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## Outcome measures in Duchenne muscular dystrophy

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# Chapter 4

Association of elbow flexor MRI fat fraction with  
loss of hand-to-mouth movement in patients with  
Duchenne muscular dystrophy

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## Abstract

### Objective

To study the potential of quantitative MRI (qMRI) fat fraction (FF) as biomarker in non-ambulant Duchenne muscular dystrophy (DMD) patients, we assessed the additive predictive value of elbow flexor FF to age on loss of hand-to-mouth movement.

### Methods

Non-ambulant DMD patients ( $\geq 8$  years) were included. 4-point Dixon MRI scans of the right upper arm were performed at baseline and at 12, 18 or 24 months follow-up. Elbow flexor FFs were determined from five central slices. Loss of hand-to-mouth movement was determined at study visits and by phone-calls every four months. FFs were fitted to a sigmoidal curve using a mixed model with random slope to predict individual trajectories. The added predictive value of elbow flexor FF to age on loss of hand-to-mouth movement was calculated from a Cox model with the predicted FF as a time varying covariate, yielding a hazard ratio.

### Results

Forty-eight MRIs of 20 DMD patients were included. The hazard ratio of a percent-point increase in elbow flexor FF for the time to loss of hand-to-mouth movement was 1.12 (95%-confidence interval 1.04-1.21;  $p=0.002$ ). This corresponded to a 3.13-fold increase of the instantaneous risk of loss of hand-to-mouth movement in patients with a 10 percent-points higher elbow flexor FF at any age.

### Conclusion

In this prospective study, elbow flexor FF predicted loss of hand-to-mouth movement independent of age. qMRI measured elbow flexor FF can be used as surrogate endpoint or stratification tool for clinical trials in non-ambulant DMD patients.

### Classification of Evidence

This study provides Class II evidence that qMRI FF of elbow flexor muscles in patients with DMD predicts loss of hand-to-mouth movement independent of age.

## Introduction

Duchenne muscular dystrophy (DMD) is characterized by muscle weakness in a proximal to distal gradient. Independent ambulation is generally lost in the early teens, and occurs years before loss of hand-to-mouth movement (LoHM).<sup>1</sup> While the first drugs for ambulant DMD have received conditional approval, results cannot be extrapolated to later stages of the disease due to progressive and irreversible replacement of muscle by fat and fibrosis causing a reduction in target tissue.<sup>2,3</sup> Conducting clinical trials in DMD is challenging and may be facilitated by objective biomarkers that can be used for stratification or as surrogate endpoint. Quantitative MRI (qMRI) fat fraction (FF) of the vastus lateralis muscle has been shown to predict loss of ambulation in DMD.<sup>4,5</sup> Importantly, this predictive value must be additive to age as any parameter that consistently changes over time will correlate to a decline in function in a progressive disease. Upper arm qMRI FF increases over time and correlates with function cross-sectionally.<sup>6,7</sup> We studied the additive predictive value of elbow flexor FF (FF<sub>EF</sub>) for LoHM to age in a prospective study in non-ambulant DMD patients.

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## Methods

We included male non-ambulant, genetically confirmed DMD patients aged  $\geq 8$  years between March 2018 and July 2019. Patients were recruited from the Dutch Dystrophinopathy Database<sup>8</sup>, and via Dutch outpatient clinics and patient organizations. Exclusion criteria were MRI contra-indications (e.g. spinal fusion, daytime respiratory support or inability to lie still for 45 minutes), exposure to an investigational drug  $\leq 6$  months prior to participation, and recent ( $\leq 6$  months) upper extremity surgery or trauma. 122 eligible patients were approached for participation, and details on this recruitment have been reported previously.<sup>9</sup> Patients visited the Leiden University Medical Center (LUMC) for a half-day of assessments at baseline, 12 and 18 months. Due to the COVID-19 pandemic, some follow-up visits were postponed from 12 to 18 months and from 18 to 24 months or missed. Telephone calls every 4 months were used to evaluate LoHM.

### Standard Protocol Approvals, Registrations, and Patient Consents

The medical ethics committee of the LUMC approved the study, and we obtained written informed consent from patients and legal representatives. The study was registered on ToetsingOnline (NL63133.058.17, [www.toetsingonline.nl](http://www.toetsingonline.nl)).

