ABSTRACT. Nine ambulatory subjects with myotonic dystrophy participated in a supervised 12-week progressive high-resistance training program. Knee extensor muscles were trained 3 times a week with free weights, 3 × 10 repetitions at 80% of 1RM. One leg was randomly chosen for training and the other served as control. Six patients completed the training program. In the trained leg, 1RM increased from 16.4 ± 3.4 kg to 21.8 ± 2.6 kg (p = 0.0002). There was no difference between pre- and post-training concentric or eccentric isokinetic values at 30°/second in either leg. Muscle biopsy from m. vastus lateralis in the trained leg revealed no systematic difference in the degree of histopathological abnormalities before and after training. After training, there was a tendency toward increase in cross-sectional area of type I muscle fibres. However, the number of subjects was too small to draw conclusions regarding the effects of training on the histopathological changes. Magnetic resonance imaging revealed no difference in the m. quadriceps area after training. In conclusion, patients with myotonic dystrophy improved their muscle strength without any observed negative side effects after a 12-week high-resistance training program.

Key words: heavy strength training; magnetic resonance imaging; muscle biopsy; myotonic dystrophy; strength measurement.

INTRODUCTION
Muscular weakness is a major problem in subjects with neuromuscular diseases (NMD) whose functional capacity is dependent on the severity and distribution of muscular weakness (12). Although it is commonly known that an endurance or progressive muscle strength training regimen increases muscular endurance and/or strength in healthy subjects (10, 23), the effects in patients with NMD has been studied far less, and results concerning muscular trainability in these patients are conflicting (12). It is therefore of great importance to elucidate the muscular trainability and any possible harmful effects of exercise training in patients with slowly progressive neuromuscular diseases.

The present study focused on patients with myotonic dystrophy (DM), all at a similar functional level. DM is an autosomal dominant multisystemic disorder. It is the most common muscular dystrophy in adults, with an estimated frequency of at least 1 in 8,000 (9). The disease is characterized by a variable phenotype which includes progressive muscle weakness, myotonia and cataract, but also cardiac conduction disturbances, testicular atrophy, frontal balding and, in some early onset cases, mental retardation.

The aims were to evaluate effects of a supervised dynamic high-resistance training program on muscle strength, muscle area and muscle fibre histopathology in ambulatory patients with DM, and to evaluate the degree and distribution of muscle affection in the thighs.
chosen for training and muscle biopsy and the other leg served as control.

Patients 1–4 and 6–9, aged between 22 and 48, all had a classical DM phenotype, including moderate to severe weakness and atrophy of distal limb muscles and facial muscles, with varying degrees of myotonia. The degree of paresis was evaluated according to Kendall et al. (11). Foot dorsiflexion amounted to 2 (inability of full dorsiflexion leading to foot drop during walking), except in patient no. 5, for whom the corresponding figure was 4 (significant power of full foot dorsiflexion). Knee extension amounted to 4 in all patients (significant power of full knee extension). The duration of clinical weakness varied between approximately 4 and 20 years. Two patients occasionally used one crutch (nos. 3 and 6), whereas the others used no walking aids.

All patients were instructed to maintain their normal daily living activity level during the study. Informed consent was given, and the study was approved by the local ethics committee.

Strength measurements

Maximal voluntary dynamic knee-extensor strength was measured in both legs with an isokinetic dynamometer, KinCom 500H (Chattecx Co., Chattanooga, U.S.A.), and by one repetition maximum (1RM) (6). The range of motion for strength measurements was from 90° of knee flexion to full knee extension (0°).

The patients went through a learning session followed by a one-hour rest before the actual test session.

During isokinetic testing, the patients sat with the pelvis and thigh of the tested leg stabilized with non-elastic straps. The position of hip and knee was 90°. The axis of the knee joint was aligned with the axis of the lever arm. Three curves were produced in concentric and eccentric actions, respectively, at an angular velocity of 30°/second. Only curves with a high reproducibility were accepted. During testing, the patients were verbally encouraged to exert to their maximal performance level through the whole range of movement. The warming-up procedure consisted of 3 to 5 submaximal isokinetic contractions. Mean torque values were determined from concentric and eccentric curves in a common range where all patients had reached the pre-set angular velocity. Concentric peak torque values were determined.

