# Tracking Disease Progression in Duchenne Muscular Dystrophy: Longitudinal Changes in Quantitative MR Measures

William D. Rooney[1], Sean C. Forbes[2], William T. Triplett[3], James R. Pollaro[1], Dah-Jyuu Wang[4], Soren deVos[2], James Meyer[4], Rebecca Willcocks[3], Barry Byrne[5], Richard Finkel[6], Barry Russman[7], Erika Finanger[7], Michael Daniels[8], Lee Sweeney[9], Glenn Walter[3], and Krista Vandenborne[2]

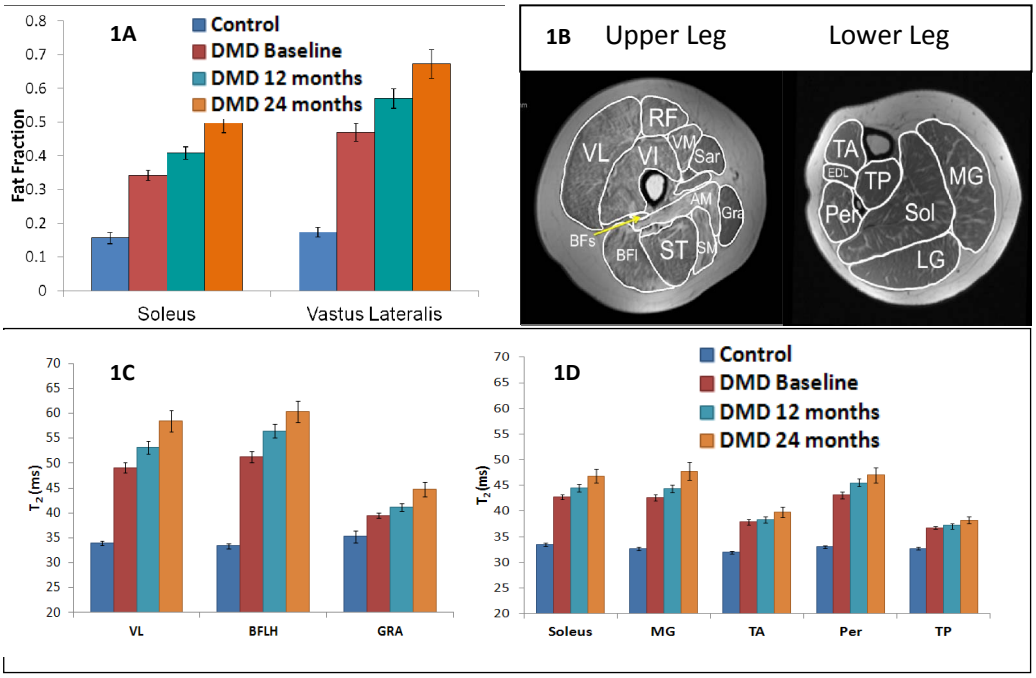
*[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, [2]Department of Physical Therapy, University of Florida, Gainesville, Florida, United States, [3]University of Florida, Physiology and Functional Genomics, Gainesville, Florida, United States, [4]Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States, [5]Department of Pediatrics, University of Florida, Gainesville, Florida, United States, [6]Neurology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States, [7]Shriners Hospital, Portland, Oregon, United States, [8]University of Texas, Austin, Texas, United States, [9]Department of Physiology, University of Pennsylvania, Philadelphia, Pennsylvania, United States*

## Synopsis:

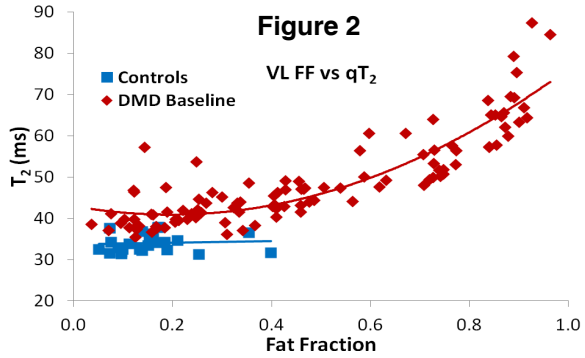
This study investigates the utility of quantitative MR measures to track disease progression in DMD. 3T Data were acquired from 125 DMD and 28 control boys. $^1$H MRS data were acquired to estimate fat fraction (FF) in vastus lateralis (VL) and soleus (Sol) muscles. MRI quantitative $T_2$ ($qT_2$) values were determined for muscles in the upper and lower leg. DMD boys were studied at baseline, and 12 month and 24 month follow-ups. Both FF and $qT_2$ are increased at follow-up with greatest absolute differences found in upper leg muscles. MRI $qT_2$ values were strongly associated with muscle FF.

