Endurance training improves fitness and strength in patients with Becker muscular dystrophy

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Studies in a dystrophinopathy model (the mdx mouse) suggest that exercise training may be deleterious for muscle integrity, but exercise has never been studied in detail in humans with defects of dystrophin. We studied the effect of endurance training on conditioning in patients with the dystrophinopathy, Becker muscular dystrophy (BMD). Eleven patients with BMD and seven matched, healthy subjects cycled 50, 30 min sessions at 65% of their maximal oxygen uptake (VO2max) over 12 weeks, and six patients continued cycling for 1 year. VO2max, muscle biopsies, echocardiography, plasma creatine kinase (CK), lower extremity muscle strength and self-reported questionnaires were evaluated before, after 12 weeks and 1 year of training. Endurance training for 12 weeks, improved VO2max by 47±11% and maximal workload by 80±19% in patients (P<0.005). This was significantly higher than in healthy subjects (16±2% and 17±2%). CK levels did not increase with training, and number of central nuclei, necrotic fibres and fibres expressing neonatal myosin heavy chain did not change in muscle biopsies. Strength in muscles involved in cycle exercise (knee extension, and dorsi- and plantar-flexion) increased significantly by 13±40%. Cardiac pump function, measured by echocardiography, did not change with training. All improvements and safety markers were maintained after 1 year of training. Endurance training is a safe method to increase exercise performance and daily function in patients with BMD. The findings support an active approach to rehabilitation of patients with BMD.

Keywords: muscular dystrophy; Becker muscular dystrophy; aerobic exercise

Abbreviations: BMD = Becker muscular dystrophy; CK = creatine kinase; DMD = Duchenne muscular dystrophy; LVEF = left ventricular ejection fraction


Introduction

Becker muscular dystrophy (BMD) is an X-linked inherited muscle disease affecting the proximal musculature of the upper and lower extremities. BMD is caused by mutations in the dystrophin gene, and is a milder variant of Duchenne muscular dystrophy (DMD). In general, patients with DMD suffer a complete loss of dystrophin due to an out-of-frame mutation, whereas BMD patients have an in-frame mutation resulting in some functional dystrophin. Dystrophin is believed to act as a link between the extracellular matrix and the contractile filaments of muscle, stabilizing the membrane during contraction. Loss of dystrophin results in a decreased level or complete absence of the remaining dystrophin-associated protein (DAP) complex from the muscle membrane, thereby causing instability of the sarcolemma (Allikian and McNally, 2007). The instability and disruption of the sarcolemma in BMD is thought to be a major contributor to the pathogenesis of the condition (Campbell, 1995; Allikian and McNally, 2007). Influx of calcium at sites of sarcolemmal damage activates protease activity, which in turn can lead to cell necrosis (Campbell, 1995) and muscle weakness (Allikian and McNally, 2007).

There is evidence to suggest that dystrophin also plays an active role in cell signalling through its association with neuron specific nitric oxide synthase (Chang et al., 1996). Nitric oxide (NO) is thought to be involved in vasodilation during exercise and metabolism of free radicals. Decreased levels of NO, found in patients with dystrophinopathy, may therefore contribute to the pathogenesis of the disease by increased oxidative stress, and relative ischaemia during exercise due to impaired vasodilation (Rando et al., 1998; Sander et al., 2000).
Based on clinical experience, patients with BMD often lead a sedentary lifestyle and have been advised to avoid excess physical exertion, as an increase in mechanical stress on the sarcolemma during muscle contraction is thought to accelerate the disease progression (Petrof, 1998). Studies of exercise in the mdx mouse model of DMD have indicated exercise-induced muscle damage (Hudecki et al., 1993; Granchelli et al., 2000). However, in these studies mice where subjected to eccentric contractions, which are known to cause muscle damage even in healthy subjects (Allen, 2001). Other studies in mdx mice have shown that 4 weeks (Carter et al., 1995), and 10–13 months (Dupont-Versteegden et al., 1994) of wheel running exercise increased fatigue resistance and muscle strength. Thus, current knowledge and assumptions of the molecular and pathophysiological background of dystrophinopathies suggest that regular exercise training in patients with DMD/BMD may be deleterious if training is eccentric, or at maximal exertion levels. Submaximal exertion may, however, have beneficial effects. The literature to date shows no systematic evaluation of endurance training in these patients.