One RM was determined by free weights adapted to a 3-kg iron shoe. The iron shoe was strapped to the foot with non-elastic straps. During testing, the patients were sitting on a bench leaning backwards, supporting themselves with their fully extended arms. The exercised leg was positioned with the femur horizontal. In this position, the patients lifted and lowered the lower leg with increasing weight added on, until 1RM was defined (6). The patients were verbally encouraged to exert to their maximal performance level through the whole range of movement. Between movements, the patients supported themselves with one foot on the floor in order to prevent traction of the ankle joint.

Training procedure

Progressive high-resistance strength training was performed with free weights on the iron shoe (see above), with a target load of 80% of 1RM 3 times a week for 12 weeks. In order to prevent excessive muscle soreness, the load was gradually increased up to 80% of 1RM. Thus, for the first week, the load was 60% of 1RM, the second week 70%, and 80% thereafter. The patients performed 3 sets of 8 repetitions. The duration of each repetition was approximately 9 seconds consisting of concentric, isometric and eccentric phases, each phase lasting 3 seconds, paced by a metronome and verbal guidance. Between repetitions, there was a 10-second rest, and between sets, a 2-minute pause. During testing, the patients were verbally encouraged to exert to their maximal performance level through the whole range of movement. The same two authors (SE, AW) provided constant supervision during all training sessions. One RM was determined once a week to update training load.

Magnetic resonance imaging (MRI)

The cross-sectional area of the quadriceps muscle to be studied (the rectus femoris muscle was excluded, since it runs over two joints) was determined in the exercised leg within a week before and after the training period, by MRI using whole-body superconductive equipment (1.5 T Signa, General Electric Co., software release 5.3). T1 weighted transaxial images (TR/TE 500/17ms, FOV 48 × 24 cm, matrix 572 × 192), with one 10-mm slice 25 cm superior to the knee joint, were analysed. Only signals between 30 and 300 were accepted for measurement, in order to diminish influence from fat and cortical bone.

Additional transaxial and coronal images (slice thickness 10 and 8 mm with slice space 10 and 2 mm, respectively), T1 weighted and fast inversion recovery sequences (FMPIM; T1 150ms, TR/TE 3500/17ms) were used for visual evaluation of the degree and distribution of muscle affection in the entire thigh.

Muscle biopsy

Muscle biopsies were taken from the vastus lateralis muscle of the training leg using the percutaneous chonchotome technique (14, 19). Care was taken to assure that the biopsies before and after training were taken at the same location and at approximately the same depth for each patient. The specimens were quickly frozen in freon-22, cooled with liquid nitrogen (−190°C) and stored at −75°C until further processed. Cross-sections of 10 µm were cut in a cryostat operating at −25°C. The sections were stained with haematoxylin-eosin and modified trichrome (7), myofibrillar ATPase (mATPase) (3, 18) and NADH-TR (21).

The classification of muscle fibre types was based on their ATPase-staining characteristics (3). The number of different fibre types was calculated from photographic prints of randomly selected areas of the biopsy, comprising 400–500 fibres, and the proportions of each fibre type were calculated.

The cross-sectional areas and the “lesser diameters” of the muscle fibres were measured directly from the microscope via a CCD camera (Hamamatsu C3077, Hamamatsu Photonics KK, Japan) connected to an image analysis processor (Vidas, Kontron Bildanalyse, GmbH, Munich). Measurements were made on 100 type I and 100 type II fibres from each biopsy specimen. If the total number of fibres of the respective type was less than 100, then all the fibres of that specific type were measured. The morphological and morphometrical analyses were performed blindly.

Statistics

Muscle biopsy data were analysed using the Wilcoxon signed-rank test for paired observations. A two-way analysis
of variance (ANOVA) with repeated measures for non-parametric dependent measures was used for analysis of differences in muscle fibre area and fibre types before and after training. The level of significance was set to \( p < 0.05 \).

**RESULTS**

One woman (no. 8) and the two men (nos. 7 and 9) withdrew from the study: one patient (no. 9) during the first week due to reasons not related to the study, one (no. 7) after six weeks due to unwillingness to continue because of subjective lack of strength improvement, and the third (no. 8) after eight weeks of training due to severe back pain. The six patients who participated during the whole training period completed 76\% (range 69 to 85\%) of all training sessions. MRI of the thighs was performed on all patients but one (no. 6) before and five (nos. 1–5) before and after the training period.

