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Skeletal muscle water T_2 as a biomarker of disease status and exercise effects in patients with Duchenne muscular dystrophy

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Abstract

The purpose of this study was to examine exercise effects on muscle water T_2 in patients with Duchenne muscular dystrophy (DMD). In 12 DMD subjects and 19 controls, lower leg muscle fat (%) was measured by Dixon and muscle water T_2 and R_2 ($1/T_2$) by the tri-exponential model. Muscle water R_2 was measured again at 3 hours after an ankle dorsiflexion exercise. The muscle fat fraction was higher in DMD participants than in controls ($p < .001$) except in the tibialis posterior muscle. Muscle water T_2 was measured independent of the degree of fatty degeneration in DMD muscle. At baseline, muscle water T_2 was higher in all but the extensor digitorum longus muscles of DMD participants than controls ($p < .001$). DMD participants had a lower muscle torque ($p < .001$) and exerted less power ($p < .01$) during exercise than controls. Nevertheless, muscle water R_2 decreased (T_2 increased) after exercise from baseline in DMD subjects and controls with greater changes in the target muscles of the exercise than in ankle plantarflexor muscles. Skeletal muscle water T_2 is a sensitive biomarker of the disease status in DMD and of the exercise response in DMD patients and controls.
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Keywords: Duchenne muscular dystrophy; Magnetic resonance imaging; Exercise; Skeletal muscle; Fat fraction; Water T_2

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common X-linked lethal childhood disease, with an incidence of about 1 in 5000 newborn boys [1,2]. Even with clinical intervention boys and young men lose independent mobility during teen years. The pelvic and thigh muscles are involved early and are severely affected with fatty degeneration. The disease progression is slower in the lower leg muscles than in the proximal leg muscles. Among the lower leg muscles, the ankle dorsiflexor muscles including the tibialis anterior and extensor digitorum longus are relatively spared in younger boys with DMD [3–5].

In recent years promising new therapeutics have been entering in clinical trials for DMD. Robust biomarkers are needed to measure disease progression and therapeutic response in a smaller number of individuals over a shorter timeframe in clinical trials. Expression of dystrophin, the protein product of the *DMD* gene [6], has been used as an outcome measure in clinical trials. However, accurate quantification of dystrophin has been challenging and requires the invasive procedure of a muscle biopsy [7]. The magnetic resonance imaging (MRI) measure of the water transverse relaxation time (T_2) was identified as a biomarker of dystrophin expression to therapeutic levels in a dog model of DMD [8].

It is well established that dystrophin provides mechanical stability to the sarcolemma [9,10]. Absence of dystrophin leads to sarcolemmal fragility with consequent muscle fiber degeneration and progressive replacement of muscle by fat and connective tissue [11]. Environmental factors including contractile stress during exercise appear to exacerbate the damage in dystrophin-deficient muscle fibers [12]. Muscle water T_2 is sensitive to changes of muscle injury or edema after exercise and can be used to identify the muscles from which creatine kinase, an indicator of sarcolemmal leak, is released

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into the circulation [13]. Muscle water T_2 abnormalities have been shown to relate to membrane leakiness and inflammation in animal models of DMD. An increase in muscle T_2 has been reported in the hindlimb muscles of *mdx* mice after downhill running [14]. However, in a study of DMD patients muscle T_2 was not sensitive and gadolinium contrast administration was required to demonstrate exercise effects by MRI [15]. In these studies, muscle T_2 was calculated based on a mono-exponential model, which is increased by both fatty infiltration and changes in the water component in skeletal muscle. Mdx mice do not develop significant fatty infiltration, and consequently T_2 directly reflects the muscle water component. In contrast fatty infiltration masks increases in muscle water T_2 in human dystrophic muscle [16,17].

A recently proposed tri-exponential model [18] enables extraction of water T_2 from the multi-echo signal decay by taking into account the large T_2 differences between the fat and water components. Pilot data showed that the tri-exponential model measures muscle water T_2 independent of fat values in skeletal muscle [18]. In this study, we examined volitional ankle dorsiflexion exercise effects on skeletal muscle water T_2 as measured by the tri-exponential model in the lower leg muscles of DMD subjects participating in a clinical trial and in age-matched healthy volunteers.