We hypothesized that moderate aerobic training may safely improve the physical conditioning in patients with BMD, similarly to that observed in a number of other muscular dystrophies (Olsen et al., 2005; Orngreen et al., 2005; Sveen et al., 2007). This hypothesis is encouraged by training in a few DMD patients (Vignos and Watkins, 1966; Scott et al., 1981). Furthermore, recent studies in mdx mice suggest that low intensity training decreased markers of oxidative stress in skeletal muscle (Kaczor et al., 2007). In this study, we investigated the effect of short-term (12 weeks), and long-term (1 year), aerobic exercise on work performance, muscle strength, self-assessed well-being and muscle morphology in patients with BMD.

**Methods**

**Subjects**

Eleven men with BMD (age; 32 ± 4 years: weight; 73 ± 5 kg: height; 178 ± 2 cm), and seven healthy, sedentary men (age; 36 ± 5 years: weight; 81 ± 5 kg: height; 178 ± 3 cm) completed a 12-week training programme. By sedentary we mean that persons did not engage in any form of exercise training besides a maximum of 1–2 weekly physiotherapy sessions. The initial protocol aimed for 12 weeks of training. However, several patients wanted to continue training after the 12 weeks, and we therefore extended the supervised protocol to a total of 12 months. Six of the 11 patients continued training after 12 weeks. The five other patients discontinued because of personal reasons, such as busy work schedules or long distance to the test facility. They did not discontinue due to adverse effects or lack of efficiency. Patients included in this study, represent a relatively mild BMD phenotype. The strength of lower extremity muscles of the patients is shown in Table 1.

Inclusion criteria for this study were: (i) BMD diagnosis based on mutations of the dystrophin gene and/or absent or decreased levels of dystrophin on western blot investigations; (ii) a sedentary lifestyle; (iii) the ability to tread the cycle ergometer used in this study for 30 min; (iv) no concurrent medical condition. Pre-existing cardiac involvement was not an exclusion factor. All, except one patient, had large, in-frame deletions of one or several exons of the dystrophin gene. For these patients, multiplex western blots showed truncated, and severely downregulated dystrophin levels, as well as downregulated levels of z-sarcoglycan and b-dystroglycan. The patient in whom no deletion was found, had almost absent dystrophin of normal size and almost absent levels z-sarcoglycan and b-dystroglycan on western blot.

All patients with BMD were ambulant, with onset of symptoms at age 8 ± 2 years. Three patients had asymptomatic cardiomyopathy [left ventricular ejection fraction (LVEF); 35–45%), of whom two had dilatation. Forced vital capacity (FVC), and forced expiratory volume in one second (FEV1) were on average decreased by 14 ± 2%, which is within normal limits. One patient had experienced repeated episodes of exertional myoglobinuria.

The primary end-points of this study were maximal oxygen uptake (VO2max), maximal workload (Wmax), plasma creatine kinase (CK) levels and self-reported questionnaires.

**Training programme**

Subjects trained at home on a stationary cycle ergometer for 12 weeks at a heart rate corresponding to 65% of their VO2max. A total of 50, 30 min training sessions were completed. The number of weekly sessions increased progressively during the first 4 weeks, reaching five sessions per week the final 8 weeks. Six of the 11 patients with BMD continued training for a total of 12 months. They trained three times per week, after completion of the first 12-week training protocol. Healthy controls did not participate in the extended 12-month training programme, since it is known that further training improvement does not occur in healthy subjects with this protocol (Hickson et al., 1982, 1984).

