 % in C6, and 4.6 to 13.6 % in controls, and the *vastus lateralis* muscle was more involved than the soleus in both MD (Fig. a). Muscle ^1H_2O T_1 values were 1393 ± 28 ms and 1457 ± 31 ms and 1405 ± 29 ms in control, DMD and C6 respectively, leading to similar correction factors applied to the estimated water signal in FF computation (1.137, 1.146, 1.139, respectively). On the other hand, muscle ^1H_2O T_2 was significantly elevated ($p<0.001$) in all MD muscles (DMD=31.4±1.2 ms; CMD 29.8±1.6 ms) compared to control (28.2±0.8 ms). Figure b shows the relationship between FF determined by MRI using the 6P model and FF measured by ^{1}H-MRS. We found that the 6P model algorithm resulted in a relationship closer to identity between MRI and MRS results. However, the relationship between FF determined by MRI using the 6P model and FF measured by MRS showed a deviation from linearity at low FF (below 0.2) (b), which was even more pronounced at lower signal-to-noise (5º angle). Noise bias correction successfully improved the agreement between MRI and ^{1}H-MRS results at low FF for the 20º flip angle acquisitions (c), (R^2 = 0.93). However a larger variability was observed at very low SNR (5º flip angle).

Conclusion. This study investigated the use of chemical shift-based imaging in dystrophic muscles in a large cohort of patients, and validated the quantitative measure of FF by direct comparison with co-registered ^{1}H-MRS. While T_1 bias was negligible in our conditions of acquisition, best agreement between MRI and MRS was obtained with a combination of a 6-peak spectral model and noise bias correction. Our results indicated that MRI performed over a large range of FF values, which makes chemical-shift based MRI a robust tool for the longitudinal assessment of MD with progressive fatty infiltration, and has the potential to be used as a complementary quantitative measure in clinical trials.

References: [1] Dixon WT, Radiology, 1984; [2] Yu et al., JMRI, 2007; [3] Hernando D, MRM, 2010; [4] Hamilton, MRM, 2001; [5] Miller, MRI, 1993. **Acknowledgment:** NIAMS/NINDS R01AR056973, NIH U54AR052646, Parent Project Muscular Dystrophy. The authors would like to thank Diego Hernando for providing the Matlab code for the calculation of water, fat and field maps, and Wei Lin for helpful discussions.