Reproducibility of Skeletal Muscle MR Measures in Children: A Multi-Center Study of Duchenne Muscular Dystrophy

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Target Audience: This study will benefit those with interests in: 1) using MR to evaluate skeletal muscle composition, 2) strategies to improve MR data quality in children, 3) multi-center MR studies, or 4) muscular dystrophies.

Introduction: Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder that is due to a mutation in the dystrophin gene and has an incidence of 1 in 3600-6000 male births (1). DMD is characterized by progressive muscle deterioration, loss of functional abilities, and reduced life expectancy. To date, treatments have shown limited effectiveness and currently there is no cure for DMD. However, there are a number of interventions that have shown promise in preclinical and early clinical trials. As a result, there is a need for sensitive and reliable biomarkers to track disease progression and provide a surrogate means to evaluate the efficacy of therapeutic interventions in clinical trials. Due to the low prevalence of DMD, these trials require that data be acquired at multiple centers. Therefore, the **purpose** of this study was to describe the design of a multi-center study examining lower extremity skeletal muscles of children with DMD using MRI/MRS and to evaluate the reproducibility of these measures across multiple centers and from day-to-day within sites.

Methods: Standardized procedures with MR operator training and quality assurance assessments were implemented, and data were acquired at three geographically distant sites using different 3T MRI instruments (Philips Achieva, Siemens Verio, or Siemens TIM Trio) and RF coil configurations. MR measures were acquired twice on separate days in boys with DMD (n=96, 8.5 (SD 2.3) years) and unaffected boys (n=22, 9.8 (1.9) years). Day-to-day variability of maximal cross sectional area (CSAmax), contractile area, transverse relaxation time constant (T_2), and lipid fraction were compared. Initial evaluation of reproducibility was accomplished within and between sites using identical two-compartment (fat and water) coaxial phantoms and unaffected adult subjects that visited each site (n=2). *Acquisition:* Lower extremity skeletal muscles were evaluated using T_1-weighted 3-D gradient echo (GE) images with spectral presaturation by inversion recovery (SPIR) fat suppression and without fat suppression, T_2-weighted spin echo images with and without fat suppression (4-8 axial slices, TR 3 s, 16 TE's: 20-320 ms, 7 mm slice thickness, 3.5 mm slice gap) and single voxel STEAM ^{1}H-MRS of the soleus (SOL; composition: TR 3s, TE 108 ms, 16X4 phase cycles and relaxometry: TR 9s; 16 echoes: 11-288 ms, 4 phase cycles; Fig. 1). *Analysis:* CSAmax was measured by manually tracing muscles using the fat suppressed GE images in OsiriX software (v3.8.1; http://www.osirix-viewer.com). Contractile area of muscles was estimated using an interactive data language (IDL; ITT Exelis; McLean, VA) custom written program based on histogram signal intensity of muscle and lipid, as previously described (2). T_2 maps were calculated for lower leg and thigh muscles by voxel-wise estimation of T_2 by fitting a single exponential equation to the magnitude signal intensity (S) from spin-echo images with TE values from 40-100 ms; $S(TE)=S_0*\exp(-TE/T_2)$. Lipid fraction was measured using automated phasing and area integration of ^{1}H spectra. In order to minimize the impact of subject motion on data quality, spectra were stored dynamically (16 X 4 phase cycled averages) and outliers were omitted. The spectroscopic T_2 values were derived using the amplitude peak height of the ^1H_2O signal using complex principal component analysis, then the decay curve subsequently resolved using a mono-exponential model. All spectroscopic analysis was performed using fully automated procedures.

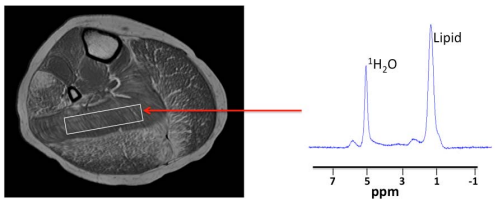

Figure 1. Example axial lower leg GE image and ^{1}H-MRS spectrum of a DMD subject.

Results: CSAmax, lipid fraction, and MRI- and MRS-T_2, and lipid fraction were consistent across sites in the phantom (CV < 3%) and in adult subjects that travelled to each site (CV 2-7%). High day-to-day reproducibility was observed in CSAmax, contractile area, lipid fraction, MRI- and MRS-T_2 in controls and boys with DMD (Table 1).

Table 1. Summary of MR measures of SOL

	Controls			DMD		
MR measure	**Day1**	**Day2**	**CV(%)**	**Day1**	**Day2**	**CV(%)**
CSAmax (cm^2)	12.6 (2.9)	12.7 (2.8)	2.4 (1.5)	17.5 (6.9)*	17.5 (6.8)*	3.8 (3.6)
Contractile Area(%)	98.8 (1.6)	99.2 (0.6)	0.4 (0.9)	93.0 (10.5)*	94.1(12.9)*	4.7(9.9)*
MRS, lipid fraction	0.23 (0.08)	0.23 (0.08)	7.7 (6.4)	0.36 (0.17)*	0.36 (0.17)*	6.0 (5.0)
MRS, T_2 (ms)	28.4 (0.7)	28.2 (0.6)	1.5 (1.5)	31.8 (2.8)*	31.8 (2.5)*	2.8 (3.2)
MRI, T_2 (ms)	33.6 (1.7)	33.6 (1.6)	1.3 (1.1)	42.8 (5.7)*	43.0 (5.5)*	2.2 (2.5)
MRI, T_2 fatsat (ms)	32.3 (1.0)	32.2 (1.1)	1.7 (1.4)	38.2 (3.8)*	38.2 (3.3)*	2.8 (2.5)

* Denotes Significantly Different than Controls. Values indicate mean (SD)

Conclusions:

This study demonstrates feasibility for use of MR to measure skeletal muscle size, composition, and MR signal relaxation properties across multiple centers. The high level of reproducibility across sites and low day-to-day variability within sites observed in this study provides support for using MR to measure muscle involvement in children with DMD in multi-center studies.

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References

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