**Muscle strength**

One RM values increased from 16.4 \( \pm \) 3.4 kg before to 21.8 \( \pm \) 2.6 kg after training (\( p = 0.0002 \)) in the exercised leg, whereas there was no difference in the control leg (from 17.2 \( \pm \) 3.5 to 18.5 \( \pm \) 3.8). For individual 1RM values in the trained leg during the training period, see Fig. 1.

There was no significant difference in isokinetic concentric *peak* torque values (Table I), nor in concentric or eccentric *mean* torque values, between pre- and post-training measurements in the exercised (concentric from 61.3 \( \pm \) 9.8 to 70.2 \( \pm \) 15.1 Nm, eccentric from 94.3 \( \pm \) 25.3 to 96.2 \( \pm \) 35.8 Nm) and non-exercised legs (concentric from 67.7 \( \pm \) 12.4 to 71.4 \( \pm \) 14.3 Nm, eccentric from 106.8 \( \pm \) 21.7 to 106.0 \( \pm \) 11.8 Nm).

**MRI**

There was no significant difference in the calculated individual muscle cross-sectional area of the three portions of the quadriceps muscle, according to MRI, between pre- and post-training measurements (4090 \( \pm \) 591 and 4154 \( \pm \) 585 mm\(^2\), respectively).

In all patients but one (no. 5), it was possible to visually observe changes in a mosaic pattern of muscle degeneration, and intramuscular patchy areas of high signal on T1-weighted images, with lower signal intensity on FMPIR images corresponding to fat. Further, muscle atrophy of different degrees in individual muscles was observed in five patients (nos. 1–3, 7 and 8), whereas in some muscles, the cross-sectional area was well preserved (although fatty degeneration was marked). There was a total fatty replacement of muscle tissue in the distal parts of vastus intermedius muscles in four patients (nos. 1, 2, 7, and 8), whereas muscle tissue was generally well preserved in the proximal parts (Figs. 2 and 3). All visually observed muscular changes were symmetrical and appeared more prominent in the distal parts of the thighs. There was a selective sparing of rectus
femoris muscles (Figs. 2 and 3). Otherwise, no constant pattern of muscle affection was observed. In one patient (no. 4), all muscles appeared with a normal signal intensity and size, apart from adductor longus muscles, which had a patchy appearance and were slightly atrophied. She was also the youngest of the patients (22 years old). No signs of inflammatory changes were observed in any patient.

**Histopathology**

Pathological changes, consistent with those typically found in DM patients (17), were found in six out of seven biopsies (Fig. 4). These included a marked variation in fibre size, and scattered atrophic fibres intermingled with hypertrophic fibres, sometimes exhibiting splitting phenomena. The number of fibres with central, often multiple, nuclei had increased. In some fibres, the nuclei were radially oriented. Central nuclei were seen in both type I and type II fibres. Other architectural changes, such as sarcoplasmic masses, were commonly encountered in the subsarcolemmal zones. In three patients, some of the hypertrophic fibres had the appearance of “whorled fibres”. The staining for oxidative enzymes (NADH-TR) was normal in all patients but one, for whom some fibres had a moth-eaten appearance. Fibre necrosis and ring-fibres were occasionally seen.

There was a normal fibre type differentiation with a variation in fibre sizes for types I and II. The atrophic

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**Table I. Individual knee-extensor isokinetic concentric peak torque values (Nm) in the exercised and control leg before and after twelve weeks of high-resistance training**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exercised leg Before</th>
<th>Exercised leg After</th>
<th>Control leg Before</th>
<th>Control leg After</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>116</td>
<td>112</td>
<td>118</td>
</tr>
<tr>
<td>2</td>
<td>108</td>
<td>105</td>
<td>95</td>
<td>102</td>
</tr>
<tr>
<td>3</td>
<td>113</td>
<td>119</td>
<td>116</td>
<td>107</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>73</td>
<td>69</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>118</td>
<td>126</td>
<td>123</td>
<td>130</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
<td>–</td>
<td>91</td>
<td>–</td>
</tr>
</tbody>
</table>

mean, SD 95.5 ± 21.9 107 ± 20.8 101 ± 20.8 106 ± 19.8

(– not performed).

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**Fig. 2.** Axial MR T1 weighted image, TR/TE 500/17, of the thighs, 25 cm above the knee joint in one of the DM patients (no. 1). Note the fatty degeneration of vastus intermedius muscles and the selective sparing of rectus femoris muscles.