### MRI acquisition and analysis

4-point Dixon scans were acquired of the right upper arm on a 3T MRI scanner (Ingenia, Philips Healthcare, Best, The Netherlands) using two circular 15cm coils. Participants were positioned on the right side with the right shoulder and elbow in 90° flexion, because pilot experiments suggested this to be the most comfortable position and this position placed

the upper arm muscles more towards the center of the MRI scanner. If this was uncomfortable a supine position was chosen. Dixon scans were acquired with 33 slices and a voxel size of 1x1x10mm (repetition time 310ms, first echo 4.40ms, echo spacing 0.76ms, flip angle 20°), and aligned perpendicular to the humerus bone. Dixon water and fat images were generated using in-house developed software (Matlab 2016a, The Mathworks of Natick, Massachusetts, USA) with a 6-peak lipid spectrum, where B0 maps were calculated from the phase data of the first and last echoes. Regions of interest (ROI) were drawn on the muscle border of the elbow flexors (biceps and brachialis muscles) by one reviewer (K.J.N.) on 5 contiguous slices around a central slice (Figure 1A) using online software (mipav.cit.nih.gov). The central slice was located at 40% distance from the elbow based on the length of the humerus bone. The same reviewer performed quality control of elbow flexor ROIs, where scans with ROIs that contained artefacts or insufficient signal were excluded. ROIs from different time-points on similar slices in the same participant were also compared by this reviewer and adjusted in case of discrepancies. ROIs were eroded by two voxels, and  $FF_{EF}$  was calculated as a weighted mean value by averaging elbow flexor voxels of all eroded ROIs from the reconstructed fat and water images and correcting for partial saturation due to T1 effects by:

$$FF = \frac{1.05 \times \text{Fat}}{1.25 \times \text{Water} + 1.05 \times \text{Fat}}$$

### Clinical assessments and endpoint

Performance of the Upper Limb (PUL) 2.0 was assessed for the right arm at all visits. LoHM was defined as the inability to move a filled glass independently to the mouth using the right hand and allowing support of the elbow on a table, similar to the PUL hand-to-mouth item where a 200gram weight is used. Age at LoHM was prospectively established to a month's precision. If LoHM had occurred before baseline, month and year were established retrospectively using a detailed interview and clinical documentation.

### Statistical analysis

The difference in  $FF_{EF}$  between baseline and 12 months follow-up was assessed using Wilcoxon signed-rank test. The additive predictive value of  $FF_{EF}$  to age on LoHM was calculated using a Cox proportional hazards model as described previously.<sup>4</sup> For this, we applied a logit transformation to  $FF_{EF}$  to allow use of standard statistical methods that rely on a gaussian distribution. A linear (mixed) model was fitted to the transformed data with age as the only covariate and a random slope per individual. The fitted lines were transformed back to the original scale using a logistic transformation, after which individual  $FF_{EF}$  trajectories were predicted at any time. The Cox proportional hazards model was fitted with the predicted  $FF_{EF}$  as a time-varying covariate, yielding a hazard ratio (Wald test;  $p < 0.05$ ). The primary research question of this study was: does  $FF_{EF}$  have additive predictive value to age on LoHM in non-ambulant DMD patients? The level of evidence was assigned as Class II during the review process.

## Data availability

Anonymized data and analysis software can be made available to qualified investigators.

## Results

Twenty-two DMD patients participated, but two patients refused the MRI. One patient switched to a medication trial after baseline, one patient discontinued after 12 months follow-up because of traveling distance, and eight visits were canceled due to COVID-19 restrictions. One 12 months follow-up scan was excluded due to insufficient signal. Forty-eight MRIs of 20 DMD patients were included, where 12 patients had three MRIs, four patients two and four patients one. All patients used glucocorticoids, but one patient had temporarily ceased treatment six weeks prior to baseline due to weight gain. Patient's characteristics at baseline, and FF<sub>EF</sub> results and PUL scores at different time-points are presented in Table 1. LoHM had occurred before baseline in two patients, and occurred during the study in nine. Median decline in PUL total score over 12 months was 3 points (n=15; range -1 to 8). Median decline in PUL elbow domain score was 2 points (range 0 to 4; Figure 1B). There was a significant mean annual increase in FF<sub>FE</sub> of 5.9% ± 5.4% (p<0.01).

