

Quantification of lower limb muscle fatty atrophy by 3-point Dixon MRI in chronic neuromuscular diseases - a potential outcome measure

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Introduction: Recent advances have provided potential treatments in neuromuscular conditions such as the inherited nerve disease Charcot-Marie-Tooth disease 1A (CMT1A) (1) and the acquired muscle disease inclusion body myositis (IBM) (2). Clinical trials need outcome measures that are valid, reliable and sensitive to change. Current outcome measures have proven insensitive to detecting change, especially in CMT1A as progression is very slow (1). Qualitative lower limb muscle MRI has been used in CMT1A and IBM to define patterns of muscle involvement, including fatty infiltration (3,4). Three-point Dixon chemical-shift based fat-water separation (5) provides fat and water images which can be combined to create a fat-fraction map from which mean values across defined regions of interest (ROIs) can be obtained. This technique has shown good test-retest reliability in lower limb muscles in healthy subjects (6). The aims of this study were to quantify the degree of fatty infiltration in lower limb muscles of patients with CMT1A and IBM compared to healthy controls and to correlate MRI measures of fat-infiltration with accurately measured knee and ankle strength.

Methods: We studied 20 patients with genetically confirmed CMT1A (11 male, 9 female, mean age 43y), 20 patients with probable or definite inclusion body myositis (7) (16 male, 4 female, mean age 67y) and 28 healthy controls (16 male, 12 female, mean age 53y). All underwent 3T MRI (Siemens TIM Trio) including axial 3-point Dixon acquisitions in both thighs and calves (2D gradient echo sequence; 3 acquisitions TE=3.45, 4.6, 5.75ms respectively, TR=100ms, $\alpha=10^\circ$, NEX=4, slice thickness=10mm, thigh level: 512x256matrix, 410x205mm FOV; calf level: 512x240matrix, 400x188mm FOV). All participants underwent lower limb strength testing using the CSMi HUMAC NORM Testing System, including measurements of peak isometric torques of knee flexion and extension and ankle dorsiflexion and plantarflexion. ROIs were drawn bilaterally for the muscles listed in table 1 encompassing the whole muscle cross-section at a standard anatomical level by a single observer (AF) blinded to diagnosis (figure 1D). "Remaining cross-sectional muscle area" was calculated for each muscle by multiplying the total muscle cross-sectional area at mid -thigh or mid-calf level by 1-fat fraction: a composite measure taking into account both muscle atrophy and fat replacement. Statistical analysis was performed using SPSS 18.

Results: Typical right thigh and calf fat fraction maps are shown in Figure 1. Table 1 shows patient-group mean %fat-fractions for each ROI were increased in both patient groups relative to controls for all calf ROIs and in IBM patients for all thigh ROIs (all $p<0.01$ at calf level in both groups, all $p<0.001$ at thigh level in IBM group, unpaired t-test). The anatomical distribution of fat-fraction increase was similar to established patterns on qualitative MRI. Excellent correlation between myometry measures and relevant remaining cross-sectional muscle-group area is demonstrated in figure 2.

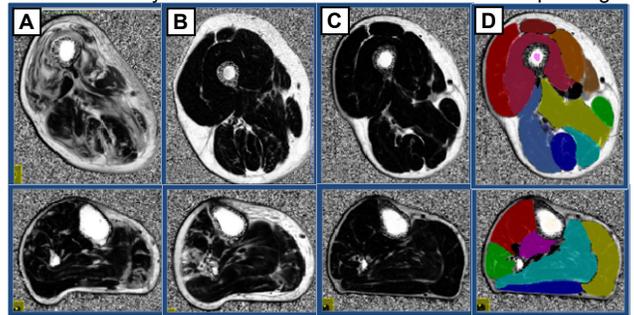


Figure 1: Axial fat fraction maps of right mid-thigh (top row) and right mid-calf (bottom row) from an IBM patient (A), CMT1A patient (B) and healthy control (C): black = 0% fat, white = 100% fat. For the control, whole-muscle ROI are demonstrated in (D)