**Fig. 3.** Coronal MR inversion recovery image (FMPIR/90, TR/TE 3500/17_Ef) of the thighs in one of the DM patients (no. 1). The distal parts of quadriceps muscles appear with fatty degeneration.
fibres were mostly of type I. Necrosis of a few fibres was encountered in one patient.

There was no systematic difference in the degree of histopathological abnormality before and after training. However, the patient who quit due to lack of subjective improvement (no. 7) exhibited more extensive pathology in his biopsy after training, with many atrophic fibres and an increase in the degrees of fat and connective tissue.

**Fibre type proportions and fibre sizes**

No statistically significant change in proportion of fibre types was noted after the training period (type I from 33.9 ± 5.3 to 38.9 ± 8.8% and type II from 66.1 ± 5.3 to 61.1 ± 8.8%), nor in fibre size (Table II). When looking at individual values, however, five of seven patients had an increased cross-sectional area of type I fibres (Table II). One patient showed no major difference, and in one patient (no. 7), type I fibres decreased in size (Table II). If the latter patient, who quit the study after six weeks due to lack of subjective improvement, was excluded, a tendency towards an increased fibre size was noted for type I ($p = 0.062$), but not for the other fibre types.

**DISCUSSION**

This constantly supervised high-resistance training study has shown a significant strength gain in knee extensor muscles according to 1RM after 12 weeks of high-resistance training in patients with DM. Training load could be increased in all patients that completed the training. Patients sometimes complained of transient knee pain during training, but the pain was never so severe that training had to be terminated. One patient (no. 8), who had experienced back pain for several years, experienced increasing discomfort during the training period and decided to quit the training regimen. Otherwise, there were no reports of any negative side effects of the training regimen.

In many DM patients, a striking feature is the marked degree of apathy and inertia, and of the congenital form of mental retardation, all of which are symptoms that might influence training compliance. However, the motivation level for training was generally high, and by far the most common reason for not attending the training sessions was illness. Two patients completed only one isokinetic pre-training session due to lack of motivation. However, we believe that the acquired data reflect their maximal performance, since there were no systematic differences between the two pre-test measurements in the other patients, and since high reliability in isokinetic measurements has also been reported in men with mental retardation (22).

The necessary motivation for maximal performance during training sessions seemed to be well maintained throughout the training period in our patients. The raise in 1RM, observed in all but the one patient who withdrew from the study due to subjective lack of strength improvement (no. 7), supports this observation.

The initial gain in strength due to training is regarded as due to neural adaptation, and the succeeding gain is increasingly related to muscle
fibre hypertrophy (16, 20). Muscle fibre hypertrophy can be observed within two months in the normal muscle, and plays an increasing role in strength gain thereafter (20, 23). However, in diseased muscle such as that of DM patients (cf. above), fibres adapting to the training regimen by hypertrophy might not contribute to the total muscle cross-sectional area to such an extent detectable by MRI. The lack of difference in total muscle cross-sectional area of m. quadriceps before and after training, according to MRI, is thus not surprising after such a limited training period. The coefficient of variation for determination of muscle area by the same examiner (GJ) was also found in previous measurements <2 (unpublished data). Further, after twelve weeks of resistance training, we would expect negative effects on the muscle fibre to be detectable.

The finding that the observed increase in 1RM was not paralleled by an increase in isokinetic strength is in accordance with other studies (2, 8). Since 1RM was measured with the same device and in the same way as the training was performed, the increase in 1RM could be ascribed to training specificity (2, 8). The present results are partly in accordance with a previous study (13) where training was performed at 80% of 1RM, and training effects were evaluated by isokinetic and isometric strength measurements. In this partly supervised training study, no difference in muscular strength was observed between the training and control groups. However, in the training group, an increased functional performance was reported, indicating positive training effects.

As a positive side effect, three patients experienced less foot drop in the exercised leg after the training period. During training, the iron shoe stimulates active dorsiflexion of the foot, and the observed functional improvement thus indicates a training-induced increase in foot dorsiflexor muscle strength.

