

MR supports therapeutic effects of corticosteroids in 5-7 year old boys with DMD

Ishu Arpan¹, Rebecca Wilcock¹, Sean Forbes¹, Donovan Lott¹, Claudia Senesac¹, William Triplett¹, Michael Daniels², Barry Byrne³, Bill Rooney⁴, Erika Finanger⁴, Richard Finkel⁵, Barry Russman^{4,6}, Gihan Tenneko⁵, Dah-Jyuu Wang⁷, Glenn Walter⁸, H. Lee Sweeney⁹, and Krista Vandenborne¹

¹Physical Therapy, University of Florida, Gainesville, Florida, United States, ²University of Texas, Texas, United States, ³Pediatrics and Molecular Genetics & Microbiology, University of Florida, Gainesville, Florida, United States, ⁴Oregon Health & Science University, Oregon, United States, ⁵Neurology, The Children's Hospital of Philadelphia, Pennsylvania, United States, ⁶Shriners Hospital for Children, Oregon, United States, ⁷Radiology, The Children's Hospital of Philadelphia, Pennsylvania, United States, ⁸Physiology and Functional Genomics, University of Florida, Gainesville, Florida, United States, ⁹Physiology, University of Pennsylvania, Pennsylvania, United States

Target Audience: This study will benefit those interested in implementing magnetic resonance imaging (MRI) and spectroscopy (MRS) for monitoring skeletal muscle response to disease progression as well as therapeutic interventions in muscular dystrophies or other neuromuscular disorders characterized by muscle damage, edema, inflammation or fatty tissue infiltration.

Introduction: Duchenne muscular dystrophy (DMD) is one of the most debilitating forms of the muscular dystrophy. Currently, there is no cure for the disease. Glucocorticosteroids (Prednisolone and Deflazacort) have been reported to slow down the disease progression in DMD¹⁻⁴. However, the mechanism by which corticosteroids preserve muscle function in DMD is not fully understood. Magnetic resonance imaging (MRI) and spectroscopy (MRS) can provide information about skeletal muscle pathologies that are associated with the disease process of DMD, such as inflammation and fatty tissue infiltration⁵⁻⁷. Therefore, the purpose of this study was to utilize MR measures to study the effects of corticosteroid treatment on lower extremity muscles of 5-7 year old boys with DMD.

Methods: MR data were acquired from 15 young boys with DMD treated with corticosteroids (mean age: 6.1±0.1 yrs) and 15 age-matched corticosteroid-naïve boys (mean age: 6.1±0.1 yrs) using 3T MR systems at three institutions. T_2 -weighted spin echo (SE) images [4-8 axial slices, repetition time (TR): 3 s, 16 echo times (TE's): 20-320 ms, slice thickness: 7 mm, slice gap: 3.5 mm] were acquired on the lower leg and thigh. In addition, two sets of unsuppressed localized ^1H MRS scans were acquired. To measure the relative intramuscular fat fraction a single voxel STEAM spectra (TR: 3 s, TE: 108 ms, NA: 64) was acquired in both the soleus (Sol) and vastus lateralis (VL) muscles. In addition, spectroscopic relaxometry sequences using ^1H -MRS STEAM were implemented to quantify $^1\text{H}_2\text{O}$ T_2 in the Sol (TR: 9 s; 16 TE's: 11-288 ms, NA: 4) and VL (TR: 9 s; 4 TE's: 11-252 ms, NA: 4). Finally, functional performance of all boys was assessed using a timed 6-minute walk test (6MWT). In addition to cross-sectional comparisons at baseline, longitudinal analysis of the change in fat fraction over one year was measured in a subset of DMD boys in both the corticosteroid treatment (n=9) and corticosteroid naïve group (n=6).