The heart rate zones were established through an incremental cycle test to exhaustion (MedGraphics CPE, St.Paul, MN, USA), where VO2max and Wmax were established. Workload was increased every other minute until exhaustion. Level of exertion was monitored by heart rate and the Borg visual analogue scale (Borg, 1990). Increments were adjusted so that the duration of the test was kept between 12 and 15 min. After 10 min of rest, a 10 min cycle test at 65% of VO2max was performed to identify the corresponding target heart rate for training at home. Cycle ergometers and pulse-watches (Accurex, Polar, Finland), were provided to the subjects by the investigators. The watch was programmed with the individual's heart rate interval, and provided the subjects with visual and auditory feedback during training. It also recorded date, duration and heart rate throughout each training session. Downloaded pulse-watch data was collected after 6 and 12 weeks, and 6 and 12 months of training to ensure compliance. Weekly telephone consultations the first 12 weeks, and monthly calls for those patients choosing to continue training for a year, were used to monitor each subject's progress and motivation level. In addition, each subject completed a training diary wherein they recorded the days they trained, as well as days they were sick or on vacation. They were encouraged to note any adverse effects or benefits observed with training.

**Muscle biopsy**

The vastus lateralis muscle is one of the main muscles trained in cycling, but also the primary muscle affected by the disease.
Biopsies of this muscle, as well as regular plasma CK analyses and self-reported adverse effects were used as safety markers in this study. Sufficient muscle material was obtained via needle biopsies from the left vastus lateralis muscle in 5 of 11 patients before and after the 12-week training period, and in two of the six patients training a full year. Knee extension strength in the patients, in whom we were not able to procure a muscle biopsy, was under half that measured in the other patients, and they had extensive atrophy making a needle biopsy difficult. Five of seven healthy controls were biopsied before and after 12 weeks of training. Biopsies were stained with Ulex, HE and ATPase at pH 4.3 and analysed for muscle fibre size and type, necrosis and capillary density (TEMA analysis programme, Check Vision, Stoevring, Denmark). Apoptosis was determined as the number of fibres that were TUNEL-positive with cleaved fragmented PARP-positive nuclei divided by the total number of fibres in the biopsy. Regeneration of muscle was assessed by counting central nuclei (Schmalbruch, 1976), by neonatal myosin heavy chain staining (Sartore et al., 1982) and staining for the myogenic transcription factors, MyoD and Myogenin.

**Plasma CK**

As a marker of exercise-induced muscle damage (Clarkson et al., 2006), plasma CK measurements were planned weekly during the 12-week training period, and monthly for those continuing their training for 12 months. Plasma lactate and heart rate are well known markers of relative exertion level, and were used to indicate whether the subjects had reached the same level of exertion before and after training (Ástrand and Rodahl, 1986).

**Muscle strength**

Muscle strength was measured by one examiner (M.L.S.) in all subjects, using a hand-held dynamometer type CT 3001 (CITEC hand held dynamometer, C.I.T. Technics, Groningen, The Netherlands) (Beenakker et al., 2001) in muscles of the lower extremity, listed in Table 1. Verbal encouragement was provided during testing. Intra-observer variability of strength testing was below 5%.

**Table 1 Absolute strength in newtons and percentage of normal strength before training, and the percentage increase in muscle strength in patients completing 12 weeks and 12 months of endurance training**

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>n = 10</th>
<th>12 weeks</th>
<th>n = 6</th>
<th>12 weeks</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength (Newtons)</td>
<td>(percentage of normal)</td>
<td>(percentage increase)</td>
<td>(percentage of normal)</td>
<td>(percentage increase)</td>
<td>(percentage increase)</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>145 ± 9</td>
<td>8 ± 4</td>
<td>145 ± 10</td>
<td>61 ± 6</td>
<td>(7 ± 3)</td>
</tr>
<tr>
<td>Hip extension</td>
<td>188 ± 15</td>
<td>2 ± 4</td>
<td>191 ± 16</td>
<td>60 ± 7</td>
<td>(3 ± 7)</td>
</tr>
<tr>
<td>Hip adduction</td>
<td>91 ± 14</td>
<td>−6 ± 27</td>
<td>94 ± 13</td>
<td>40 ± 8</td>
<td>(14 ± 7)</td>
</tr>
<tr>
<td>Hip abduction</td>
<td>127 ± 12</td>
<td>22 ± 7*</td>
<td>128 ± 11</td>
<td>54 ± 6</td>
<td>(18 ± 6)*</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>120 ± 16</td>
<td>5 ± 11</td>
<td>132 ± 16</td>
<td>53 ± 9</td>
<td>(16 ± 4)*</td>
</tr>
<tr>
<td>Knee extension</td>
<td>124 ± 19</td>
<td>14 ± 12</td>
<td>107 ± 19</td>
<td>30 ± 8</td>
<td>(31 ± 15)*</td>
</tr>
<tr>
<td>Foot Dorsiflexion</td>
<td>133 ± 13</td>
<td>13 ± 6*</td>
<td>115 ± 8</td>
<td>49 ± 5</td>
<td>(15 ± 4)*</td>
</tr>
<tr>
<td>Foot plantar flexion</td>
<td>183 ± 9</td>
<td>20 ± 4*</td>
<td>206 ± 7</td>
<td>69 ± 3</td>
<td>(16 ± 4)*</td>
</tr>
</tbody>
</table>

