UPPER LIMB MUSCLE FAT-WATER QUANTIFICATION IN NON-AMBULANT DUCHENNE MUSCULAR DYSTROPHY

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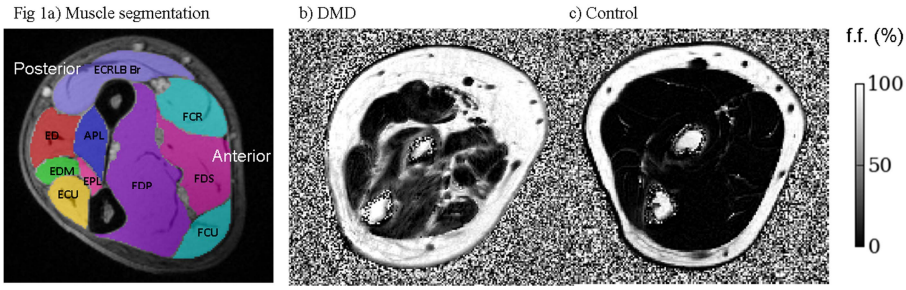
TARGET AUDIENCE: Clinicians and researchers with an interest in neuromuscular disorders and quantitative MRI.

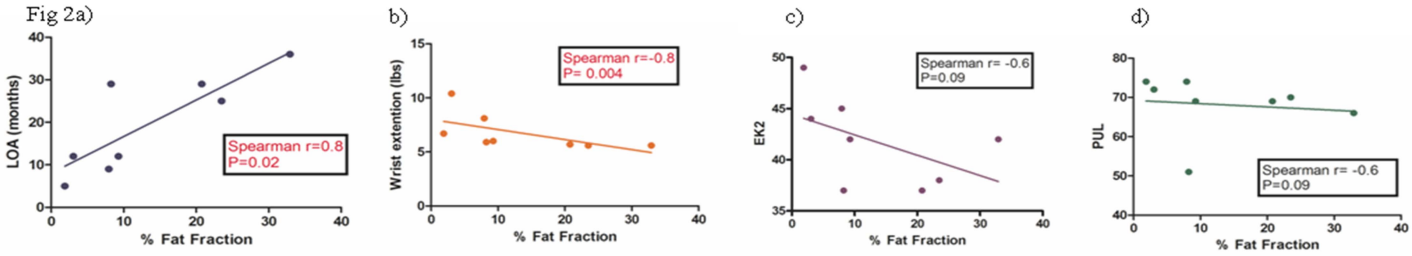
OBJECTIVE: Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder affecting ~1:5000 male births which leads to progressive muscle wasting and loss of ambulation by 12-14 years. Recently there have emerged promising new potential genetic treatments, including the development of exon skipping with anti-sense oligomers to produce dystrophin restoration in muscle. Currently, outcome measures rely on invasive muscle biopsies and insensitive functional tests such as the 6-minute walk test (6MWT). Muscle MRI could offer valuable alternative non-invasive longitudinal measures of outcome in dystrophic muscle. Furthermore, the opportunity to evaluate the upper limb will permit inclusion of non-ambulant individuals not able to perform the 6MWT. The disease-related time-course of relevant MRI index changes are currently unknown in the non-ambulatory DMD population, particularly in the upper limb. In this work, 3-point Dixon fat-fraction imaging was used to compare fat-infiltration in the forearm muscles of non-ambulant DMD patients versus healthy controls. Within the DMD patients the relationship between fat-fraction scores and clinical functional assessments was also investigated.

