Muscle T_2 measurement and gadolinium uptake in Duchenne Muscular Dystrophy: effect of exercise in DMD boys and comparison with healthy controls

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Introduction Duchenne muscular dystrophy (DMD) is a genetic disorder affecting males characterised by progressive muscle weakness and wasting with muscle fibre necrosis and replacement by fat and connective tissue, due to the absence of the muscle protein dystrophin[1]. 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 first study of the pattern and involvement of fat infiltration in corticosteroid-treated DMD boys using T1w-imaging as part of an ongoing eighteen-month longitudinal study[2]. The effect of exercise on dystrophic muscle is also of interest, especially as these boys have greater functional ability on corticosteroid treatment. In healthy adults exhaustive eccentric (muscle-lengthening) exercise causes an increase in muscle T_2 with a peak between days 3 and 5 post-exercise; this change is thought to be due to oedema[3]. Dystrophin-deficient muscle is more vulnerable to eccentric stress[4], which may result in increased tissue water, manifest as an increase in T_2 or increased Gd uptake. There has been no previous attempt to characterise human DMD muscle pre- and post-exercise by MRI. This study establishes baseline differences in muscle T2 and gadolinium uptake in normal adult and steroid-treated DMD muscle after stepping exercise (where one leg performs concentric and the other eccentric contractions at a level where we do not anticipate change in healthy muscle) and, for the first time assesses the 4-day effect of such exercise in the DMD boys.

Methods *Recruitment:* 11 ambulant boys with DMD (age range 6.6 - 9.9 years, mean 8.3 years) and 6 healthy male adult volunteers (29.6 – 35.3 years, mean 33.3 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. Adult control volunteers were recruited from research staff at the Institute of Human Genetics, International Centre for Life. 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. Pre and post-Gd images of the musculature were collected using axial T1w images with fat suppression (SPIR) using a turbo spin echo sequence (TSE factor 3, low-high profile order, TR/TE/NSA = 500/10/2, slice/gap = 5/10 mm). Gd images were collected 5 minutes after hand injection of 0.1 mmol/kg Gd-DTPA-BMA (Omniscan™, Amersham) into a forearm vein. T_2 images were acquired using a turbo-spin echo sequence (TR/TE/NSA = 3000ms/25,50,75,100ms/1). For the Gd measurements, images were acquired in three blocks at mid-calf, mid-thigh and mid-pelvis: a phantom tube containing 0.2 mmol Gd solution was used to standardise intensities between images. T_2 measurements were only acquired at mid-thigh due to limitations on total scan time.

Exercise protocol: Subjects were asked not to do strenuous physical activity from one week before the pre-exercise scan until after the post-exercise scan was complete. Post-exercise scans were performed 4 days after 20 steps on/off a 20cm- high bench (scaled to 32cm for adults) with the right quadriceps performing concentric and left quadriceps performing eccentric exercise. This was a challenging exercise for the DMD boys, but not for the healthy controls such that no change in T_2 or Gd uptake was expected for healthy adults based on the previous literature: consequently, the controls were only scanned post-exercise.

Analysis: Images were analysed by using MRIcro[5] 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. A Mann-Whitney (SPSS v14) test was used to determine the significances of differences between the signal intensities of the adults and children, left and right muscles being considered separately.

Results All subjects completed the exercise test adequately. The T_2 and Gd-uptake results are shown in figure 1. Comparing the post-exercise scans of the adults and children it is seen that both muscle T_2 (fig 1a) and Gd uptake values (fig 1b) are significantly higher in DMD boys than controls: this is expected due to inflammation and greater interstitial volume in the compromised tissue. Comparing the pre- and post-exercise scans of the DMD boys, there were no significant changes in the T_2 of any of the studied muscles (fig 1c) suggesting no additional effect of exercise on interstitial volume. The Gd uptake data (fig 1d) showed a significant increase ($p < 0.05$) for both left and right tibialis anterior post-exercise. Overall, the other calf muscles showed a greater tendency to increased contrast uptake than the thigh muscles studied and Gd uptake showed greater differences than T_2 measurement.