Significance is corrected for 5% intra-observer variance. *P < 0.05. One strength test was not performed in one patient due to unavailability of the investigator at 12 weeks.

**Self-reported changes in activities of daily living**

After the 12-week training programme, patients completed a modified SF-36 questionnaire (Ware and Sherbourne, 1992), grading changes in the variables shown in Fig. 1. Patients were interviewed weekly by phone about adverse effects and progresses with the training protocol.

**DEXA scanning**

A full body DEXA scan (GE Medical Systems, Lunar, Prodigy) was performed after each cycle test. This was used to evaluate whole-body and leg changes in lean tissue and fat mass. The images were analysed using enCORE™2004 Software (v.8.5) (GE Medical Systems, Lunar, Prodigy).

**Echocardiography and pulmonary function**

Echocardiography was performed before, and after 12 weeks and 12 months of endurance training according to the American Society of Echocardiography guidelines (Lang et al., 2005).

Echocardiography was performed in the left lateral supine position. Cardiac dimensions [intra ventricular septum (IVS) thickness and left ventricular end-diastolic diameter (LVEDD)] were measured from 2D images, and LVEF was assessed in 5% intervals. Dilated cardiomyopathy (DCM) was defined as an LVEDD above 5.9 cm, if a concomitant decrease in LVEF was found. IVS thickness above 1.2 cm was defined as a sign of hypertrophy.

Pulmonary function was assessed by forced vital capacity (FVC), FEV1 before and after 12 weeks and 12 months of training. Normal values were defined as >75% of the gender-, age- and height-adjusted norm.

**Statistics**

Values are mean ± standard error. P < 0.05 (two-tailed testing) was considered significant. Within group changes with training were assessed by a paired Student’s t-test, and BMD and healthy controls were compared using non-paired Student’s t-test.

**Results**

Polar pulse-watch recordings and the patient diaries revealed 94 ± 2% (range; 75–100%), and 89 ± 3% (range; 77–100%),
compliance to the 12-week training programme in patients and healthy controls. This dropped to 82% ± 3% (range: 74–88%) for the remaining 9 months, in the six patients completing 12 months of training.

**VO₂, workload, heart rate and plasma lactate levels**

Three months of training improved VO₂max and Wmax in patients with BMD and healthy subjects (Fig. 1; P < 0.005). After 12 months of training, this effect was sustained, but did not further improve. The percentage improvement in VO₂max and Wmax was almost 3-fold higher in patients versus healthy controls (P < 0.005). Plasma lactate levels and heart rate at rest and at exhaustion did not differ significantly before and after training (Table 1), but tended to be lower when assessed after training. This emphasizes the magnitude of the training response, since patients were not pushed to the exact same level of exertion during max-tests after training.

Levels of dystrophin found in the western blot of the BMD patients included were unrelated to their training response. None of the patients included in the study experienced myoglobinuria after maximal exertion testing, or related to training sessions.

**Muscle strength**

Taking the intra-observer 5% variance of muscle testing into account, there was a significant increase in muscle strength after 12 weeks of training in hip abduction and foot dors- and plantar-flexion. This increase was maintained after 12 months of training. Furthermore, in patients training for a year, there was a 40% improvement in knee extension strength, thus involving the primary muscle used in cycling, i.e. the quadriceps (Table 2).

