Muscle fat infiltration in Limb Girdle Muscular Dystrophy 2I: a comparison of qualitative T1w and quantitative Dixon imaging

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Introduction

Limb Girdle Muscular Dystrophy 2I (LGMD2I) is caused by a mutation in the fukutin related protein gene (FKRP). Although its function is not fully understood it is associated with abnormal glycosylation of α-dystroglycan and hence disrupts the dystrophin-associated glycoprotein complex. This complex forms an essential link between the intracellular cytoskeleton and components of the extracellular matrix. This mutation leads to progressive muscle wasting and necrosis, and fat infiltration [1]. The age of onset, and rate of progression varies between cases. However, there are characteristic patterns of muscle involvement which can distinguish the disease from other muscular dystrophies [2]. The aim of this study was to (i) assess the pattern of fat infiltration of a large, multi-centre cohort using a qualitative radiological score from T1w MRI (ii) to implement a quantitative 3-point Dixon technique to have a non-invasive tool to track the progression of fat infiltration over time, which is necessary to monitor response to treatment and therapies. We compared the infiltration with matched adult controls. The 3 point-Dixon was chosen for the quantitative fat measurements to minimise the effect of B0 and B1 inhomogeneities present in standard T1w images by ensuring that the base images are proton-density weighted, and to avoid the need to calibrate internal phantoms with the patients [3].

Methods

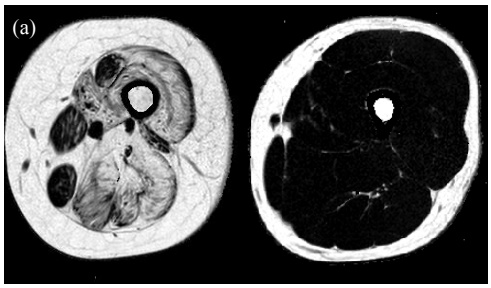
Recruitment: 13 ambulant adults with a genetically-confirmed diagnosis of LGMD2I (9M:4F age range 21 - 64 years, mean 43 years, disease duration 4-39 years, mean 19 years) were recruited and matched to 6 healthy adult controls (5M:1F age range 24-61 years, mean 42 years) *MR protocol:* All scans were performed on a 3T Philips Achieva scanner (Best, NL) using the 6 channel cardiac array coil for signal reception. T1-weighted images of the musculature from the ankles to the iliac crest were acquired using a spin echo sequence (TSE factor 3, TR/TE/NSA = 671/10/2, slice thickness/gap = 5 mm/10 mm, 256 x 192 matrix, FOV mm). A gradient echo 3 point Dixon sequence (TR/TE1,TE2,TE3 = 100ms,3.45,4.6,5.75ms, resolution 1mm, FOV 200mm) was run on the left and right legs separately: the thigh block was centred 1/3 distance up from superior border of patella towards the anterior superior iliac spine. The calf block was centred at the broadest part.

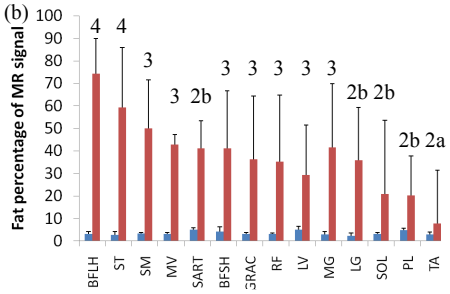
Table 1 : Description of the qualitative muscle grading scale

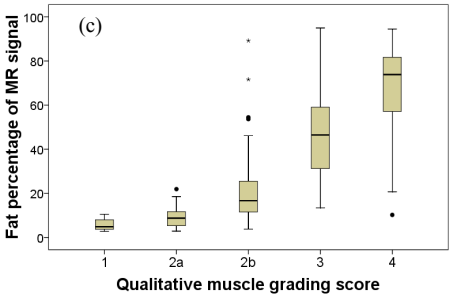
Grade	Description
0	Normal appearance
1	Early moth-eaten appearance with scattered small areas of increased signal
2a	Late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising less than 30% of the volume of the individual muscle.
2b	Late moth-eaten appearance with numerous discrete areas of increased signal with beginning confluence, comprising 30–60% of the volume of the individual muscle
3	Washed-out appearance, fuzzy appearance due to confluent areas of increased signal
4	End stage appearance,muscle replaced by increased density of connective tissue and fat,with only a rim of fascia and neurovascular tissue distinguishable.

