T_2 mapping and Single Voxel ^{1}H-MRS Detect Skeletal Muscle Involvement in Young Boys with Duchenne Muscular Dystrophy

Sean C Forbes[1], Glenn A. Walter[1], William Rooney[2], Dah-Jyuu Wang[3], William Triplett[1], Rebecca Willcocks[1], James Pollaro[2], Barry Byrne[1], Richard Finkel[4], Barry Russman[5], Erika Finanger[5], Gihan Tennekoon[3], Lee Sweeney[6], and Krista Vandenborne[1]

[1]University of Florida, Gainesville, Florida, United States, [2]Oregon Health & Science University, Portland, Oregon, United States, [3]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States, [4]Nemours Children's Hospital, Florida, United States, [5]Shriners Hospital for Children, Portland, Oregon, United States, [6]University of Pennsylvania, Philadelphia, Pennsylvania, United States

Target Audience: This study will benefit those interested in using T_2 mapping or single voxel ^{1}H-MRS to evaluate disease involvement in skeletal muscles of muscular dystrophies or other neuromuscular diseases.

Introduction: Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that is due to a mutation in the dystrophin gene.[1] DMD has an incidence of 1 in 3600-6000 male births and is characterized by progressive muscle deterioration, loss of functional abilities, and reduced life expectancy.[2] Functional deficits in motor performance, such as reduced distance walked in the timed 6 minute walk test, are often not observed in DMD until after age 7, and therefore these functional measures may not be sensitive for detecting disease progression at a young age.[3] In this study, we hypothesized that: 1) MRI-T_2 and ^1H_2O T_2 derived using ^{1}H-MRS will be sensitive to muscle involvement at a young age (5-7 years) consistent with increased inflammation and muscle damage in DMD compared to controls and 2) MRI-T_2 will increase with disease progression in DMD due to progressive lipid infiltration.

Methods: MR data were acquired from 111 boys with DMD (ages 5-14 years; mean 8.7 SD 2.3 years; 5-6.9 years, n=34; 7-8.9 years, n=34; 9-10.9 years, n=21; 11-14 years, n=22) and 26 healthy controls (age 9.6 SD 2.1 years; 5-6.9 years, n=5; 7-8.9 years, n=5; 9-10.9 years, n=10; 11-14 years, n=6) using 3T MR systems at three institutions (University of Florida, Oregon Health & Science University, and Children's Hospital of Philadelphia). The DMD subjects were identified to have exon deletions (62%), duplications (13%), or point mutations (25%) in the dystrophin gene. T_2-weighted multi-slice spin echo (SE) axial images were acquired (0.75 mm^2, 7 mm slices, 3.5 mm gap; 16 TE's, 20-320 ms evenly spaced; TR 3 s) from the lower leg (Fig. 1) and thigh. Single voxel ^{1}H-MRS data were acquired (TE 108 ms; TR 3 s; NA64) for assessment of lipid fraction using stimulated-echo acquisition mode (STEAM) from the soleus (Sol; Fig.1) and vastus lateralis (VL). Finally, ^{1}H spectroscopic relaxometry was performed using STEAM in the Sol and VL (16 TE's non-linearly spaced from 11-288 ms; TR 3 s; NA4). MRI and spectroscopic ^1H_2O T_2 values were derived using a single exponential function. Intramuscular lipid fraction was determined using area integration of the phase corrected spectra from the lipid (0.5-2.75 ppm) and ^1H_2O (4.3-5.10 ppm) regions of the spectrum.