**CK levels**

Levels of plasma CK were supposed to be taken weekly by each patients general practitioner. This was, however, not possible due to practical issues for most patients. On average, plasma CK levels were obtained every 2 weeks for most patients, although a few patients only had the blood test taken a few times in the study. However, plasma CK levels never increased during training in patients (Fig. 2).

**Self-reported changes in activities of daily living**

Self-reported questionnaires showed that a majority of subjects with BMD felt an improvement in physical endurance, leg muscle strength and walking distance after 12 weeks of training.

**Muscle histology**

Sufficient muscle was secured in half of the patients included in the study due to severe muscle atrophy. It was only possible to obtain a biopsy from two of the patients training for a full year, and therefore this data is not included. Mean muscle fibre area and type distribution, and capillary density did not increase with training in patients with BMD and healthy controls (Table 1).
Due to severe muscular dystrophy of the vastus lateralis muscle, muscle biopsies could not be obtained in all patients. Therefore, data is only included from patients in whom sufficient biopsy material could be obtained at all time points. Number of patients evaluated is shown in parenthesis. Plasma lactate levels for one patient were not included as the sample was accidentally thawed. nMHC = positive staining for neonatal myosin heavy chain.

<table>
<thead>
<tr>
<th>Patients with BMD</th>
<th>Healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before training (n)</td>
<td>12 weeks training (n)</td>
</tr>
<tr>
<td>Fibre size type I (µm²)</td>
<td>4120 ± 490 (5)</td>
</tr>
<tr>
<td>Fibre size type II (µm²)</td>
<td>5359 ± 505 (5)</td>
</tr>
<tr>
<td>Capillaries per mm²</td>
<td>398 ± 99 (5)</td>
</tr>
<tr>
<td>Central nuclei (%)</td>
<td>18 ± 3 (5)</td>
</tr>
<tr>
<td>Necrotic cells</td>
<td>0.8 ± 0.8 (5)</td>
</tr>
<tr>
<td>nMHC (%)</td>
<td>70 ± 4 (5)</td>
</tr>
<tr>
<td>Plasma creatine kinase (u/l)</td>
<td>1775 ± 755 (II)</td>
</tr>
<tr>
<td>Lactate rest</td>
<td>1.7 ± 0.1 (10)</td>
</tr>
<tr>
<td>Lactate max</td>
<td>8.7 ± 1.1 (10)</td>
</tr>
<tr>
<td>Heart rate rest</td>
<td>87 ± 6 (II)</td>
</tr>
<tr>
<td>Heart rate max</td>
<td>176 ± 9 (II)</td>
</tr>
</tbody>
</table>

One of the patients who trained for 12 months had an increase in LVEF from 35% to 50%. This improvement was paralleled by an unprecedented increase of 104% in VO₂max and 433% in Wmax. The other two patients had no change in cardiac parameters, but had an average increase of 52% in VO₂max and 82% in Wmax.

The remaining eight patients had normal echocardiography, and all patients had normal pulmonary function findings before training, and these parameters did not change with 12 weeks, or 12 months of endurance training.

**Discussion**

This study shows that: (i) 12 weeks of moderate-intensity, aerobic training is an effective and safe method to increase fitness in patients with BMD. Training increased the patient’s VO₂max and Wmax by 47 and 80%, which were 3- to 4-fold higher than that observed in healthy subjects; (ii) these considerable improvements were maintained after 12 months of training; (iii) despite the aerobic nature of the training, significant increases in muscle strength were observed in muscle groups involved in cycling; (iv) increased work capacity was paralleled by self-reported improvements in endurance, leg muscle strength and walking distance; (v) no muscle damage was inflicted as reflected by unchanged CK levels during training, and no significant changes in muscle morphology. These findings suggest that endurance training has a long-term beneficial effect in patients with BMD, and rejects the notion that patients with mild defects in dystrophin are prone to mechano-sensitive muscle damage during repeated muscle contractions. An important point is that the patients are capable of maintaining their fitness up to a year, even when training frequency was reduced by 40%, as is known to occur also in healthy controls (Hickson et al., 1984).
Table 3 Lean tissue mass and fat mass content in BMD patients before and after 12 weeks, and 12 months of endurance training

