Muscle training in muscular dystrophies

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ABSTRACT

There has been a debate for many years on whether muscular training is beneficial or harmful for patients with myopathic disorders and the role of exercise training in the management of these patients is still controversial. Much of this confusion is because of the lack of well-designed controlled training studies on this heterogenic group of disorders. Because effective therapies are still lacking, the patients have to rely on symptomatic treatment in which continuous physiotherapy plays an important role. There is thus still a need for studies evaluating the short- and long-term effects of muscular training in different types of myopathic disorders. We need to elucidate whether muscular training can increase strength and resistance to fatigue, but most importantly, we need to clarify whether training can improve specific functional abilities of the patient with myopathy. Future studies should give us specific information on what type of training, endurance or strength training, is to be preferred for different myopathies. The effect of strength training in one type of muscle disorder is not directly applicable to another, but is largely dependent on the underlying biological defect. From the studies published so far, high-resistance strength training at submaximal and possibly also at near-maximal levels seem beneficial, at least in the short perspective for slowly progressive myopathic disorders. However, the long-term effects of such training have not been systematically studied. In rapidly progressive myopathies, which are caused by deficient structural proteins such as in Duchenne's muscular dystrophy, the use of high-resistance training is far more controversial and questionable. If exercise regimens are to be used, they should preferably commence in the early stages of the disease, at which time there is still a substantial amount of trainable muscle fibres.

Keywords Duchenne's muscular dystrophy, endurance training, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy, mitochondrial myopathy, myotonic dystrophy, strength training, Welander distal myopathy.

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During the last two decades, profound advances have been made in the field of muscular dystrophies. As a result of the remarkable progress in molecular genetics, the underlying genetic defect of many of these disorders has been unravelled and in some cases provided a tool for detecting carriers by DNA testing. The identification of the gene defect responsible for Duchenne's muscular dystrophy (DMD) in 1987 (Hoffman *et al.* 1987, Koenig *et al.* 1987), has been followed by the identification of underlying gene defects in many other inherited muscle disorders and the list is continuously growing. The explosion of molecular genetic information has provided new targets for therapeutic interventions. However, despite the thrilling advances in molecular genetics, no effective therapeutic tools have emerged so far. With the exception of prednisone for DMD, no effective treatment has been found that will improve strength or even slow the progression of weakness in the various muscular dystrophies (see Tawil 1999).

While waiting for future effective therapies, the patients have to rely on symptomatic treatment in which continuous physiotherapy plays a vital role. The question often arises of whether these patients should participate in strength training programmes or not. For most inherited muscle disorders, this question cannot be accurately answered because this area has received surprisingly little scientific attention, and there are but a few studies on this topic.

In healthy individuals, it is well established that progressive resistance strength training increases muscle strength and endurance capacity (Saltin & Gollnick 1983). The role of exercise training in myopathic disorders, on the other hand, is far from clear. Because muscle weakness is usually the major problem, it would be desirable if strength training could

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help to counteract the loss of muscle tissue and the loss of strength. However, it is still debated whether muscle resistance training is beneficial or even harmful for the myopathic patient. Weakness caused by overwork has been suggested in case reports of patients with facio-scapulohumeral muscular dystrophy (Johnson & Braddom 1971) and scapuloperoneal muscular dystrophy (Wagner et al. 1986), and has also been suggested from animal studies (see Fowler 1984, Petrof 1998). Much of the confusion is based on the simple fact that there are no, or at the most very few, well-designed studies that have tried to approach these issues. Most studies have included DMD patients or a mixture of various neuromuscular disorders (e.g. Vignos & Watkins 1966, DeLateur & Giaconi 1979, Scott et al. 1981, Milner-Brown & Miller 1988, Kilmer et al. 1994). Early studies on the effects of low- to moderate-resistance training in patients with so-called muscular dystrophy reached partly conflicting results, suggesting either modest improvement or no gain (Abrahamson & Rogoff 1952, Hoberman 1955, Wratney 1958). In addition, neither of these studies was controlled. Several authors have reported beneficial effects of moderate-resistance or high-resistance training in slowly progressive neuromuscular disorders, but have included patients with a variety of disorders, which make it difficult to interpret the results for each separate disease (McCartney et al. 1988, Milner-Brown & Miller 1988, Aitkens et al. 1993, Kilmer et al. 1994). It is important that each disorder is studied separately, because the training outcome and possible negative effects caused by mechanical stress on the muscle fibres most probably differ among different types of muscle disorders. For example, the outcome of high-resistance training most probably differs between those disorders caused by abnormalities of structural proteins (e.g. DMD) and those in which the morphology is intact.