Conclusions This study demonstrates significant differences in Gd contrast uptake and T_2 values between normal adult and dystrophic muscle in patients treated with corticosteroids in all studied muscles. The additional postulated increases in Gd uptake and T_2 4 days post-exercise were generally not observed in this DMD cohort, with only the tibialis anterior (TA) showing a significant increase in contrast uptake post-exercise in both legs. This indicates that this short bout of exercise is not sufficient to cause additional interstitial or inflammatory change in most muscles after 4 days. These data suggest that Gd uptake imaging is more sensitive than T_2 measurement in characterising the difference between DMD and healthy muscle. Further longitudinal imaging of fat infiltration and T_2 values at 9 and 18 months is being conducted and will compared with longitudinal changes in muscle strength and functional test scores.

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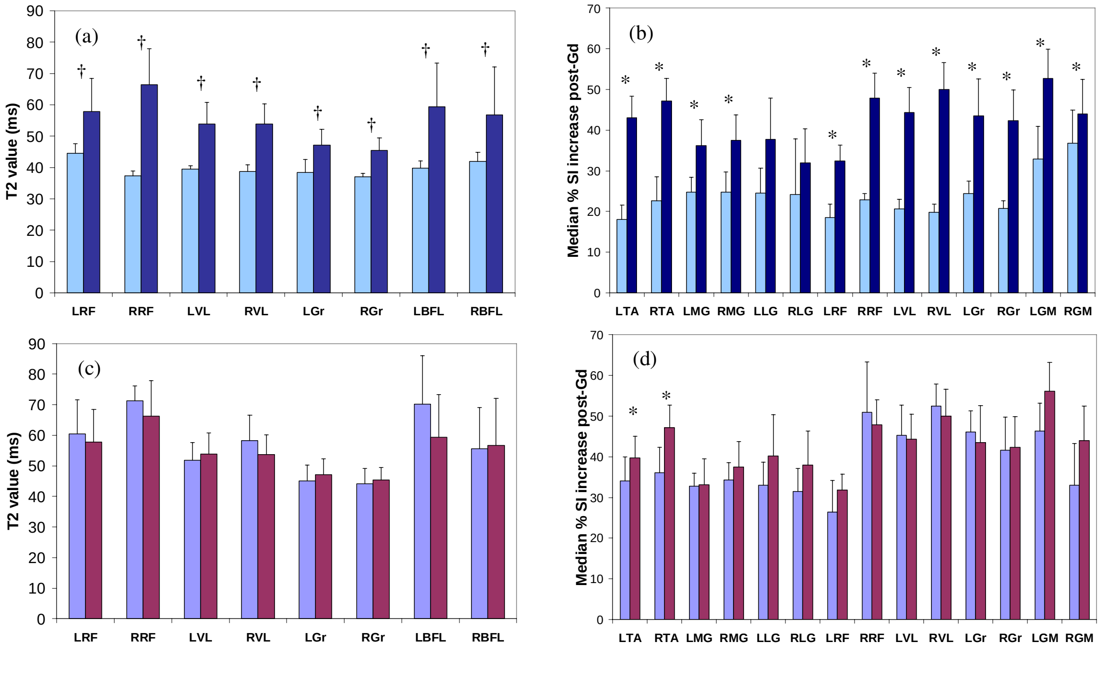

Figure 1: T_2 values for (a) adult vs. child post-exercise and (b) child pre vs. post exercise. % signal increase 5 minutes after administration of Gd for (c) adult vs. child post-exercise and (d) child pre vs. post exercise. Muscles in the right (R) and left (L) legs denoted separately.

Key to muscles
Calf muscles
TA: tibialis anterior
MG: medial gastrocnemius
LG: lateral gastrocnemius
Thigh muscles
RF: rectus femoris
VL: vastus lateralis
Gr: gracilis
BFL : biceps fem. long head
Pelvis muscle
GM: gluteus maximus