<table>
<thead>
<tr>
<th></th>
<th>Before Training</th>
<th>12 weeks Training</th>
<th>Before Training</th>
<th>12 weeks Training</th>
<th>12 month training</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 10</td>
<td></td>
<td>n = 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean tissue mass (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td>745 ± 667</td>
<td>738 ± 635</td>
<td>7017 ± 797</td>
<td>6780 ± 652</td>
<td>6811 ± 509</td>
</tr>
<tr>
<td>Left leg</td>
<td>7362 ± 603</td>
<td>7310 ± 632</td>
<td>6867 ± 731</td>
<td>6746 ± 774</td>
<td>6684 ± 508</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg</td>
<td>3735 ± 642</td>
<td>3637 ± 656</td>
<td>3763 ± 592</td>
<td>3478 ± 621</td>
<td>3454 ± 425</td>
</tr>
<tr>
<td>Left leg</td>
<td>3735 ± 666</td>
<td>3600 ± 655</td>
<td>3720 ± 627</td>
<td>3444 ± 636</td>
<td>3413 ± 445</td>
</tr>
<tr>
<td>Whole Body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean tissue mass (g)</td>
<td>48576 ± 2846</td>
<td>48102 ± 2953</td>
<td>44643 ± 2556</td>
<td>44271 ± 2746</td>
<td>44227 ± 1744</td>
</tr>
<tr>
<td>Fat mass (g)</td>
<td>23506 ± 4180</td>
<td>22838 ± 4199</td>
<td>23152 ± 3304</td>
<td>22345 ± 3995</td>
<td>22165 ± 2682</td>
</tr>
<tr>
<td>Percentage of body fat</td>
<td>31 ± 4</td>
<td>30 ± 5</td>
<td>34 ± 4</td>
<td>33 ± 5</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>Total body mass (kg)</td>
<td>75 ± 5</td>
<td>74 ± 5</td>
<td>71 ± 4</td>
<td>69 ± 3</td>
<td>69 ± 2</td>
</tr>
</tbody>
</table>

Data from one patient scanning was lost due to a computer error after 12 months of training.

Limited muscle morphology data supports that these fitness improvements can be maintained over time without signs of increased satellite cell activation, suggesting that exercise does not contribute to exhaustion of the regenerative pool of cells in muscle. Likewise, plasma CK levels were not increased with training, again suggesting that the integrity of the sarcolemma, and thus the level of muscle injury, was unaffected by training. Finally, patients in this study reported no adverse effects.

The beneficial effect of aerobic conditioning in patients with BMD does not mirror findings in most training studies of the mdx mice, on which current recommendations for exercise in dystrophinopathies are based (Sacco et al., 1992; Granchelli et al., 2000). Granchelli et al. (2000) found a 19% decrease in normalized strength of hindlimb muscles after training mdx mice twice weekly for 30 min on a speed treadmill. Similarly, Sacco et al. (1992) concluded that exercise was detrimental in mdx mice, based on an eccentric training regime and testing of muscle strength. A primary end-point of muscle strength, however, may not be appropriate alone as efficacy measure when assessing effects of endurance exercise, and eccentric exercise is known to cause muscle damage even in healthy subjects (Allen, 2001). In line with a positive training response in our BMD patients, lower intensity endurance exercise has been shown to be safe and improve muscle strength and endurance in mdx mice (Dupont-Versteegden et al., 1994; Carter et al., 1995; Kaczor et al., 2007).

To date, no study has investigated the effect of training in patients with BMD. Only limited evidence exists for training in DMD, but these studies all focussed on strength training. Most studies are difficult to interpret, due to small study size, design and pooling of patient data from a number of muscle conditions. An improvement of weight-lifting capacity in DMD patients has been reported, following 1 year of daily weightlifting (Vignos and Watkins, 1966; Scott et al., 1981). On the other hand, lack of vasodilatation in contracting muscle due to insufficient production of NO, causes relative hypoperfusion in working muscle of Duchenne boys (Sander et al., 2000), which may cause muscle injury during exercise. NO production and nitric oxide synthase expression, have not been studied in patients with BMD.