There are many problems in designing a training study for patients with muscular dystrophies. Inherited myopathies are rare disorders, and to obtain a reasonable number of patients the investigator usually has to include patients who differ regarding age, sex, symptom severity, distribution of weakness and rate of progression.

The potential for improvement depends on initial muscle strength and endurance and on the intensity, frequency and nature of the exercise programme, as well as on the motivation of the patients. The compliance may not be optimal and in order to avoid this potential problem, the training should be continuously supervised. This has rarely been the case in the training studies published so far. A continuously supervised training regimen may of course cause practical problems besides the fact that it is rather time consuming. Different training studies are not immedi-

ately comparable because they have used training protocols which differ regarding intensity of training, duration of the training period, muscle groups studied, if isometric or isokinetic training was used, and choice of controls. Another potential problem is the choice of test method, which ideally should be quantitative, reproducible and reliable.

Even if all these potential pitfalls have been circumvented and controlled, the fundamental issue remains. Does an increase in muscle strength, as measured in selected muscle groups, necessarily lead to an improved functional ability for the individual patient? This may not necessarily be the case. In order to obtain such information, muscle strength training studies have to be supplemented with studies on the functional outcome of different training regimens. This may cause additional difficulties because there are very few validated protocols for functional tests published, and they may not necessarily be applicable to the specific type of functional impairment of the patient group that is to be studied.

In other words, our current knowledge of how strength training affects the myopathic patient is limited and further studies are needed. Not only is this of utmost importance for the rehabilitation of these patients, but a better understanding of how the trained muscle behaves in genetically well-defined myopathic disorders may give information which will increase our understanding of physiological mechanisms of training in healthy muscles.

In the following, this review presents a summary of previous training studies performed on patients with various myopathic disorders.

MUSCULAR DYSTROPHIES

Dystrophinopathies

These disorders comprise of a severe form (DMD) and a milder form (Beckers muscular dystrophy, BMD), and both are caused by a disturbed production of a cell membrane associated protein called dystrophin. In DMD there is usually a total, or near-total absence of dystrophin, whereas in BMD, there is an expression of aberrant but partially functional forms of dystrophin. In BMD, clinical subtypes can be recognized that closely correlate with the amount and quality of dystrophin expressed in skeletal muscle. These disorders are X-linked and the mutated gene is located on the short arm of the X-chromosome (Xp21). The dystrophin gene is very large which probably, at least partly, accounts for its high spontaneous mutation rate (for review see Tsao & Mendell 1999).

Abnormalities of dystrophin result in disruption of the linkage between the intracellular cytoskeleton and

extracellular matrix, leading to sarcolemmal instability (see Tsao & Mendell 1999). Dystrophin deficient muscle fibres are more vulnerable to injury and less able to sustain muscle repair (see Swash & Schwartz 1997).

Based on these observations it would seem questionable to advise exercise programmes for DMD and BMD patients that would lead to an elevated mechanical stress on the muscle fibres. However, in one early study which included patients with various forms of muscular dystrophies, an improvement of weight-lifting capacity was noted after one half-hour weight-lifting training per day over a 1-year period (Vignos & Watkins 1966). The improvement reached a plateau after approximately 4 months. The degree of improvement related to initial strength and DMD patients were reported to be less able to sustain this improvement as compared with patients with other forms of muscular dystrophies. The authors concluded that resistive exercise can improve muscle strength in different forms of muscular dystrophy, but that the exercise programme should be started early in the course of the disease. Isokinetic submaximal strength training was reported to improve strength slightly in four DMD boys without any negative side-effects (DeLateur & Giaconi 1979). The absence of deterioration in the short-term as a response to mild-moderate exercise has been indicated also by other investigators (Scott *et al.* 1981). In studies where an improvement of muscle function was found, this was preferentially seen in individuals having the least impairment of muscle function and during the first weeks of training. There is a case report of a manifesting female carrier of DMD who achieved increased strength after a 12-week high-resistance concentric–eccentric resistance training programme with three training sessions a week (Bohannon & Jones 1986).

