

# Progression of fat infiltration in calf, thigh and pelvic muscles in Duchenne Muscular Dystrophy: quantification by MRI over an 18 month period

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**Introduction** Duchenne muscular dystrophy (DMD) is a genetic disorder affecting males in which the muscle protein dystrophin<sup>1</sup> is not expressed. DMD is characterised by progressive muscle weakness and wasting, with muscle fibre necrosis and replacement by fat and connective tissue. However, it is known that not all muscle groups are affected equally at any given time in the course of the disease. With several new therapies for DMD reaching the stage of clinical trials, quantitative, non-invasive measures of the degree and progression of muscle involvement are essential for clinical studies. Previously, we reported the baseline timepoint of the pattern and involvement of fat infiltration in corticosteroid-treated DMD boys vs controls using T1w-imaging as the initial part of an ongoing eighteen-month longitudinal study<sup>2</sup>, and the effect of exercise on T<sub>2</sub> measurement and gadolinium uptake<sup>3</sup>. This study reports the longitudinal fat infiltration over the 18 month time period as measured by T<sub>1</sub>-weighted imaging and measurement of the T<sub>2</sub> relaxation time, which is dependent on both fat infiltration and oedematous change.

**Methods** **Recruitment:** 11 ambulant boys with DMD (age range at baseline 6.6 - 9.9 years, mean 8.3 years) were recruited. The boys' families were initially approached at their routine clinic visits and consent was taken after a home visit to further discuss the study. A favourable opinion was obtained from the local Research Ethics Committee prior to commencement of the study.

**MR protocol:** All scans were performed on a 3T Philips Achieva scanner (Best, NL) using the in-built body r.f. coil for transmission and reception. T1-weighted images of the musculature from the ankles to the iliac crest were acquired using a turbo spin echo sequence (TSE factor 3, low-high profile order, TR/TE/NSA = 671/10/2, slice thickness/gap = 5 mm/10 mm, 256 x 192 matrix interpolated to 512 x 384, bandwidth/pixel = 438 Hz). The children were scanned using a field of view of 380mm and 3 stacks of 16 slices. T<sub>2</sub> measurements were acquired using a turbo-spin echo sequence (TR/TE/NSA = 3000ms/25,50,75,100ms/1). T<sub>2</sub> measurements were only acquired at mid-thigh due to limitations on total scan time. All subjects were scanned at baseline, and 9 months and 18 months later.

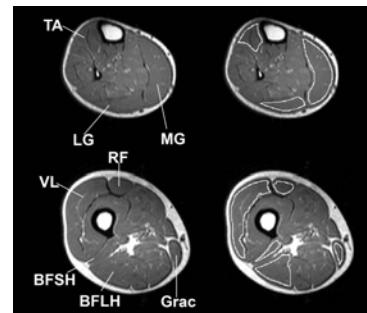
**Analysis:** Images were analysed by using MRIcro<sup>4</sup> on a standard desktop PC to draw regions of interest at mid-calf, thigh and pelvis. Conservative ROIs were drawn avoiding areas of chemical shift artefact and blood vessels at the margin of muscles. The signal intensity in the T<sub>1</sub>-weighted images was divided by the signal intensity of the bone marrow at that level. An exponential fit was applied to calculate the T<sub>2</sub> relaxation value. The Wilcoxon signed rank test was used to compare the longitudinal time points.

**Results** Figure 1 indicates the ROIs analysed. Figure 2 shows the T<sub>1</sub>-weighted signal intensity of the muscle compared to the bone marrow. In general, the muscles of the pelvis and thigh showed greater progression of fat infiltration than the calf. Within this trend however, it was found that the biceps femoris long head (BFLH), vastus lateralis (VL) and rectus femoris (RF) showed the largest progression, while the gracilis and biceps femoris short head were spared by comparison. The T<sub>2</sub> data for thigh muscles (figure 3) supported this conclusion with significant ( $p < 0.02$ ) T<sub>2</sub> increases in both those muscles with significant fat infiltration (VL, RF, BFLH) but also in the gracilis (Grac), where a significant decrease in intensity was detected. There were individual differences in the rate of progression: figure 4 compares two individuals with the median result for BFLH.

