Water T$_2$ Values are Elevated in Duchenne Muscular Dystrophy Independent of Fat Infiltration

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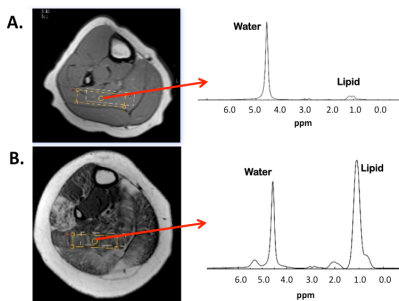[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, United States, [2]Department of Physical Therapy, University of Florida, Gainesville, FL, United States, [3]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [4]Department of Physiology and Functional Genomics, University of Florida, Gainesville, FL, United States, [5]Pediatrics, University of Florida, Gainesville, FL, United States, [6]Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, United States, [7]Shriners Hospital, Portland, OR, United States, [8]Department of Physiology, University of Pennsylvania, Philadelphia, PA, United States

Introduction: Duchenne muscular dystrophy (DMD) is characterized by sarcolemmal fragility, myofiber degeneration, inflammation, increased synthesis and deposition of extracellular matrix proteins and the replacement of contractile tissue with fatty infiltrate and connective tissue.[1] Quantitative transverse relaxography (qT$_2$) of ^{1}H MR signals has shown excellent sensitivity for the detection of muscle pathology associated with DMD[2] and strongly correlates with clinical assessments.[3] Muscle lipid content increases with DMD disease progression[1-4] and is readily quantified using MRS techniques. MRI determined qT$_2$ values are known to increase markedly with DMD disease progression and this behavior may in part or in whole be due to increased lipid contribution to the observed ^{1}H MRI signal. The purpose of this study was to investigate the influence of muscle lipid content on MRI qT$_2$ values and independently assess the behavior of MRS determined [1]H$_2$O qT$_2$ values in DMD as a function of muscle lipid content.

Methods: Data were acquired from 30 DMD boys (ages 5-13 y, mean 8.9 y (2.1; SD)) and 8 healthy controls (HC; 9.7 y (2.1)) on 3T MRI instruments at three institutions. Axial images of the lower leg were collected using a non-fat suppressed multi-slice Carr Purcell Meiboom Gill (CPMG) sequence with in-plane resolution (0.75 mm)^2, 7 mm slices, 3.5 mm gap; 16 echoes (20-320 ms; evenly spaced) and TR3000. ^{1}H MRS data were acquired to estimate [1]H$_2$O T$_2$ without contamination from lipid signal and to determine muscle composition using a non-water suppressed STEAM single voxel approach. The qT$_2$ MRS data were collected with 16 TE values non-linearly spaced from 11-288 ms with TR3000/NA4, and the composition MRS data with TE108/TR3000/NA64.


Figure 1. ^{1}H MRS of soleus. Single voxel spectroscopy data were collected from the soleus to quantify lipid content and to estimate [1]H$_2$O T$_2$ values without contamination from lipid. The images at the left show axial T$_2$-w MRI from a healthy control (**A**) and DMD (**B**) lower leg with the MRS voxel indicated by white-dotted rectangles. The acquired spectra are shown at the right with [1]H$_2$O and lipid peaks indicated. The increased lipid content and its spatial distribution is evident in the T$_2$-w MRI of (B) and readily quantified by MRS.

MRI and MRS T$_2$ values were determined using a single exponential function. The lipid fraction was calculated by integrating the phase corrected signal from the lipid region (0.5-1.9 ppm) and dividing by the [1]H$_2$O and lipid signals. Mean values and standard deviations are presented. P values were determined from t-tests and corrected for multiple comparisons.

Results and Discussion: Figure 1 shows a T$_2$-w axial slice through the soleus with a representative non-water suppressed ^{1}H spectrum. Intra-site reproducibility of all measures was excellent: MRI T$_2$ (covariance 1.7%), MRS T$_2$ (2.3%), and lipid fraction (5.5%). Inter-site agreement also was excellent: MRI T$_2$ (5.5%), MRS T$_2$ (1.4%), and lipid fraction (17.8% - for HC which had small lipid fractions). The group average values for lipid fraction, MRI qT$_2$, and MRS qT$_2$ results are summarized in Table 1. Significant between group differences were found for all measures. [1]H$_2$O T$_2$ values measured from MRS were significantly lower than T$_2$ values determined using non-fat suppressed MRI acquisitions and there was a strong correlation with lipid fraction measured by MRS and MRI T$_2$ (**Figure 2A**). This supports the notion that fat infiltration is largely responsible for increasing MRI T$_2$ values observed with age in DMD boys.[3] However, even in the absence of

Table 1.

