

# Natural progression of fatty infiltration and beneficial effects of non-pharmaceutical intervention in FSHD detected by quantitative MRI

Barbara Janssen<sup>1</sup>, Nicoline Voet<sup>2</sup>, Rob Arts<sup>1</sup>, Christine Nabuurs<sup>1</sup>, George Padberg<sup>3</sup>, Alexander Geurts<sup>2</sup>, Bazio van Engelen<sup>3</sup>, and Arend Heerschap<sup>1</sup>  
<sup>1</sup>Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, <sup>2</sup>Rehabilitation, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, <sup>3</sup>Neurology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands

**Introduction:** With a prevalence of 1:20,000 Facioscapulohumeral dystrophy (FSHD) is one of the most common muscular dystrophies. FSHD is associated with contraction of D4Z4 microsatellite repeats on chromosome 4q35, which may lead to a stabilized distal DUX4 transcript [1]. This product has toxic effects on muscular tissue, but the trigger for its synthesis is not yet known. The disease is typically characterized by asymmetric involvement of specific muscles with muscle weakness and fatty infiltration. Facial and scapular muscles are usually the first to be affected, followed by pelvic and lower limb muscles. Currently no treatment is available for these patients. Recently, we established several MR detectable biomarkers for FSHD, with muscular fat fraction as the most valuable one, and used these to characterize a large cohort of patients [2].

The aim of this study was to employ the muscular fat fraction as a biomarker to follow the natural progression of the disease and to assess the effects of two non-pharmaceutical interventions: cognitive behavioral therapy (CBT) and exercise training (AET).

**Materials and methods:** *Recruitment:* Genetically proven FSHD patients were included, average age 55 (range 25-76). Patients were randomly placed in the control group (n=9), CBT group (n=7) or AET group (n=8). The clinical severity was assessed by the Ricci score [3] and muscle strength determined with a quantitative fixed myometry testing system [4].

*MR protocol:* All patients underwent a baseline MR measurement (at time T0), the therapy groups had a 2<sup>nd</sup> MR exam after 7 months (4 months after completing the intervention) and the control group after 4 months of usual care (at time T1). MR was performed on a Siemens Trio 3T system using a <sup>1</sup>H volume coil to measure the upper leg of the patient. A marker was positioned at 1/3 of the distance between spina iliaca anterior superior and patella. For qualitative assessment T1-weighted images were acquired with a spin-echo sequence (TR/TE: 530 ms/16 ms, 23 slices, slice thickness/gap: 4 mm/0.4 mm, FOV 175 mm x 175 mm). Multi spin echo MR images were recorded of the same location (TR: 3 sec, TE: 16 echo times 7.7 ms - 123.2 ms, 4-8 slices; limited by SAR, slice thickness/gap 6 mm/9 mm, FOV 175 mm x 175 mm).

*Analysis:* Fat content was derived from multi spin echo images by fitting the signal intensity to a bi-exponential function with fixed T2 relaxation times for muscle (40 ms) and fat (143 ms) [5], this was done with a custom-made IDL program calculating muscle and fat fractions. Muscle fraction = 1- fat fraction. In the upper leg we investigated rectus femoris, vastus lateralis, vastus intermedius, vastus medialis, semimembranosus, semitendinosus, biceps femoris long head and biceps femoris short head, sartorius, adductor longus, adductor magnus, and gracilis. By visual assessment and marker position the overlapping slices between the first and second measurement were selected, an average over the slices was taken so an average muscle fraction was derived for every investigated muscle for every patient at two time points.

The muscles were divided in three groups having either a normal (>0.75), intermediate (<0.75 and >0.25) or low muscle fraction (<0.25).

## Results

At baseline (T0) the average fat fraction of all upper leg muscles correlated significantly with the corresponding Ricci score of the patient and the average muscle fraction of the hamstring and quadriceps muscle groups with the muscle group strength (see Fig. 1).

The muscles of FSHD patients are nearly binary distributed in those having a normal or low fat fraction and those with a high fat fraction, and only a small number of muscles having an intermediate muscle fraction (see Fig 2. and [2]). The difference in muscle fraction between T0 and T1 was shown to be dependent on the initial muscle fraction (see Fig 2). In controls the muscle fraction decreases significantly over time in muscles having a normal or intermediary muscle fraction at T0. Remarkably, the decrease in muscle fraction was larger in the intermediary muscles (0.08±0.03) compared to the normal muscle (0.03±0.02) (p<0.001).