### Relation between hand-to-mouth movement and FF<sub>EF</sub>

Acquired and predicted FF<sub>EF</sub> data and predicted FF<sub>EF</sub> at age of LoHM are shown in Figure 1C and 1D respectively. The hazard ratio of a percent-point increase in FF<sub>EF</sub> for the time to LoHM was 1.12 (log hazard ratio 0.11; 95%-confidence interval 1.04-1.21; p=0.002). This hazard ratio corresponds to a 3.13-fold increase of the instantaneous risk of LoHM in patients with a 10 percent-points higher FF<sub>EF</sub> at any age. An FF<sub>EF</sub> growth chart (Figure 2A) and survival chart for preserved hand-to-mouth movement (Figure 2B) illustrate relationships between percentile FF<sub>EF</sub> curves and LoHM trajectories.

**Table 1. Patient characteristics**

Characteristics at baseline	DMD patients n=20
Age, years	13.5 (12.5-16.4)
Righthanded	16 (80%)
Steroid use	
Prednisone intermittent	10 (50%)
Deflazacort intermittent	9 (45%)
Deflazacort daily	1 (5%)
Height, m	1.55 (1.46-1.66)
Weight, kg	65.1 (51.4-82.2)
Body mass index, kg/m <sup>2</sup>	27.6 (23.3-31.1)

**Table 1.** Continued

Characteristics at baseline	DMD patients n=20
Age at start steroid use, years	5.6 (4.4-7.9)
Age at loss of ambulation, years	11.5 (10.0-12.9)
Loss of hand-to-mouth movement before inclusion	2 (10%)
PUL 2.0 total score baseline, points	21 (19-34)
Elbow flexor fat fraction baseline, %	50.9 (42.4-72.4)
Characteristics at follow-up	
PUL 2.0 total score 12 months, points	20 (17-30) <sup>n=15</sup>
PUL 2.0 total score 18 months, points	24 (16-29) <sup>n=11</sup>
PUL 2.0 total score 24 months, points	17; 20; 37 <sup>n=3</sup>
Elbow flexor fat fraction 12 months, %	60.2 (44.4-78.1) <sup>n=14</sup>
Elbow flexor fat fraction 18 months, %	67.9 (53.8-84.4) <sup>n=11</sup>
Elbow flexor fat fraction 24 months, %	23.3; 38.6; 86.1 <sup>n=3</sup>
Loss of hand-to-mouth movement during follow-up	9 (45%)
Age at loss of hand-to-mouth movement, years	15.3 (10.4-18.2) <sup>n=11</sup>
No loss of hand-to-mouth movement during follow-up	9 (45%)
Age last follow-up for patients with preserved hand-to-mouth movement, years	15.1 (14.4-16.3) <sup>n=9</sup>

