

Soleus Muscle Water T₂ Values in Duchenne Muscular Dystrophy: Associations with Age and Corticosteroid Treatment

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Introduction: Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by a dystrophin gene mutation. DMD is a rare disease occurring almost exclusively in boys with an incidence of approximately 1 in 5000 live male births;¹ in the U.S. about 400 boys are born with DMD each year. The disease is characterized by sarcolemmal fragility, myofiber degeneration, inflammation, increased synthesis and deposition of extracellular matrix proteins and ultimately replacement of contractile tissue with fatty infiltrate and connective tissue.² Currently, there is no cure for DMD, but corticosteroid treatment offers functional improvements including short term increase in muscle strength and a 2-5 year prolongation of independent ambulation.¹ Quantitative transverse relaxography (qT₂) of ¹H MR signals has demonstrated excellent sensitivity for the detection of muscle pathology associated with DMD³ and strongly correlates with clinical assessments.⁴ Such measures may be useful in studies investigating the therapeutic efficacy of promising new treatments. The purpose of this study was to investigate 1) the age-dependence of soleus muscle ¹H₂O T₂ values in healthy controls and DMD boys, and 2) the effect of DMD corticosteroid treatment on soleus muscle ¹H₂O T₂ values.

Methods: Data were acquired from 83 DMD boys (ages 5-13 y, mean 8.7 y (2.1 y; SD)) and 22 healthy controls (9.8 (2.1) y) on 3T MRI instruments at three institutions. T₁-weighted images of the lower leg were collected using 3D gradient echo sequences (TE2.46/TR25/FA20) with and without fat suppression. ¹H MRS data were acquired to estimate ¹H₂O T₂ without contamination from lipid signal using a non-water suppressed STEAM single voxel approach. The qT₂ MRS data were collected with 16 TE values non-linearly spaced from 11-288 ms with TR3000/NA4 (see **Figure 1**) T₂ values were determined using a single exponential function. A subset of boys were selected to investigate the effect of corticosteroid use on ¹H₂O T₂ values. Three age matched subgroups were selected **i**) DMD boys without a history of corticosteroid use (DMD-; n = 16, mean age 7.1 (1.8) y), **ii**) DMD boys on corticosteroids for at least 6 months (DMD+; n=34, mean age 7.1 (1.0) y), and **iii**) healthy control boys (control; n = 9, mean age 8.0 (1.5) y)

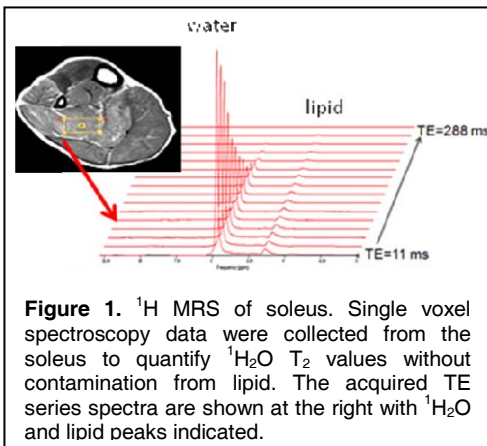


Figure 1. ¹H MRS of soleus. Single voxel spectroscopy data were collected from the soleus to quantify ¹H₂O T₂ values without contamination from lipid. The acquired TE series spectra are shown at the right with ¹H₂O and lipid peaks indicated.

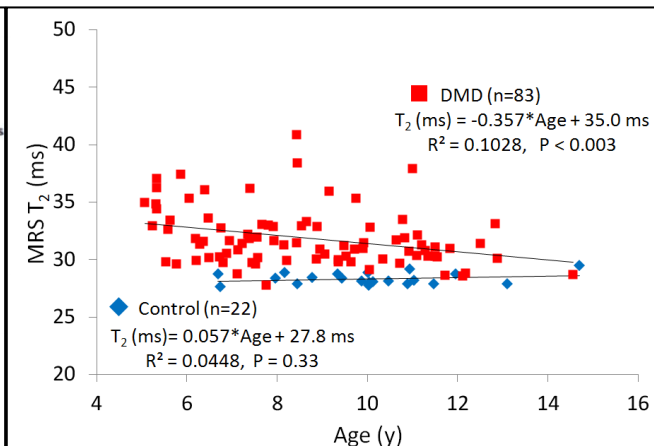


Figure 2. Muscle ¹H₂O T₂ values decrease with age for DMD boys but not healthy controls. Data collected from a cross-sectional analyses of DMD and control boys. Average T₂ values are increased in DMD compared to controls (P < 0.0001).

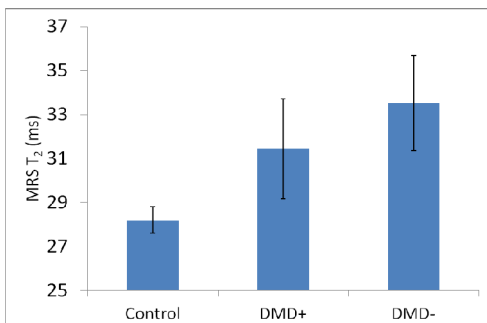


Figure 3. Soleus muscle water proton T₂ values are lower in DMD boys on corticosteroid therapy (DMD+) compared to DMD boys not on corticosteroids (DMD-) [P < 0.004]. Significant differences in muscle water proton T₂ values are observed between both DMD groups and controls.

Results and Discussion: Intra- and inter-site reproducibilities of: MRS ¹H₂O T₂ values both were excellent with less than 3% covariance for each. **Figure 1** shows a T₂-w axial slice through the soleus with a representative non-water suppressed single voxel ¹H MRS TE series. An important advantage of the MRS approach is that it allows measurement of the ¹H₂O signal properties without contamination from lipid – a confound common to MRI studies. The average ¹H₂O T₂ values were significantly different between groups with 28.3 (0.6) ms and 31.9 (2.1) ms for control and DMD boys, respectively. ¹H₂O T₂ values for the control boys did not change with age but decreased significantly with age for the DMD boys (**Figure 2**), Interestingly, the greatest difference in soleus ¹H₂O T₂ values were found for the youngest boys. Elevated ¹H₂O T₂ values early in the disease process likely reflect underlying pathology increased sarcolemmal water permeability, muscle remodeling, including inflammation, and myofiber degeneration.^{2,6} Induction of inflammatory cascades is an early and sustained feature of DMD; Chen and colleagues report marked inflammatory signatures in presymptomatic infants (8-10 months) and symptomatic boys (5-12 y) using mRNA profiling.⁵ Corticosteroids, such as Prednisone and Deflazacort, are effective disease modifying therapies for DMD, and are potent anti-inflammatory drugs. We compared muscle ¹H₂O T₂ values in corticosteroid treated and untreated DMD boys and found a significant reduction in treated boys (see **Figure 3**). This finding suggests that some fraction of the elevated ¹H₂O T₂ value in early DMD is associated with inflammation and that qT₂ measures may provide a sensitive tool to investigate anti-inflammatory treatment response. The age-dependent decrease in soleus muscle ¹H₂O T₂ in the DMD group likely reflects reduced inflammation due to corticosteroid treatment, and increased lipid and fibrosis as disease progresses and contractile tissue is lost.

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