	T$_2$ MRI (ms)	[1]H$_2$O T$_2$ MRS (ms)	Lipid Fraction
DMD (n=30)	44.8 (6.0)	31.2 (1.7)	0.40 (0.17)
HC (n=8)	34.0 (2.6)	28.0 (0.6)	0.19 (0.07)
p	0.0041	0.00013	0.024

increased lipid fraction (primarily young DMD boys), soleus [1]H$_2$O T$_2$ values are elevated (**Figure 2B**); perhaps "pattern 2" using the schema of Marden et al.[4] Interestingly, we find a significant negative association between soleus [1]H$_2$O T$_2$ and lipid fraction in DMD (**Figure 2A**), perhaps indicating increased fibrotic changes with advanced disease. Thus, increasing T$_2$ values with DMD progression observed from non-fat suppressed MRI measurements likely reflect increased water early in disease (at low lipid fraction), and increasing contributions from fat signals late in disease. Elevated [1]H$_2$O T$_2$ values early in the disease process likely reflect underlying pathology including inflammation, increased sarcolemmal water permeability, and myofiber degeneration.
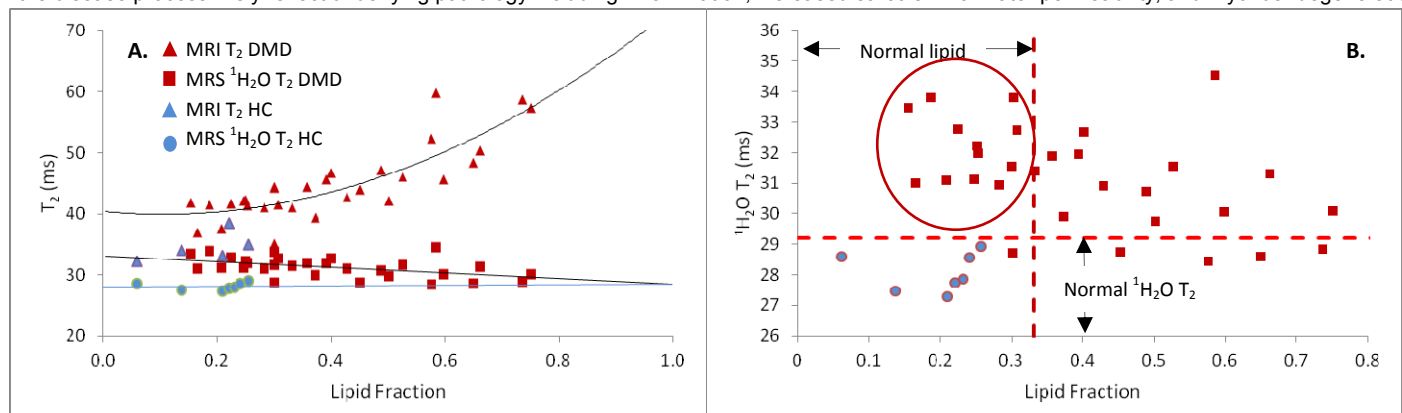
Figure 2. (A) Soleus MRI T$_2$ (non-fat suppressed) in DMD (red triangles) and HC (blue triangles) as function of lipid content determined from ^{1}H MRS. The DMD MRI T$_2$ values show a strong quadratic dependence on muscle lipid (r=0.84; p < 10^{-6}; T$_2$~80 ms at lipid fraction =1). [1]H$_2$O T$_2$ values were determined from MRS and are displayed as a function of lipid fraction for DMD (red squares) and HC (blue circles). DMD [1]H$_2$O T$_2$ values decrease linearly with lipid fraction (r=0.48, p < 0.01). **(B)** This panel focuses on the [1]H$_2$O T$_2$ values with lipid fraction to illustrate that even in the absence of increased lipid, soleus [1]H$_2$O T$_2$ values are elevated strongly in most DMD boys – red squares within red oval. The red dotted lines represent 95% confidence intervals based on the healthy control data.

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