The dilemma that exercise may inflict structural damage to muscle cells with defective dystrophin, causing acceleration of disease progression, not only does not seem to hold true based on our findings, but the improvements in BMD patients were also higher than that seen in other patients with muscular dystrophies tested with the same protocol (Olsen et al., 2005; Orngreen et al., 2005; Sveen et al., 2007). One BMD patient in this study had a much higher response to training as compared with the rest of the group, but even with exclusion of his data, the mean improvement in VO2max and Wmax of the other patients was still much higher than that seen in the previous studies mentioned above. Part of the explanation for this difference in training response, could be a higher baseline VO2max in patients with facioscapulohumeral disease (Olsen et al., 2005) and myotonic dystrophy (Orngreen et al., 2005). However, patients with LGMD2I, who had a similar phenotype to our patients with BMD, including muscle strength and identical baseline VO2max, had significantly lower improvements in VO2max (Sveen et al., 2007). This finding may relate to the fact that patients with BMD are more sedentary than patients with LGMD2I, or it may be a disease-specific response. Baseline fitness has been shown to affect the magnitude of the training response in healthy subjects (Shephard, 1968).

The marked improvements in fitness shown by this study in a group patients with BMD spanning from the age of 19–52 years, are paralleled by the self-reported questionnaires, as well as verbal feedback obtained throughout the study by way of weekly telephone calls. This questionnaire has been used many times in previous training studies and has shown consistent improvements in endurance as found in this study (Olsen et al., 2005; Orngreen et al., 2005; Sveen et al., 2007). The questionnaire did not prove to be inclusive enough, however, as patients also reported marked improvements in balance, and decreased fall tendency. Improvement in their ability to walk up stairs did not occur.
There is a 27% (3 of 11 patients) prevalence of cardiac involvement in the patients included in this study, which is lower than the 47% reported in a recent study of Danish BMD patients (Sween et al., 2008). With the exception of one patient who had a great improvement in work capacity, training responses did not differ between BMD patients with or without cardiac involvement. The patients included in this study had an LVEF down to 35%, which is considered mild to moderate. Further investigations will have to show the effect of training other patients with more severe heart failure. Endurance training is generally recommended for patients with cardiomyopathy, and a beneficial effect on pump function was also suggested in our BMD patients, as left ventricular function improved significantly in one of three patients with cardiomyopathy. Until studies on patients with severe cardiac involvement are made, we recommend that patients with severe cardiac involvement should be trained with caution and close supervision.

The clear response to aerobic conditioning in patients with BMD shown in this study may not be extended to other exercise intensities or types of exercise. Furthermore, a number of BMD patients are too weak to perform the kind of training used in our study either due to muscle atrophy or impaired cardiac function. As with exercise in healthy individuals, motivation is a major limiting factor in this form of treatment. This study had a very high compliance, due in large part to weekly telephone consults with patients to occasionally provide motivation as well as assess progress. In patients with BMD, this form of training could be incorporated into regular supervised physiotherapy sessions to avoid high dropout rates.

The findings in this study suggest that defects of dystrophin do not render patients susceptible to mechanical damage when engaging in regular, moderate-intensity and aerobic exercise. It is important to note that patients with BMD have a much milder phenotype, and have higher levels of functioning dystrophin compared with patients with DMD, thus making these findings specific for BMD patients. Although this study finds no certain signs of increased muscle regeneration, a potential higher activation of satellite cells, could imply long-term loss of regenerative power in BMD patients.

Our results support a more active approach to the management of patients with BMD, which should involve frequent episodes of low- to moderate-aerobic exercise. This recommendation is based on our findings of improved conditioning levels, paralleled by self-reported improvements without apparent signs of muscle damage. Although these findings show a positive response to endurance training, further studies are warranted to examine whether there is a threshold in intensity and exercise duration that optimizes the effects of exercise without causing damage to the muscle. The effect of strength training also needs to be investigated.

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