Inspiratory muscle training obtained by breathing against a resistive load has been reported by some investigators to improve ventilatory strength and endurance (DiMarco *et al.* 1985, Martin *et al.* 1986, Vilozni *et al.* 1994, Wanke *et al.* 1994), whereas others report no significant effects (Smith *et al.* 1988, Rodillo *et al.* 1989, Stern *et al.* 1989). Respiratory improvement was noted in those patients with only moderate impairment of lung function, but not in those with severely impaired lung function (Vilozni *et al.* 1994). On the contrary, in DMD patients with advanced disease, added inspiratory resistance may be hazardous, as a result of the reduced compliance of the lungs and chestwall which forces the inspiratory muscles to work close to their fatiguing threshold (Smith *et al.* 1987).

These studies indicate that certain forms of muscle training may be beneficial for the DMD/BMD patient, especially if initiated early in the disease process. It is suggested from the above studies that low-resistance training should be preferentially used. This may have beneficial effects on metabolic enzyme activities and possibly also have modulatory influences on the composition of isoforms of contractile proteins. It also seems probable that training regimens that may impose a high mechanical stress on individual muscle fibres, such as high-resistance and eccentric muscle training, should be avoided because this may lead to an increased muscle injury and death of myofibres. In patients with severely impaired lung function, added inspiratory resistance as part of a training programme may be potentially hazardous and should be avoided (Smith *et al.* 1987).

Limb-girdle muscular dystrophy

Limb-girdle muscular dystrophies (LGMD) constitute a group of genetically determined progressive muscle disorders. The pelvic and/or shoulder girdle muscles are primarily or predominantly involved. However, LGMD2B is caused by a mutation of the dysferlin gene and is allelic to Miyoshi myopathy in which there is an onset of weakness in calf muscles (Liu *et al.* 1998). In some families, there are members who present with onset either in distal or proximal muscles. The LGMDs are inherited either as autosomal dominant (LGMD1A-E) or autosomal recessive (LGMD2A-H) disorders. The molecular defect in many of the LGMD involves membrane-associated proteins, such as γ-sarcoglycans (LGMD2C), α-sarcoglycans (LGMD2D), β-sarcoglycans (LGMD2E), δ-sarcoglycans (LGMD2F), which form a distinct complex within the dystrophin–glykoprotein complex (DGC). Defects in the sarcoglycans also affect other components of the DGC, resulting in membrane instability (Roberds *et al.* 1993, Lim & Campbell 1998, Straub *et al.* 1998). The molecular defect in LGMD2A is that of a muscle-specific calcium activated neutral protease (calpain-3), not related to the DGC (e.g. Spencer *et al.* 1997).

Because many of the LGMDs are caused by defects in structural proteins in the DGC, a similar approach as in DMD/BMD is on theoretical grounds probably justified, in which high-resistance and eccentric training should be avoided, whereas low-resistance training may be justified. On the other hand, in those forms of LGMD where non-structural proteins are involved, high-resistance training may very well be proven to be beneficial. However, in the few existing reports on the effects of muscle training programmes in LGMD, the underlying molecular defect has not been known.

In the early study by Vignos & Watkins (1966) six patients with LGMD participated in a 12-month high-resistance training programme and were reported to increase in strength, although a plateau was reached

after 4 months of training. Studies on patients with various neuromuscular disorders, including only some patients with LGMD, have indicated positive effects of high-resistance training in patients with mild to moderate weakness (Milner-Brown & Miller 1988, Kilmer *et al.* 1994). It is not possible from these reports to draw any conclusions regarding the effects of muscle training in this heterogenic group of patients and further studies are needed.

Facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is one of the most common of the inherited myopathies. The cause of the disease is still unknown, but a genetic linkage to a locus on the long arm of chromosome 4 (4q35) has been demonstrated (Wijmenga *et al.* 1990, Fisher & Upadhyaya 1997).

An increase in muscle strength was reported in four FSHD patients as an effect of a 12-month high-resistance training programme (Vignos & Watkins 1966). Milner-Brown & Miller (1988) reported a 42-year-old patient with FSHD who demonstrated increased fatigue resistance and continued increase in strength during 3 years of resistance training of elbow flexors. In contrast, occurrence of possible overwork weakness was reported in a family with FSHD (Johnson & Braddom 1971). The results of these studies may be questioned on the basis of study design and the low number of patients included. There is an apparent need for studies on the effects of muscular training also in this group of patients.