Muscle fibre abnormalities commonly found in patients with DM were encountered in six of the seven patients. On the whole, there was no significant difference in the degree of muscle fibre pathology, or in the composition of different fibre types, before and after the training period. However, the variations in pathology, fibre type composition and fibre size are considerable between different biopsy samples from the same person, even from the same location. This is especially true in pathologic muscles, where highly abnormal areas can be found adjacent to more normal parts of the muscle. It is obvious that any conclusions from the present biopsy material must be drawn with great caution, especially considering the small number of patients. Thus, it is hardly surprising that statistical evaluation of fibre size data failed to reach significant levels. If individual values were considered, a slightly different picture developed. The fibre size of type I fibres was increased in five patients, whereas one patient showed no difference. This supports the idea that the gain in strength can be partly ascribed to fibre hypertrophy in addition to neuromuscular adaptation. The patient that quit the study due to lack of improvement was the only one with a decrease in fibre size in the after-training biopsy. This biopsy also exhibited an increased amount of fat and connective tissue, in addition to the many atrophic fibres. However, whether this has any clinical relevance is most uncertain. It might merely represent a sampling bias, as discussed above. Further, this patient exhibited a significant loss of isokinetic strength in the control leg six weeks from the start of training (from 117 Nm to 85 Nm), whereas there was no change in the trained leg.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Type I area (µm²)</th>
<th>Type IIA area (µm²)</th>
<th>Type IIB area (µm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>1</td>
<td>1877</td>
<td>4574</td>
<td>4253</td>
</tr>
<tr>
<td>2</td>
<td>3175</td>
<td>11136</td>
<td>4775</td>
</tr>
<tr>
<td>3</td>
<td>4781</td>
<td>11120</td>
<td>6026</td>
</tr>
<tr>
<td>4</td>
<td>6107</td>
<td>8039</td>
<td>4883</td>
</tr>
<tr>
<td>5</td>
<td>4413</td>
<td>4093</td>
<td>4095</td>
</tr>
<tr>
<td>6</td>
<td>3419</td>
<td>5558</td>
<td>7811</td>
</tr>
<tr>
<td>7*</td>
<td>5610</td>
<td>2378</td>
<td>9619</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4197 ± 1476</td>
<td>6700 ± 3471</td>
<td>5923 ± 2072</td>
</tr>
</tbody>
</table>

* The patient withdrew from training after six weeks due to lack of improvement.
The MRI finding of fatty degeneration of vastus intermedius muscles has been described by Castillo et al. (4) as characteristic in the thighs in DM. However, the general preservation of the upper parts of this muscle, which is in agreement with the progression of the disease starting in distal muscles, has not been described previously. The observed symmetrical distribution of muscle involvement and the sparing of the rectus femoris muscle of the quadriceps muscle are in agreement with previous reports (1, 5).

Since the pathology varies in different NMDs, the effects of exercise training on muscle strength and endurance are likely to differ. Further, muscular trainability is related to the degree of muscular impairment (15). This implies that subjects with fewer symptoms should respond better to strength or endurance training programs. Thus, when designing exercise training studies for elucidation of muscular trainability, there should not be a variety of diseases or a large difference in functional level or muscular function among the participating subjects.

If high-resistance training is concluded to be effective and “safe” for ambulatory DM subjects, it indicates that function could probably be maintained longer, or that functional deterioration might be delayed.

To our knowledge, this is the first constantly supervised training study being reported for DM. Our strong impression is that it may be hazardous to draw conclusions concerning muscular trainability from non-supervised training, since even during our constantly supervised training sessions, motivation for maximal performance required continuous supervision and verbal encouragement.

Muscle training studies aiming at evaluating muscular trainability in DM should be supervised. They should include patients with similar functional levels of the studied muscles, different gender groups and a control group to eliminate confounding hormonal and crossover effects, respectively. However, none of this was possible in this study, due to the limited number of patients at our hospital who met the inclusion criteria. Further studies should be of long enough duration for compensatory phenomenon to be expected, to allow elucidation of possible deleterious effects on muscle fibre properties.

In conclusion, ambulatory patients with DM improved in muscle strength without any observed negative side effects during twelve weeks of high-resistance training. These results indicate that ambulatory patients with DM who are strong enough to raise the lower leg against an external load of 3 kg could benefit from a high-resistance training program. Due to the limited number of patients, further research is needed in order to draw conclusions about trainability concerning muscular strength in patients with DM. Further, it is reasonable to assume that among DM patients, there are sub-groups with different or no training potential, depending on the degree of muscular affection.

ACKNOWLEDGEMENTS

The research was supported by grants from the Karolinska Institute, the Swedish Society of Medicine, the Swedish Medical Research Council (3875) and the Research Council of the Swedish Sports Federation.

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Accepted January 15, 1998

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