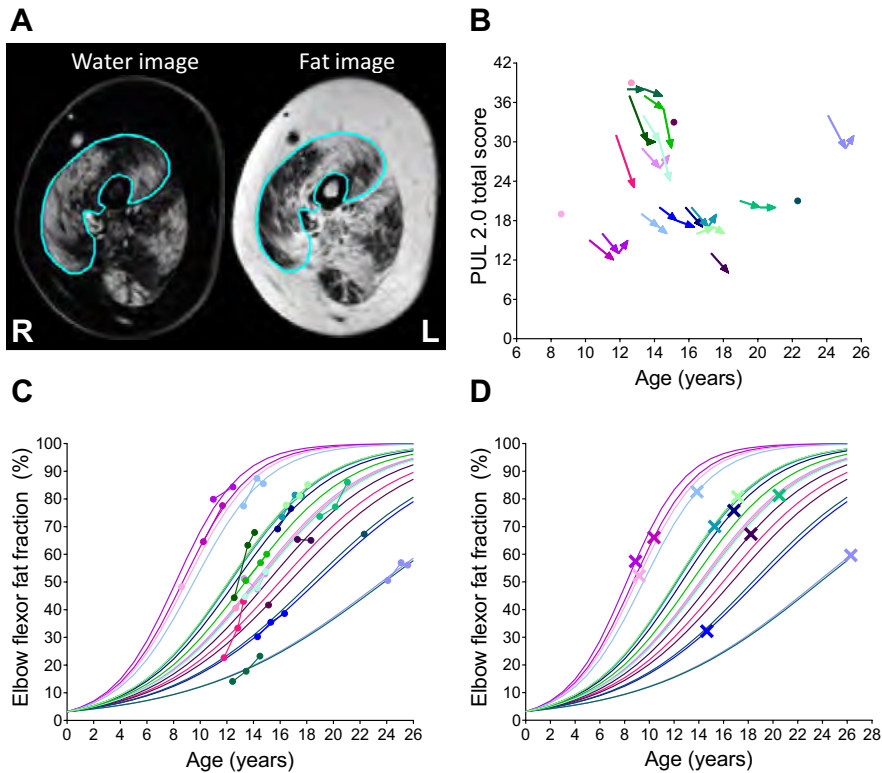
Abbreviations: DMD = Duchenne muscular dystrophy. PUL = Performance of the Upper Limb. Values are median (first; third quartiles), number of patients (%), or the actual values of all patients. If a certain value was not available for all patients, the number of patients for whom the data was available was presented after the result with  $n$  = number.

## Discussion

In this prospective study, we show that  $FF_{EF}$  predicts LoHM in non-ambulant DMD patients on top of age. This added predictive value is essential, because parameters that consistently change over time will always correlate with functional tests in a progressive disease.

Previous studies demonstrated that qMRI muscle FF increases over time and correlates with function cross-sectionally in DMD.<sup>6, 7, 10, 11</sup> However, any outcome measure that consistently changes over time will correlate to declining measures of function in a progressive disease. Two previous studies demonstrated the added predictive value of vastus lateralis FF on top of age on the clinical outcome loss of ambulation, and thus showed for the first time that muscle FF adds to the assessment of disease severity.<sup>4, 5</sup>

$FF_{EF}$  increased according to a sigmoidal curve, similar to the vastus lateralis FF in ambulant patients.<sup>4, 5</sup> The hazard ratio of 1.12 was comparable to that of the vastus lateralis FF for the time to loss of ambulation.<sup>4</sup> These data thus support the use of qMRI FF as objective



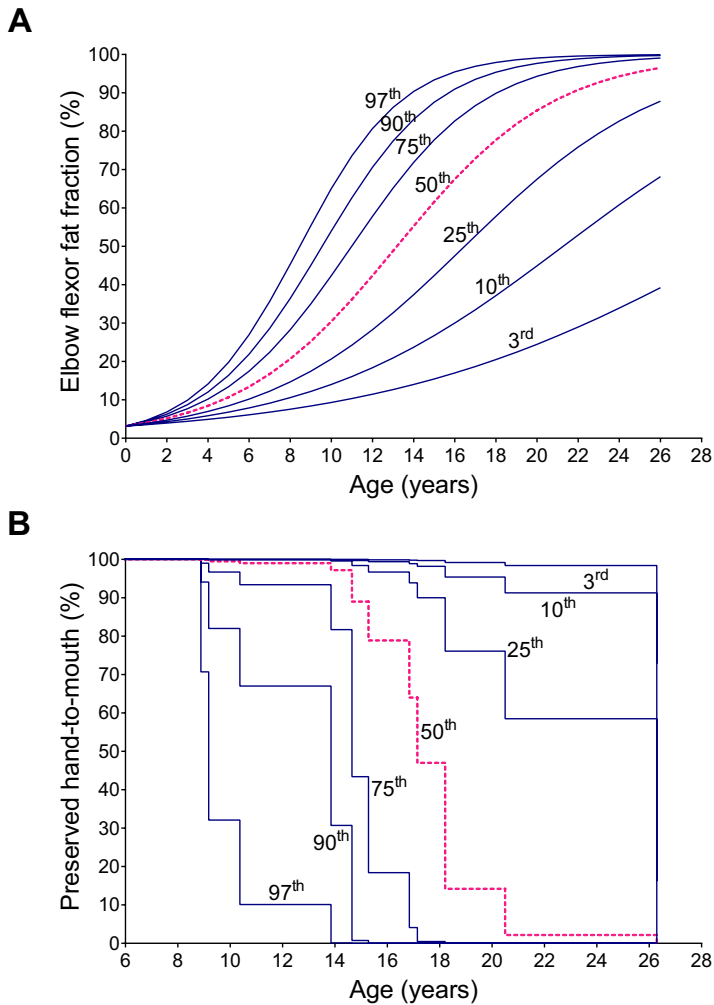
**Figure 1. Longitudinal clinical and elbow flexor fat fraction (FF<sub>EF</sub>) data**