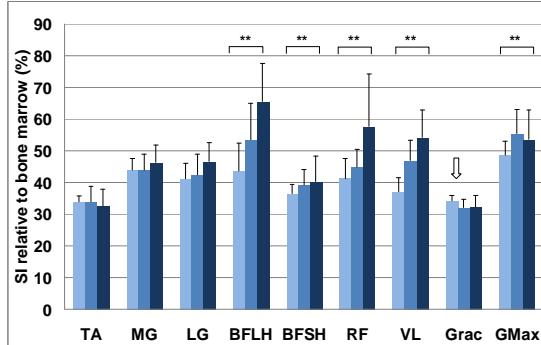
**Conclusions** This work demonstrates the quantitative longitudinal progression of fat infiltration in DMD subjects over an 18 month period using simple T1-weighted and T<sub>2</sub> measurement sequences. The increase in signal intensity on T1-weighted imaging is primarily due to the infiltration of fat, and this effect is likely to dominate these T<sub>2</sub> measurements without fat suppression. Trials of therapy for DMD are dependent on identifying appropriate muscles to study where a significant change in infiltration can be demonstrated in a realistic time-frame. This work provides the first quantitative, longitudinal MRI study of this condition and provides valuable information for planning such trials. Although B<sub>1</sub> inhomogeneity issues may reduce the power of the quantitative measures, the present simple approach is sufficient to detect longitudinal change. Additional statistical power may be gained by using 3-point Dixon methods to eliminate the effect of B<sub>0</sub> and B<sub>1</sub> inhomogeneities or by full T<sub>1</sub> mapping.

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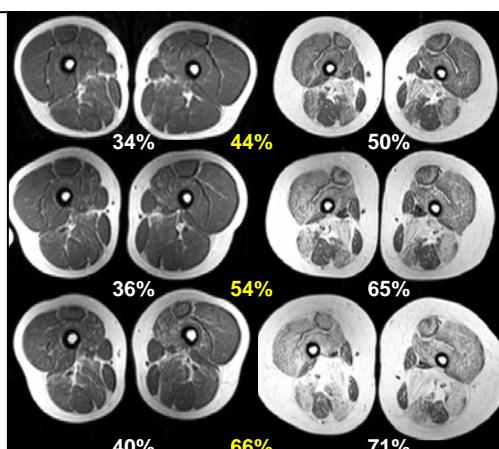
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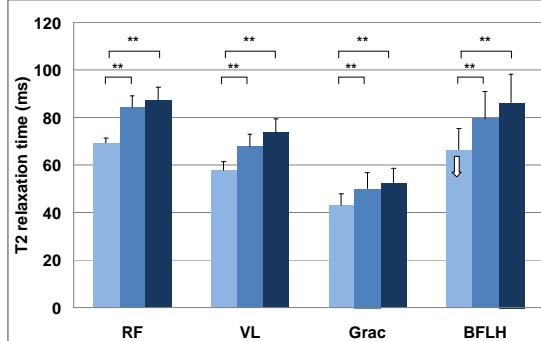
**Figure 1** : Thigh and calf T1w image of a healthy child volunteer showing regions of the muscles marked as for the (radiological) right leg. Key: TA=tibialis anterior, LG = lateral gastrocnemius, MG = medial gastrocnemius, VL = vastus lateralis, RF = rectus femoris, Grac = gracilis, BFLH = biceps femoris long head, BFSH = biceps femoris short head, GMax = gluteus maximum (not shown).



**Figure 2:** Longitudinal signal intensity of selected muscles on T1w imaging compared to bone marrow intensity for 11 DMD children at baseline (light blue), 9 months (medium blue) and 18 months (dark blue). Bars show median values for the group with error bars showing half the interquartile range. Brackets indicate significant with \*\*  $p < 0.02$  (Wilcoxon signed rank test)



**Figure 4** : Progression of fat infiltration over an 18 month period for two of the DMD children in the thigh muscles (left and right, top row = baseline, middle = 9 months and bottom = 18 months). Figures indicate the SI in the biceps femoris long head relative to bone marrow for that individual. Gracilis and biceps femoris short head are less affected.



**Figure 3:** Longitudinal T<sub>2</sub> relaxation time of selected muscles intensity for 11 DMD children at baseline (light blue), 9 months (medium blue) and 18 months (dark blue). Bars show median values for the group with error bars showing half the interquartile range. Brackets indicate significant \*\*  $p < 0.02$  (Wilcoxon signed rank test)