Muscle	CMT1A		IBM		Controls	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
THIGH						
Rectus Femoris	6.2	12.1	31.8	19.5	2.9	1.9
Vastus Medialis	4.9	8.6	38.5	18.6	2.6	1.2
Vastus Intermedius	5.2	11.4	36.7	20.4	2.2	1.4
Vastus Lateralis	6.7	14.3	45.3	21.2	3.2	1.4
Semimembranosus	6.8	5.4	19.5	17.5	4.6	2.6
Semitendinosus	6.4	5.3	22.8	24.1	4.0	2.3
Biceps Femoris	5.3	5.2	10.6	8.4	4.1	2.3
CALF						
Anterior Group	15.1	21.2	9.7	11.6	2.5	3.3
Peroneal Group	23.4	27.9	16.6	15.1	4.4	4.1
Lateral Gastrocnemius	16.8	27.2	24.8	25.1	3.3	3.2
Medial Gastrocnemius	19.2	28.2	51.6	24.5	4.0	3.3
Soleus	12.8	22.7	15.9	16.8	4.0	4.5
Tibialis Posterior	13.3	22.0	8.1	12.2	2.7	3.9

Table 1: Muscle ROI fat fractions (group mean and s.d., %), left and right sides combined

Discussion: MRI-measured muscle fat-fraction at mid calf is increased in CMT1A patients and increased at both mid-thigh and mid-calf in IBM patients compared with healthy controls. "Remaining cross-sectional muscle area" has validity as an outcome measure in CMT1A and IBM with excellent correlation with functional measures of muscle strength. Longitudinal data are now needed to assess the sensitivity to change of MRI-assessed muscle fat as an outcome measure in neuromuscular diseases

References: 1. Pareyson D et al. Lancet Neurol. 2011; 10:320. 2. Solorzano GE et al. Rheum. Dis. Clin. North Am. 2011; 37:173. 3. Gallardo E et al. Brain. 2006; 129:426. 4. Cox FM et al. 2011; 50:1153. 5. Glover GH et al. Magn. Reson Med. 1991; 18:371. 6. Sinclair CDJ et al. Neuromuscular Disorders. 2010; 20:S28. 7. Tawil R et al. Curr Opin Rheumatol 2002; 14:653.2

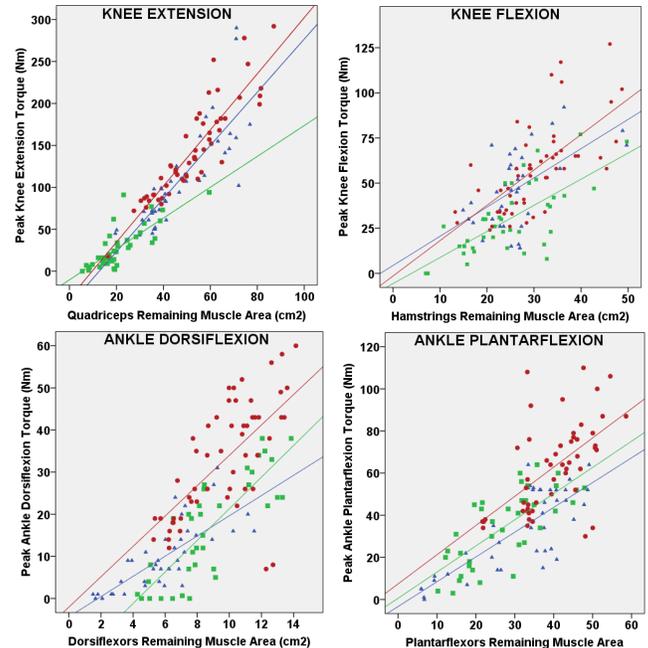


Figure 2: Functional versus MRI measures. For each muscle-group the peak isometric strength of corresponding movement is plotted against "cross sectional area of remaining muscle". Controls-red circles, IBM-green squares, CMT1A-blue triangles. Best fit lines are shown. Strong correlation is seen in all cases with $R=0.57-0.90$, all $p<0.001$.