In (A) an example of a region of interest (ROI) drawn on the elbow flexor muscles (line) is shown on a water image (left) and corresponding fat image (right). In (B) longitudinal Performance of the Upper Limb (PUL) 2.0 total scores (maximum 42 points) are plotted versus age. PUL total scores decrease with age, but there is a large variation of scores between Duchenne muscular dystrophy (DMD) patients of similar ages. In (C) FF<sub>EF</sub> results that were acquired are plotted versus age, as well as FF<sub>EF</sub> results that were predicted using a logit transformation, linear (mixed) model and logistic transformation. Patients with higher FF<sub>EF</sub> results at younger ages or faster FF<sub>EF</sub> increases had steeper predicted FF<sub>EF</sub> slopes. In (D) predicted FF<sub>EF</sub> results are plotted versus age and predicted FF<sub>EF</sub> at age loss of hand-to-mouth movement are shown with a cross. The colors used in (B), (C) and (D) are unique for each participant.

biomarker in different stages of the disease. Predicted FF curves can be used for stratification in clinical trials or as surrogate endpoint, limiting sample size and duration.

The rate of change in FF, for instance one-year change, could be used as biomarker in trials where the therapeutic effect over that period of time can be compared to placebo or another therapy, and the power calculation could be based on the more or less 'linear' middle part of the FF curve as that is where the fastest change is expected to happen. This will require stratification of the cohort with respect to baseline FF, as is now commonly done for functional tests.<sup>10</sup>





**Figure 2. Elbow flexor fat fraction ( $FF_{EF}$ ) growth chart and survival chart of preserved hand-to-mouth movement**

In (A) we generated an  $FF_{EF}$  growth chart with a 3<sup>rd</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup> and 97<sup>th</sup> percentile curve from the predicted  $FF_{EF}$  data. (B) Using the resulting hazard ratio, we transformed the predicted  $FF_{EF}$  growth curves to a 3<sup>rd</sup>, 10<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, 90<sup>th</sup> and 97<sup>th</sup> percentile survival curve for preserved hand-to-mouth movement. A patient on the 3<sup>rd</sup> percentile in the  $FF_{EF}$  growth chart is also on the 3<sup>rd</sup> percentile in the survival chart.

We assessed the timing of reaching the clinical endpoint via regular phone calls in between clinical assessments. In our experience, patients and caregivers are able to define such important endpoints within a month's precision. This increases the power of our survival analyses compared to standard natural history studies where clinical assessments are performed at six or 12 months intervals only. It reduced the burden for participants and

allowed continuation of the protocol despite COVID-19 related restrictions. The importance of hand-to-mouth movement is stressed by its incorporation in the widely used Brooke upper extremity rating scale, the PUL and DMD Upper Limb Patient Reported Outcome Measure, where patients and families confirmed its clinical relevance.<sup>12, 13</sup>

Limitations of this study are the small sample size, which did not allow modelling the intercept of the  $FF_{EF}$  curves. Restrictions due to the COVID-19 pandemic also led to some missing data. It's important to replicate results in other cohorts with different steroid regimes.

In conclusion,  $FF_{EF}$  predicted loss of hand-to-mouth movement independent of age in non-ambulant DMD patients. This establishes qMRI FF as biomarker in DMD and potentially facilitates the design of clinical trials, either via stratification or use as surrogate endpoint.

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