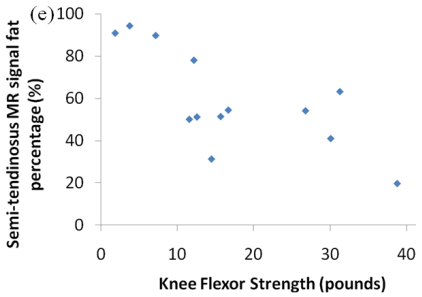
Analysis: The T1w images were analysed on a whole muscle basis by an experienced observer scoring the whole muscle according to a recognised scale (Table 1, [2]). The muscles considered were, in the calf, lateral gastrocnemius (LG), medial gastrocnemius (MG), soleus (SOL), tibialis anterior (TA) and peroneus longus (PL): in the thigh, biceps femoris long and short heads (BFLH and BFSH), semitendinosus (ST), semimembranosus (SM), medial vastus (MV), lateral vastus (LV), sartorius (SART) and gracilis (GRAC). For the 3 point Dixon, the algorithm of Glover [3] was used to produce fat and water only images, and thence to produce an image delineating percentage fat in the visible MR signal. Using ImageJ, regions of interest were drawn in one slice at mid-calf and thigh. ANOVA analysis was followed by consideration of pairwise differences using the student t-test. *Myometry:* Patient strength in knee extensor and knee flexor motions was measured using a hand-held myometer (Microfet, Hoggan, UT).

Figure 2 : (a) 3 point Dixon fat % from LGMD2I patient (left) and control (right) thigh, (b) bars show quantitative fat % for LGMD2I patients (red) and controls (blue) with median qualitative score above bars (c) Comparison of qualitative grade and measured fat percentage, (d) Correlation between knee extensor strength and lateral vastus fat % and (e) between knee flexor strength and semi-tendinosus fat %









Results

From the qualitative T1w data, 182 muscles were assessed: no muscles were assessed to be normal (grade 0) while over half (98) were rated in the top two qualitative grades. From the quantitative Dixon data (fig 2a), all muscles were affected more significantly in the LGMD2I patients than in the controls (fig 2b, at least $p < 0.02$ for every muscle). Though there was overall correlation between qualitative and quantitative assessments of infiltration ($\kappa = 0.79$, $p < 0.0005$,fig 2c), there was considerable variation in fat infiltration within qualitative grades, particularly for muscles with lower grades which would be of interest for studies of therapy. On comparison of the fat infiltration with myometry, fat infiltration in the vastus lateralis correlated strongly with knee extensor strength ($\kappa = -0.84$, $p < 0.0005$, fig 2d) and fat infiltration in the semi-tendinosus correlated with knee flexor strength ($\kappa = -0.72$, $p = 0.006$, fig 2e): myometry for hip flexors, abductors and adductors was found not to have a simple relationship with the fat infiltration of relevant muscles.

Conclusions

The 3-point Dixon method is a powerful method for determining fat infiltration in the muscles of patients with LGMD2I and can be expected to prove powerful in determining the progression of the infiltration over 12 months. The work indicates that qualitative perception and quantitative measurement of fat infiltration can vary widely. Future analysis will look at the relationship between the Dixon measurements and longitudinal variation of fat infiltration. This survey has indicated the limitations of qualitative scores in providing sensitive measures for longitudinal trials. This study is ongoing in collaboration with centres in Paris, London, Copenhagen and Munich to expand the cohort size.

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