Muscular fat fraction determination by quantitative T2-MRI, reproducibility in facioscapulohumeral muscular dystrophy and healthy volunteers

Linda Heskamp[1], Barbara Helena Janssen[1], and Arend Heerschap[1]
[1]*Radiology, Radboud university medical center, Nijmegen, Netherlands*

Purpose

Muscular fat fraction determined by quantitative T2-MRI (qT2-MRI) has proven to be a valuable biomarker in the clinical assessment of patients with facioscapulohumeral muscular dystrophy (FSHD)[1]. Moreover, recently we showed that this biomarker can detect pre-clinical involvement, has prognostic value, and allows to follow natural progression of muscle deterioration over a four-month period[2]. Therefore, this biomarker seems very well suited for follow-up studies and to objectively evaluate FSHD therapies. When fat fraction determined by qT2-MRI will be chosen as a primary outcome it requires accurate knowledge of the reproducibility of this measure to determine the number of participants that need to be included in a trial in order to establish an effect (power estimation).
The *aim of this study* was to calculate the reproducibility of qT2-MRI determined muscular fat fraction in patients with the common muscular dystrophy FSHD as well as in healthy volunteers.

Methods

Recruitment: Eight genetically proven FSHD type-1 patients (4 male, mean age: 55±11 years, clinical severity score[3]: 2.4±0.9) and four healthy young volunteers (2 male, mean age 22±1 years) were included.
MR protocol: MR was performed on a 3T Siemens Trio using a ^{1}H volume coil around one upper leg of the subject. The qT2-MRI measurement was performed in duplicate after at least one hour and at maximum one day after the first measurement. A marker was positioned at 1/3 of the distance between the spina iliaca anterior superior and patella, to allow for accurate slice matching between the two measurements. 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)[1]. This was done with a custom-made IDL program calculating muscle and fat fractions, producing fat fraction maps of the image (Fig. 1A) Muscle fraction = 1-fat fraction. Regions of interest were carefully drawn for every individual muscle to yield a muscle specific fat fraction (Fig. 1B).
Reproducibility assessment: The reproducibility was assessed by a Bland-Altman analysis. These analyses were performed using Prism 5.0 (GraphPad Software, San Diego, California, USA).

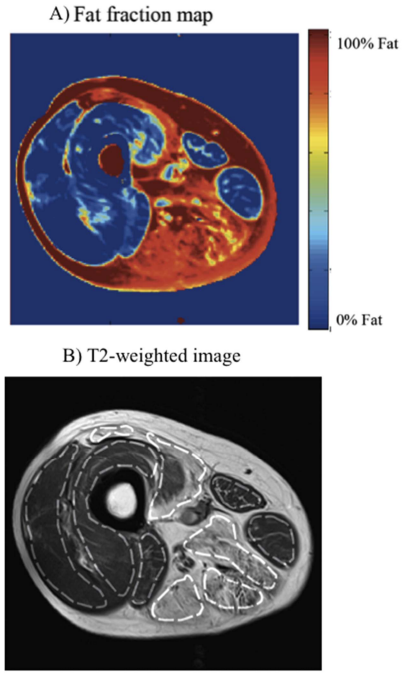

Figure 1: A) Quantitative fat fraction map of a FSHD patient with severe fatty infiltration in the hamstring muscles. Muscular fat fraction ranges from 0 to 100%. B) Corresponding T2-weighted MR image. Regions of interest were carefully drawn on every individual muscle.

Results

Duplicate qT2-MRI measurements of skeletal muscle were performed and the fat fraction analysis was performed in duplicate for every single muscle. This resulted in duplicate values for 80 FSHD muscles and 45 muscles of healthy subjects. The fat fractions from both measurements were subjected to a Bland-Altman analysis. For the FSHD muscle this revealed a coefficient of repeatability for the determination of muscle specific fat fraction of 6.5 % (1.96 * SD). The 95 % limits of agreement were -5.2 % and 7.8 % (Fig. 2). The reproducibility of the fat fraction assessment was independent of the fat fraction.
The reproducibility was found to be much higher for the healthy volunteers, with a coefficient of repeatability of 2.8% and 95% limits of agreement for -2.5% to 3.2% (Fig. 2).

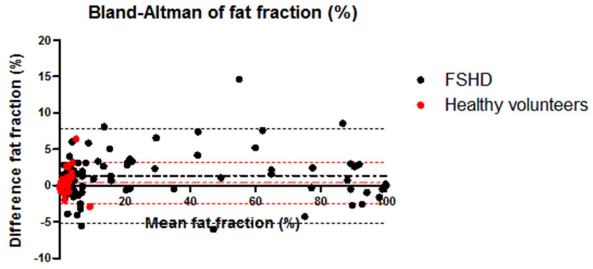

Figure 2: Bland- Altman analysis of the MRI determined muscle specific fat fraction. The dot-dashed line indicates the mean difference and the dashed lines indicate the limits of agreement (95% CI). The reproducibility of the method is high for healthy volunteers compared to patients with FSHD. This is likely due to the limited range of fat fraction found in healthy subjects, in contrast to the entire range (0 – 100%) in patients with a FSHD.

Discussion

Our analysis shows that muscle specific fat fraction can be reliably determined with a coefficient of repeatability of 6.5% in FSHD muscle, and is independent of fat fraction. In healthy subjects higher coefficients of repeatability are found[1, 4, 5], in agreement with our findings of a coefficient of repeatability as low as 2.8%. However, this cannot be taken as representative for patients because the range of fat fraction observed in healthy volunteers is very limited (0 – 8%) compared to the range of fat fractions found in patients (0 - 100%). The difference between the patients and the healthy volunteers may be explained by the difference in age between the two cohorts.
For accurate power estimations for future trials knowledge on the reproducibility or measurement error is crucial. With a coefficient of repeatability of 6.5% a treatment effect of 8% would be determinable when 9 data-points are included in each group. Meaning 9 patients per group for a muscle specific analysis. For a general analysis 9 patients would yield data from at least 90 muscles. With this coefficient of repeatability this would mean that treatment effects of around 2.5% would be picked up by statistical analyses of that data. For instance, this validates the group size in our study in which changes due to the progression of fat infiltration in FSHD patients were recorded[2].

References

1.Kan HE, et al. Neuromuscul Disord (5) 2009; 2.Janssen BH, et al. PLoS One (1) 2014; 3.Ricci E, et al. Ann Neurol (6) 1999; 4.Morrow JM, et al. Eur Radiol (7) 2014; 5.Willis TA, et al. PLoS One (8) 2013

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