



Timed function tests, motor function measure, and quantitative thigh muscle MRI in ambulant children with Duchenne muscular dystrophy: A cross-sectional analysis

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Abstract

The development of new therapeutic agents for the treatment of Duchenne muscular dystrophy has put a focus on defining outcome measures most sensitive to capture treatment effects. This cross-sectional analysis investigates the relation between validated clinical assessments such as the 6-minute walk test, motor function measure and quantitative muscle MRI of thigh muscles in ambulant Duchenne muscular dystrophy patients, aged 6.5 to 10.8 years (mean 8.2, SD 1.1). Quantitative muscle MRI included the mean fat fraction using a 2-point Dixon technique, and transverse relaxation time (T2) measurements. All clinical assessments were highly significantly inter-correlated with $p < 0.001$. The strongest correlation with the motor function measure and its D1-subscore was shown by the 6-minute walk test. Clinical assessments showed no correlation with age. Importantly, quantitative muscle MRI values significantly correlated with all clinical assessments with the extensors showing the strongest correlation. In contrast to the clinical assessments, quantitative muscle MRI values were highly significantly correlated with age. In conclusion, the motor function measure and timed function tests measure disease severity in a highly comparable fashion and all tests correlated with quantitative muscle MRI values quantifying fatty muscle degeneration.

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1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disease affecting 1 in 3500–6000 male births [1]. It is characterized by a progressive and irreversible replacement of

normal muscle with connective and adipose tissue. Dystrophin, which is the disease causing gene product, is present in many different tissues throughout the body. However, the disease pathology is predominantly seen in skeletal and heart muscle leading to continuous loss of muscle function and early death [2,3].

With the development of new therapies for DMD, sensitive outcome measures are needed to capture disease progression and monitor treatment effects/efficacy.

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The 6-minute walk test, measuring the 6-minute walk distance (6MWD) and motor function measure (MFM) are validated and highly reproducible clinical assessments in DMD [4]. Both tests have been used in clinical trials in DMD before and were shown to be able to predict loss of free ambulation [5–7]. Also, both measures show a certain improvement in test performance in DMD patients up to 7 years of age, which must be taken into consideration when using these tests as outcome measures [5,6,8,9]. However, the use of the 6MWD as well as other timed motor function tests is limited by loss of ambulation occurring in DMD around the age of 8–12 years. In contrast, the MFM assessing three dimensions of motor performance can be continuously used throughout the course of the disease [5]. The MFM has been evaluated for the use in DMD trials and is recommended by the European Medicines Agency (EMA) as a clinical outcome measure equal to the 6MWD [10].

All clinical assessments have the common disadvantage of being dependent on patient collaboration and interaction with the examiner. In contrast, muscle MRI has the advantage of being relatively independent of patient collaboration. Pathological changes such as edema and fatty replacement can be uncovered and quantified. In previous studies in DMD, quantitative thigh muscle MRI (qMRI) values highly correlated with clinical outcome measures and a cut off value of 50% mean fat fraction (FF) in the thigh was found to predict loss of free ambulation [8,11,12].

The aim of this study was first to correlate the MFM with the 6MWD and timed function tests and second, to compare the MFM, the 6MWD and timed function tests with the degree of fatty degeneration assessed by qMRI using a T2 and 2-point Dixon (2PD) method in DMD patients. According to previous work indicating that a 6MWD of <350m was predictive of rapid decline in ambulation [6,13–15], a subgroup analysis including boys ≥ 7 years of age with a 6MWD of ≥ 350 m was done in order to consider an even more homogenous group of patients. This study was designed to define the most promising clinical and imaging efficacy outcomes for future clinical trials.

2. Patients and methods

2.1. Patients

Baseline data from 47 ambulant DMD patients who participated in the “Treatment with L-citrulline and metformin in Duchenne muscular dystrophy”-study were included in the current analysis. A subgroup of patients was selected with a 6MWD of ≥ 350 m and older than 7 years of age at inclusion. Patients were recruited from our outpatient clinic and from the patient registries of Switzerland, Germany and Austria. Ethical approval was obtained from the local Ethics Committee (Ethics Committee of the two Basel Cantons (EKBB 63/13) and the Swiss Drug Agency (Swissmedic 2013DR3151). The trial was registered under ClinicalTrials.gov (NCT01995032) prior to recruitment. Inclusion criteria consisted of genetically or immunohistochemically confirmed diagnosis of DMD, age 6.5–10 years at inclusion; MFM D1 subdomain of $> 40\%$; ability to walk 6 minutes on plain surface without walking aids; no other significant medical condition or malignancy; no participation

in any therapeutic trial 3 months prior to inclusion; stable treatment with corticosteroids for > 6 months or no previous corticosteroid treatment. Written informed consent was given by all caregivers.

2.2. Clinical assessments

Clinical assessments consisted of the MFM, the 6MWD, the timed 10-meter walk/run test (10MWT) and the supine up time. As defined by the study protocol, all exams were done in the same chronological order for all patients, with the physiotherapeutic evaluation prior to MRI scanning. Physical assessment was done by experienced physiotherapists, accredited in Lyon, France to use the MFM [5]. For the 6MWD, all children walked over a total of six minutes on a hard, flat surface in a hallway. Turning points were clearly marked on the walls of the hallway to ensure repeatability. In addition, the 10MWT and the supine up time were assessed in a standardized fashion. For details please refer to the previously published study protocol [16].

2.3. Magnetic resonance imaging

All MRIs of the thigh muscles (extensors, flexors and adductors) were performed as previously described [11]. In short, all patients were scanned on a 3 Tesla clinical scanner (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany) in feet first supine position using peripheral angio 36 channel and spine coils. Repeatability of positioning was assured similar to Fischmann et al [17]. After localizers and slice positioning was done, a three dimensional (3D) gradient echo sequence with two different echo times for in-phase and opposed-phase imaging was acquired. A multi-contrast spin echo (SE) sequence with 14 echo times was used for quantification of transverse relaxation times (T2).

Total scanning time per patient was below 30 minutes. To help children endure the scanning procedure, a caregiver was present at all times in the scanner room seated within view of the patient. Each child could watch a movie of his choice for the whole of the scanning time. All scans were performed by one MRI technician (TH) with a broad experience in research imaging and neuromuscular imaging. The 2-point Dixon (2-PD) method was used to evaluate the mean fat fraction (FF, %). Regions of interest (ROI) were drawn manually by one reader and were checked for quality by one experienced second reader. ROIs were drawn in three slices of the in phase images of the 2-PD with the same imaging levels as the multi-contrast SE images. Images were not co-registered. If there was no patient movement between the two scans, ROIs could be transferred. Otherwise, they were redrawn on the multi-contrast SE images. ROIs included whole muscle area for extensors, flexors and adductors for each leg respectively, with a minimal rim of muscle tissue at the border to the surrounding fat tissue. Relative fat content maps were generated from the pixelwise fat fraction given $f / (f + w)$ (f = fat, w = water). All MRI evaluations were performed blinded to clinical status and MFM measurements.

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