2. Materials and methods

2.1. Participants and study design

In this cross-sectional study, MRI of the lower leg skeletal muscles was acquired at baseline and at 3 hours post-exercise in ambulatory subjects with DMD and age-matched healthy volunteers. All patients were on oral corticosteroids with a dose equivalent to prednisone 0.75 mg/kg/day. The DMD participants traveled to the NIH Clinical Center during the screening phase of a clinical trial evaluating an oligonucleotide therapy (NCT01462292). The healthy volunteer boys were recruited from the NIH Clinical Research Volunteer Program registry. Subject eligibility, inclusion and exclusion criteria have been described elsewhere [19]. All subjects were asked to avoid excessive physical activity beyond their normal levels for a week prior to the study visit.

The NIH imaging study was registered on clinicaltrials.gov (NCT01451281) and was in compliance with the NIH Privacy Act and approved by an NIH Institutional Review Board. Informed written assent and consent were obtained from each subject and parent or guardian before participation in the study.

2.2. The ankle dorsiflexion exercise

A portable device (Ankle IntelliStretch device, RehabTek, Chicago, IL) was used for volitional concentric ankle dorsiflexion exercise and to measure the biomechanical data. The device has FDA Class I approval and has been used in children for both passive stretching and voluntary exercise [20,21]. It is equipped with a torque sensor, a servomotor, and a digital controller. The device was connected to a computer for display and user interface. The user interface allowed adjustment of the applied torque value, motion velocity, and difficulty levels of the exercise games, such as assistance level and resistance level, according to each participant's ability. The participant was seated in a comfortable chair with his upper body strapped against the backrest of the chair and the device in front at an appropriate distance to keep the knee flexed at 30 degrees to eliminate the restraining effect of the gastrocnemius muscle on ankle dorsiflexion [22]. The leg was secured by the leg support and the foot was attached onto the footplate with the ankle joint aligned to the rotation axis of the device. The participant was asked to play computer games by voluntary ankle dorsiflexion movements that began from the neutral position of the ankle joint. Plantarflexion movement was restricted to avoid muscle injury related to eccentric lengthening. Before exercise ankle passive range of motion, active range of motion, and maximum dorsiflexion torque at neutral position were assessed using the IntelliStretch device. The range of the moving target in the computer games was scaled to fit the range of motion of the ankle dorsiflexion in each child. The resistance level was determined by each child's ability to maximally dorsiflex his ankle as a measure of his ankle dorsiflexion strength. The resistance level added by the device was never greater than 50% of maximal ankle dorsiflexion strength in each participant. The duration of the exercise for each participant was limited by his exercise tolerance (generally 25–30 minutes). None of the participants reported muscle soreness or fatigue either during or after exercise. Note that the ankle device allowed setting the exercise parameters according to the abilities of a participant and physical exhaustion was avoided during muscle activity.

Exercise performance data were analyzed using in-house MATLAB scripts. The total work performed by the subject during each period of exercise was computed by a two-step process. First, linear regression was used to estimate the foot sagittal plane moment of inertia from the individual's age, height, and body mass [23,24]. Work performed during exercise was calculated as the area under the angular acceleration-angle curve multiplied by the estimated moment of inertia. Power was computed as the work divided by the time of movement execution. For each subject, the work (J) and power (W) reported are aggregate totals summed across the entire exercise session.

2.3. MRI acquisition

MR images of the lower leg were acquired on a 3T Verio scanner (Siemens, Erlangen, Germany) at the NIH Clinical Center. An 8-element knee coil was used for the lower leg. Subjects were placed in the feet-first supine position inside the magnet bore and the legs were secured with foam pads. All scans were performed on the same scanner. T_1-weighted turbo spin echo images were acquired consisting of 21 slices of 5 mm thickness with a slice gap of 5 mm and 1.5 mm in-plane resolution. For water T_2 determination, a standard non-fat saturated multi-slice multi-echo sequence was acquired with a TR = 5000 ms, nominal flip angles = 90° and 180°, and a train of 12 echoes with TEs ranging from 14.3 ms to 171.6 ms with 14.3 ms echo-spacing. The field of view was equal to 126 × 180 mm^2, with a pixel size of 0.7 mm^2, covering 15 slices of 5 mm

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