METHODS: To date, 8 non-ambulant DMD patients (mean age: 13.6 years, range:12,17; on either intermittent or daily prednisolone; mean duration of non-ambulation 20 months, range: 5-36; mean body mass index (BMI) 24.9, range: 20.9-28.5) and 10 gender-matched volunteers (mean age: 14.6, range: 13-17; mean BMI 21.5, range: 16.5-25.4) were examined with MRI and clinical functional assessment. Imaging of the dominant forearm was performed at 3T (Siemens Skyra) with a surface matrix coil in the head-first supine position using 3-Point Dixon imaging[1] (2D gradient echo TE1/TE2/TE3/TR=3.45/4.60/5.75/102ms, flip angle α=10°, 9x6mm axial slices, slice gap 12mm, FOV 18x18cm, matrix 320x320, axial resolution 0.56x0.56mm, NEX=4). Images were post-processed offline and phase-unwrapped with the FSL Prelude tool. The separated fat (f) and water (w) images were used to calculate the fat fraction (f.f.) map according to f.f.(%)= 100*f/(w+f). Segmentations of the 10 principle forearm muscles were made on a single central slice of the TE=3.45ms image using ITKSnap software (extensor carpi ulnaris (ECU), extensor digitiminimi (EDM), extensor digitorum (ED), extensor pollicislongus (EPL), abductor pollicislongus (APL), extensor carpi radialislongus/brevis and brachioradialis (ECRLB Br), flexor digitorumprofundus and flexor pollicislongus (FDP), flexor digitorumsuperficialis and palmarislongus (FDS), flexor carpi ulnaris (FCU), flexor carpi radialis (FCR) (Fig 1a)). The segmentations were applied to the f.f. maps to calculate mean f.f. in each muscle and overall f.f, defined as the average f.f. of all 10 muscles. The cross-sectional area of each muscle was recorded in mm^2.

Clinical functional assessment of each patient comprised 3 components: (1) Performance of Upper Limb (PUL) module, a validated 74 point function scale for motor performance relating to everyday life[2], (2) wrist extension myometry carried out using a microfet2 myometer with a round flat transducer pad, and (3) EgenKlassification (EK2) interview used to determine performance of tasks in daily life (total score=51).[3] The time to loss of ambulation (LOA) in months was also recorded.



RESULTS: Example f.f. maps for a patient and control are shown in Fig. 1b&c. The overall mean f.f (±SD) in DMD was significantly higher than healthy controls: 13.4±11%vs 0.8±0.1% (p=0.002), and in all individual muscles (all p<0.015) except ED (p=0.1). The ECRLB Br group was the most affected with f.f.=28.5±21.6% in DMD compared to 2.0±2.0% in healthy controls (p<0.001). The total mean area was reduced in DMD (1735±331mm^2) compared to healthy controls (2398±821mm^2) (p=0.04), dominated by differences in ECRLB Br, FCR and FDS. The anterior muscles of the forearm were most atrophied (1066±241 mm^2 (DMD) *vs.* 1564±534mm^2 (controls) (t-test p=0.03). LOA correlated with overall f.f. (Spearman r=0.8, p=0.02) (Fig.2a).Wrist extension myometry (lbs) correlated with overall f.f. (Spearman r=0.8, p=0.004) (Fig 2b). Trends suggested a possible relationship between f.f and PUL (Spearman r= -0.6, p=0.09) and between f.f.and EK2 (Spearman r= 0.6, p=0.09) (Figs 2c&d).



DISCUSSION In this on-going study, preliminary data show that quantitative MRI provides indices of abnormality in the forearm of non-ambulant DMD individuals. The overall f.f was increased compared to healthy controls, with ECRLB Br showing greatest involvement, while the overall area was decreased in DMD compared to healthy controls, with anterior muscles more severely affected. Correlation with clinical data showed that the degree of fat infiltration increased with time of non-ambulation. We further demonstrated a correlation with muscle f.f. and impaired function, i.e. loss of strength in wrist extension, performance of upper limb, and patient-reported daily life activities.

CONCLUSION: Our initial data supports MRI fat quantification as a potential objective biomarker to monitor disease progression in the upper limb in DMD showing significant correlation between putative MRI pathological indices and clinically meaningful endpoints.

REFERENCES: [1] Glover G. JMRI 1991;1:521-530. [2] Mayhew A. Dev Med Child Neurol 2013;55:1038, [3] Steffensen. Physiother Res Int 2001;6:119.
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