Results and Discussion: MRI- T_2 values were significantly lower in the lower leg muscles of boys on corticosteroid treatment compared to corticosteroid naïve boys [Sol: 38.6±0.8ms vs. 45.6±0.9ms; Medial gastronemius (MG): 37.9±0.4ms vs. 46.2±1.3ms; Peroneals (Per): 37.8±0.6ms vs. 43.8±1.0ms], Tibialis anterior (TA): 35.5±0.6ms vs. 37.7±0.7ms; & Tibialis posterior (TP): 36.6±0.7ms vs. 38.8±0.8ms, p≤0.05]. Similar results were observed in VL (39.6±0.7ms vs. 46.3±1.5ms, p≤0.05) and the Biceps femoris long head muscles (BFL): 39.8±0.9ms vs. 46.6±1.9ms, p≤0.05), but not in the Gracilis (38.7±1.2 vs. 40.7±1.2, p=0.6). MRS- T_2 values in Sol and VL muscles of the treatment group were also lower (p≤0.05), indicating less inflammation/damage in the muscles of boys on steroid therapy (Fig: B). Therefore, the results of this study support the proposed role of corticosteroids in reducing inflammatory processes in skeletal muscles in DMD⁸. In addition, the intramuscular fat fraction was significantly lower (p≤0.05) in the muscles of boys on corticosteroid treatment compared to corticosteroid naïve boys (Fig: C). These findings were further supported by the analysis of longitudinal changes in intramuscular fat fraction over one year. The boys on corticosteroid treatment had significantly less change in fat fraction (p≤0.05) compared to corticosteroid naïve boys over one year (Fig: D). While both MRI and MRS showed positive effects of corticosteroids on skeletal muscles of 5-7 years old boys with DMD, no significant difference could be detected in the 6MWT across the groups (Corticosteroid-naïve: 348.0±15.7 and Corticosteroid: 367.4±15.5, p=0.4). Although the 6MWT has been established as a clinically meaningful outcome measure in DMD, these data indicate that it may be less sensitive in monitoring muscle response to disease progression or therapies, especially in younger boys with DMD.

Conclusion: MRI/MRS results showed that T_2 values and fat fraction were significantly lower in thigh and leg muscles of boys with DMD in the treatment group; suggesting reduced inflammation/damage and fat infiltration with corticosteroid treatment. These findings support the therapeutic effects of corticosteroids on muscle quality in 5-7 year old boys with DMD. In addition, these results demonstrate the potential of MRI and MRS to monitor muscle response to anti-inflammatory and other potential therapeutic interventions in young boys with DMD.

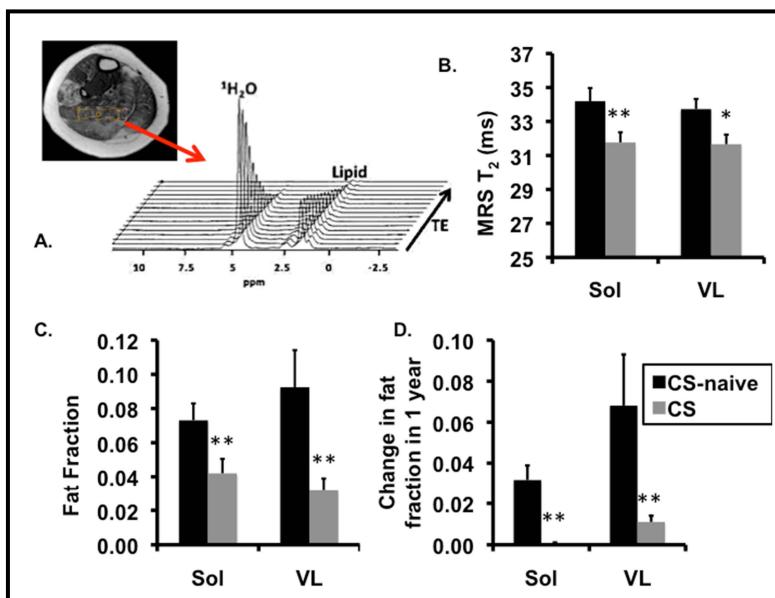


Figure: An example SE image of the lower leg with voxel placement in the soleus (Sol) muscle is depicted with the corresponding spectra acquired during the spectroscopic relaxometry scan (A). Cross-sectional comparisons of MRS T_2 (B) and fat fraction (C) among boys on corticosteroid (CS) treatment and corticosteroid-naïve (CS-naïve) boys and the longitudinal changes in fat fraction over one year in the Sol and vastus lateralis (VL) muscles of both groups are shown (D). Values are represented as mean ± SE; ** p≤0.01 & * p≤0.05.

References: 1) Brooke MH, Fenichel GM et al. Archives of Neurology 1987;44(8):812-7. 2) Mendell JR, Moxley RT, Griggs RC et al. New Eng J of Medicine 1989;320(24):1592-7. 3) Griggs RC, Moxley RT et al. Clinical Investigation of Duchenne Dystrophy Group. Archives of Neurology 1991;48(4):383-8. 4) Angelini C, Pegoraro E et al. Muscle & Nerve 1994;17(4):386-91. 5) Huang Y, Majumdar S, Genant HK et al. J Magn Reson Imaging. 1994;4(1):59-64. 6) Kim HK, Laor T, Horn PS et al. Radiology. 2010;255(3):899-908. 7) Torriani M, Townsend E, Thomas BJ et al. Skeletal Radiol. 2011. 8) Kissel JT, Burrow K, Rammohan KW et al. Neurology 1991;41(5):667-72.

Grant Support: NIAMS/NINDS R01AR056973