Candidate skeletal muscle outcome measures for therapy trials: dependence of MRI measures upon age, gender and weight

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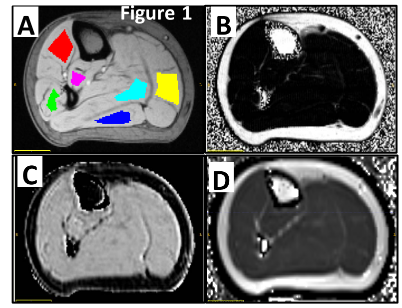
Purpose: Quantitative skeletal muscle MRI offers strong candidate outcome measures for imminent therapy trials in neuromuscular diseases such as inclusion body myositis or limb girdle muscular dystrophy. Muscle fat content, which reflects chronic pathology, can be measured using the 3-point Dixon fat/water separation method [1,2], and more acute muscle water changes can be examined with T2-relaxometry [1] or magnetisation transfer (MT) imaging [3]. The dependence of these measures upon age, gender or *body habitus* is a key factor in assessing their suitability as outcome measures. We aimed to investigate these dependencies in the thigh and calf-level muscles of healthy volunteers.

Methods: With ethical approval and consent 47 healthy volunteers, 23 male, ages (mean ± s.d.; range) 44.4 ± 17.0y; 21.5-81.0y, weight; 44-115kg. Thigh- and calf-level lower limb imaging was performed at 3 Tesla (Siemens TIM Trio) feet-first supine with surface matrix coils and field of view (FOV) 400x200mm (thighs) and 400x188mm (calves). The 3-point Dixon technique (2D GRE, TR/TE1/TE2/TE3=100/3.45/4.60/5.75ms, flip angle $\alpha = 10^{o}$, NEX=4, 512x256 matrix 10x10mm slice, 10mm gap) was used to generate water (W) and fat (F) images according to [4] and fat-fraction (F.F.) maps calculated as F.F. = 100% x F/(F+W). Pseudo-T2 maps were generated from a dual-echo TSE acquisition ($TR/TE_1/TE_2$=5500/16/64ms, 10 slices with 10mm slice gap, 256x128matrix, α=180º, NEX=2) assuming mono-exponential decay. 3D-FLASH images (TR/TE=65/3ms, α =10º, BW=440Hz/pixel, 40x5mm partitions) with (M_1) and without (M_0) an MT saturation pulse (10ms Gaussian, 1200Hz offset 500° amplitude) were used to calculate the MT-ratio MTR = $(M_0-M_1)/M0 \times 100$ in percentage units (p.u.). B1 maps were generated with the double angle method [5] (TR/TE=7000/11ms, 128x64 matrix, 40x10mm slices, α_1, $\alpha_2 = 60^{o}, 120^{o}$) in order to correct MTR maps for B1 inhomogeneities according to [6] using a mean correction factor *k*=0.0085.



For each subject, regions of interest (ROI) were drawn on a central slice of the first TE=3.45ms 3-point Dixon acquisition image within 6 lower leg muscles (fig1A) and 10 thigh muscles bilaterally. ROIs were drawn wholly within the muscle belly avoiding clear fascia or vessels and then transferred to co-registered fat fraction (F.F.) (Fig 1B), MT ratio (MTR) (Fig 1C) and T2 (Fig 1D) maps. Mean values for each ROI were extracted and overall mean at thigh and calf level calculated for each participant as summary measures. Multivariate regression was performed to assess the influence of demographic factors (age, gender, weight, height) on MRI measures. Height did not show independent correlation with any of the quantitative MRI parameters so was excluded from the model.

Results: Multivariate regression analysis of demographic parameters and mean quantitative MRI parameters in thigh and calf of healthy volunteers is summarised in the table. Mean muscle F.F. correlated with age in both thigh and calf. In the thigh but not calf F.F. correlated with weight.

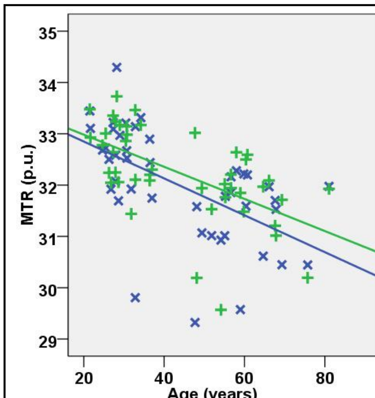


Figure 2: Relationship between mean muscle MTR and age in thigh (blue) and calf (green); p<0.001 for both

	Thigh		Calf	
	Co-eff	p	Co-eff	p
F.F. (%)	**R=0.58, p=0.001**		**R=0.42, p<0.05**	
Constant	-0.942	.150	0.573	0.399
Gender (F=1)	-0.125	.597	-0.329	0.174
Age (y)	**0.016**	**.026**	**0.014**	**0.047**
Weight (kg)	**0.025**	**.003**	0.008	0.374
T2 (ms)	**R=0.60, p<0.001**		**R=0.57, p=0.001**	
Constant	34.44	.000	34.97	0.000
Gender (F=1)	-0.163	.839	-1.175	0.142
Age (y)	**0.074**	**.003**	**0.067**	**0.006**
Weight (kg)	**0.073**	**.009**	0.049	0.064
MTR (p.u.)	**R=0.75, p<0.001**		**R=0.61, p<0.001**	
Constant	35.90	.000	33.707	0.000
Gender (F=1)	**-0.878**	**.000**	0.164	0.485
Age (y)	**-0.029**	**.000**	**-0.032**	**0.000**
Weight (kg)	**-0.030**	**.000**	-0.002	0.789

R: correlation coefficient of overall model
Co-eff: coefficient (change in qMRI per unit demographic)

The significant correlations for T_2 mirror those for F.F. MTR strongly correlates negatively with age (p<0.001) for both thigh and calf. Significant correlation with gender and weight is seen in the thigh only.

Discussion: This is the first study to investigate the influence of demographic parameters on lower-limb muscle Dixon F.F. measures and thigh-muscle T2 and MTR. T2-age and MR-age correlations in the calf are consistent with previous findings [7,8]. As might be expected, muscle fat fraction increases with age, but the magnitude is small. The FF values for a 20 vs. 80 year old were approximately 1% vs. 2%: changes due to healthy ageing are therefore negligible compared with expected disease effects, an important factor in longitudinal patient studies. It is also notable that weight influenced all three measures in the thigh but not calf, suggesting differential weight gain responses. The negative correlation between MTR and age (Figure 2) was strongest suggesting a marked change in the free-muscle-water/macromolecule-bound proton pool exchange conditions with age.

Conclusions: These data describe the influence of key demographic factors on quantitative MR indices in skeletal muscle. That quantitative MRI at 3T can reliably detect such small changes, and that the magnitudes of the variations were small compared with expected pathological changes, strengthens the potential utility of quantitative MR parameters as outcome measures in neuromuscular diseases.

References: [1] JMRI 2012;35:678-85. [2] AJR 2008;190:W8-12 .[3] J Comput Assist Tomogr. 1999;23:609–14. [4] MRM 1991;18;p371 [5] MRM:1996:35:p246, [6] NMR Biomed. 2012; 25: 262–270. [7] JMRI 2009; 29:1346-54. [8] Invest Radiol 2001;36:692– 8.