Results and Discussion: MRI-T_2, ^1H_2O T_2, and lipid fraction were greater ($p<0.05$) in DMD compared to controls (Fig. 2). In the youngest age group, DMD were different ($p<0.05$) than controls for the Sol MRI-T_2 (effect size (ES) 4.0), ^1H_2O T_2 (ES 4.3) and lipid fraction (ES 2.7) and VL MRI-T_2 (ES 2.2) and ^1H_2O T_2 (ES 2.1). In the boys with DMD, MRI-T_2 and lipid fraction were greater ($p<0.05$) in the oldest age group (11-14 years) than the youngest age group (5-6.9 years), whereas ^1H_2O T_2 was reduced in the oldest age group compared to the youngest age group (Fig. 2). The reduced ^1H_2O T_2 in older boys with DMD may be due to increased fibrosis or reduced inflammation/damage.[4] The VL presented with larger increases across age group in MRI-T_2 and lipid fraction than the Sol, suggesting that the VL muscle pathology progresses faster than the Sol. No differences were observed in these MR measures among gene mutation type.

Conclusion: MR measures of T_2 and lipid fraction revealed differences between DMD and Controls, including in the youngest age group (5-6.9 years). Furthermore, MRI-T_2 was greater in the older age group compared to the young age group, which was associated with higher lipid fractions. Overall, MR measures of T_2 and lipid fraction may be sensitive to disease involvement and potential therapeutic interventions in DMD, even in the younger boys.

References:
1. Hoffman EP, Brown RH, Kunkel LM. Cell. 1987; 51(6): 919-928.
2. Bushby K, Finkel R, Birnkrant DJ et al. Lancet Neurol 2010; 9(1): 77-93.
3. Henricson E, Abresch R, Han JJ et al. PLoS One 2012.
4. Loganathan R, Bilgen M, Al-Hafez B et al. Int J Cardiovasc Imaging. 2005; 22(1): 81-90.

Research Support: NIAMS/NINDS R01AR05697

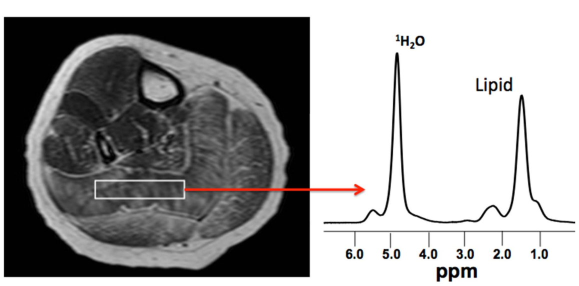

Figure 1. Example lower leg axial SE image (TE 60 ms) with single voxel ^{1}H-MRS spectrum from the soleus of a boy with DMD.

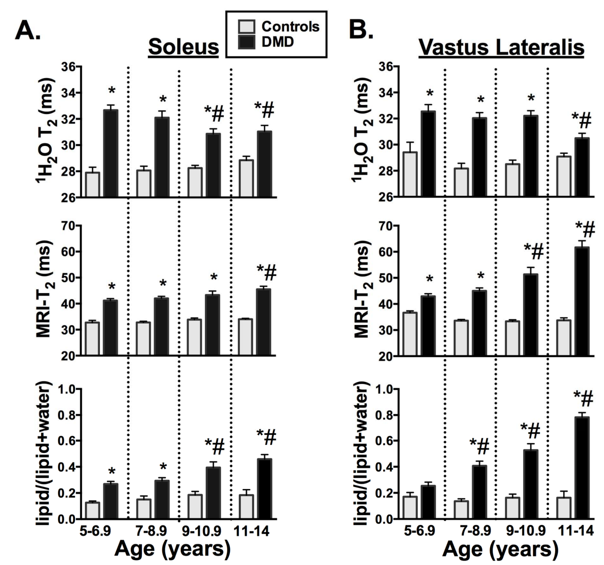

Figure 2. ^1H_2O T_2 (ms), MRI-T_2 (ms), and lipid fraction [lipid/(lipid+water)] in the soleus (A) and vastus lateralis (B) of Control and DMD age groups. Bars represent mean (SEM). * denotes significantly different ($p<0.05$) than Controls and # indicates different ($p<0.05$) than 5-6.9 age group in DMD.