**Introduction:** Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by a dystrophin gene mutation that occurs with an incidence of approximately 1 in 5000 male births.[1] 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] There currently is no cure for DMD but promising therapies have been identified and there is a pressing need for improved biomarkers sensitive for disease progression. Quantitative MRI/MRS have excellent sensitivity for detection of muscle pathology associated with DMD[3] and strongly correlate with clinical assessments.[4] $^1$H MRS determined fat fraction (FF) and MRI quantitative $T_2$ ($qT_2$) muscle measures demonstrate excellent precision and are well-suited for non-invasive serial studies.[5] The purpose of this study was to investigate the relationship between muscle FF, determined from MRS, and $qT_2$, calculated from spin-echo MRI, and the utility of these biomarkers to track disease progression in boys with DMD.

**Methods:** Data were acquired from 125 DMD boys (baseline ages 5-13 y, mean 8.6 y (±2.2 y; SD); 95 on corticosteroids) and 28 healthy controls (ages 5-15 y, mean 9.8 (±2.4) y) using 3T MRI instruments located at three institutions. Fat fraction (FF) was determined using a non-water suppressed STEAM MRS (TE108/TR3000/NA64) single voxel approach applied in the vastus lateralis (VL) and Soleus (Sol). Quantitative $T_2$ ($qT_2$) values were determined from 2D multi-slice spin echo (SE) axial scans (TE20-320/TR3000; nTE=16; in-plane resolution (0.75 mm)$^2$, 7 mm thick slices) of upper and lower leg. $qT_2$ values were assessed for 5 lower leg muscles [Sol, medial gastrocnemius (MG), peroneus (Per), anterior, and posterior tibialis (TA, TP)] and 3 upper leg muscle [VL, biceps femoris long head (BFLH), and gracilis (Gra)] using mono-exponential fits to SE data. MRS FF was determined by spectral integration of lipid (0.5-2.75 ppm) and $^1H_2O$ (4.3-5.10 ppm) signal regions and calculating the ratio of lipid to total signal. DMD subject data were collected at baseline (n=125), 12 months (n=100), and 24 months (n=48).




**Results and Discussion:** Measurements were successfully completed on 125 DMD and 28 control boys using MRS and $qT_2$ MRI of upper and lower leg. Highly significant differences between controls and DMD boys were found for both FF ($P<10^{-6}$; effect size (ES) > 2.2) and $qT_2$ ($P<10^{-6}$; (ES) > 2.3 for VL, BFLH, Sol, and Per). Paired analysis revealed significant increases in FF (see Fig 1A) and $qT_2$ (Fig. 1C, 1D) for most DMD muscle groups between baseline and 12 month, and between 12 and 24 month follow-ups. Upper leg muscles (VL, BFLH) typically showed greater involvement as measured by absolute differences in FF or $qT_2$ compared to controls. Regression analysis revealed a strong quadratic association between $qT_2$ values determined by MRI and FF determined by MRS ($R>0.875$; $P<10^{-6}$; Fig. 2) suggesting that increased $qT_2$ is largely determined by increased muscle fat content in DMD. In summary, both FF and $qT_2$ provide excellent sensitivity for tracking DMD disease progression and both are likely surrogates for the same underlying pathologic substrate: fat infiltration. $qT_2$ measures also provide outstanding spatial resolution and total tissue coverage that greatly facilitates characterizing heterogeneity of DMD disease progression in differing muscles.




**Grant Support**: NIAMS/NINDS R01AR056973

**References**: **1.** Moxley, Pandya, Ciafaloni, Fox, Campbell. J. Child Neurol. 25 :1116-1125 (2010). **2.** Zhou, Lu. J Neuropathol Exp Neurol. 69: 771–776 (2010). **3.** Huang, Majumdar, Genant, Chan, Sharma, Yu, Mynhier, Miller. J Magn Reson Imaging 4:59-64 (1994). **4.** Kim, Laor, Horn, Racadio, Wong, Dardzinski Radiology. 255:899-908 (2010). **5.** Forbes, Walter, Rooney, Wang, DeVos, Pollaro, Triplett, Lott, Willcocks, Senesac, Daniels, Byrne, Russman, Finkel, Meyer, Sweeney, Vandenborne. Radiology. 269:198-207 (2013).