In the AET group no significant differences were found between muscle fraction at T0 and T1 for the muscles with a normal muscle fraction, nor the quadriceps muscles with an initial intermediate muscle fraction. Muscles with an initial low muscle fraction even showed an increase in muscle fraction. In the CBT group the normal and intermediary fat infiltrated muscles showed no differences in muscle fraction between T0 and T1 (see Fig3).

## Discussion and conclusions

Muscle (or fat) fraction is a non invasive MR detectable biomarker with good correlations with clinical outcome measures like the Ricci score and muscle strength. The increased fat fraction for the upper leg at Ricci score 2 is worth noticing because this Ricci score is defined as having no involvement of the legs. This signifies that the fatty infiltration is already present in these muscles before clinical symptoms arise and thus can be detected in an early pre-clinical stage by quantitative MRI.

In the natural progression of FSHD over a period of four months we observed an increase in fatty infiltration with this quantitative imaging method, in the upper leg muscles of FSHD patients. Deterioration of the muscle was observed in normal as well as in intermediate fat infiltrated muscles. Interestingly, the increase in fat content is most prominent in intermediately affected muscles, which suggest that rapid progression occurs after a certain event has happened, which is in line with the current view on the genetic origin of the disease, needing a trigger for toxic transcription.

Non-pharmaceutical interventions appeared beneficial for patients since progression of the disease was not noticeable after the same period of usual care plus an intervention in muscles with a high muscle fraction. AET even showed an increase in muscle fraction in the heavily affected muscle and intermediately affected muscles appeared to be stabilized in patients which received CBT. This was also the case for the quadriceps muscles in the AET group. This training consisted of aerobic cycling exercise on a bicycle ergometer, which predominantly trained the quadriceps muscles. This suggests that a more extensive exercise program will slow down progression of fat infiltrating the muscles in these patients and even a decrease of fatty infiltration in the very heavily affected muscles.

**References:** 1. Lemmers *et al.*, Science (329), 2010; 2 Janssen *et al.*, ISMRM 2011; 3 Ricci *et al.*, Ann Neurol (45), 1999; 4 Van der Kooi *et al.*, Neurology (63) 2004; 5 Kan *et al.*, NMR Biomed (23), 2010

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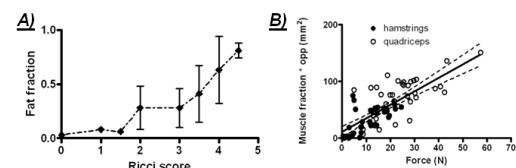


Figure 1: A) Quantitative fat fraction of lower limb correlates with patients Ricci score ( $p<0.001$ ,  $R^2 = 0.87$ ). B) Correlation between muscle fraction and force of quadriceps and hamstring muscle groups ( $p<0.001$  and  $R^2 = 0.30$ ).

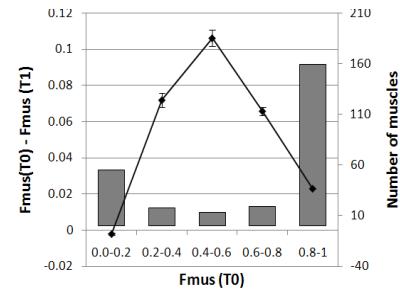


Figure 2: Distribution and progression of muscle fraction in controls at T0. Fmus indicates muscle fraction.

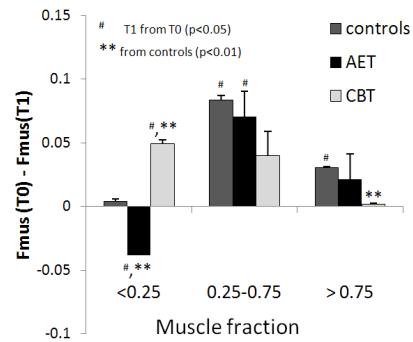


Figure 3: Changes in muscle fraction between T0 and T1, for the different therapies and different initial muscle fraction.