Myotonic dystrophy

Myotonic dystrophy (DM) is the commonest form of muscular dystrophy with adult onset and is associated with muscle wasting and myotonia as one of its main features. It is actually a multi-systemic disorder which affects many organs besides skeletal and heart muscle, including the eye, the gastrointestinal system, several endocrine functions, the brain, peripheral nerves, and the immune system (Harper 1989). The underlying mutation for the most common form, DM1, is an unstable expansion of CTG repeats in the *DMPK* gene on chromosome 19 (Aslandis *et al.* 1992, Brook *et al.* 1992, Buxton *et al.* 1992, Fu *et al.* 1992, Harley *et al.* 1992), which encodes a putative serine/threonine protein kinase. The DM1 mutation is exceptional because it is located in a part of the *DMPK* gene that does not code for the protein (Brook *et al.* 1992) and it remains a mystery how this mutation can have a dominant effect with such severe consequences. Underlying complex mechanisms have been postulated at the DNA, the RNA, and protein levels. The patho-

physiology of the many and complex symptoms in DM1 is thus still far from clear and it is probable that this is the result of several different pathophysiological mechanisms.

Unlike several other muscular dystrophies, the progressive muscle wasting in DM1 is not the result of a mutation in a structural protein encoding gene. The progressive decrease in muscle mass in DM1 has been reported to be the consequence of decreased protein synthesis by the muscles, rather than accelerated muscle destruction, which suggests an anabolic defect (Griggs *et al.* 1990). A resistance to insulin has been reported in skeletal muscles of DM1 patients, whereas hepatic insulin response is normal (Moxley *et al.* 1984). Because insulin is a major anabolic hormone for skeletal muscles, a reduced insulin response may contribute to the muscle wasting in DM1. Another major anabolic stimulus, insulin-like growth factor-1 (IGF-1), has been shown to exert metabolic effects similar to those of insulin (Froesch & Zapf 1985). Interestingly, it was reported that DM1 patients treated with IGF-1 in a placebo-controlled trial showed a significant improvement in muscle strength and muscle function (Vlachopapadopoulou *et al.* 1995). The effect was ascribed to an increased insulin sensitivity, resulting in increases in protein synthesis and lean body mass.

There have been only a few studies on the effects of strength training in DM1 patients. Lindeman *et al.* (1995) studied the effect of 24 weeks of unsupervised strength training in 14 DM1 patients, each with a matched DM1 control. They were unable to detect significant alterations in knee torques, fatiguability, or in functional abilities as measured by time scored activities. Neither were there signs of overwork weakness, or muscle fibre damage, as measured by the levels of serum myoglobin which remained unchanged. In a recent study, 12 weeks of continuously supervised high-resistance knee-extensor training resulted in a significant increase in muscle strength as measured by one repetition maximum (1RM), whereas no change was found in isokinetic concentric or eccentric torque (Tollbäck *et al.* 1999). There was no sign of increased muscle deterioration as judged from muscle biopsies taken before and at the end of training. It was concluded that ambulatory DM1 patients who are strong enough to raise the lower leg against an external load of 3 kg could benefit from a high-resistance training programme. The latter study only included six patients, but in contrast to the majority of previous training studies, the training was continuously supervised by the investigators. The authors emphasized the importance of supervising the training sessions, because their patients needed continuous supervision and verbal encouragement in order to maintain the motivation for maximal performance. The compliance

of patients is a possible confounding factor in all training studies, especially in those of DM1 patients, a patient group in which cognitive disturbances are not uncommon.

Thus, it seems that high-resistance training may increase muscle strength and can be used in DM1 patients without obvious deleterious effects on the musculature, at least in the short perspective. However, further studies are needed to evaluate the long-term effects of such training. The increase in strength can partly be explained by neural adaptation, and possibly by muscle fibre hypertrophy. A fibre hypertrophy was indicated in the study by Tollbäck et al. (1999), but was not proven statistically significant because of the low number of patients and the great variability in consecutive muscle biopsies of diseased muscle. It is also possible that the fibre hypertrophy response to high-resistance training which is observed within 2 months of training in normal muscle (Sale 1988, Tesch 1988) is delayed or diminished in diseased muscle.

One of the obvious goals with muscular training is to obtain an improved functional capacity. A statistically significant increase in muscle strength as measured in the laboratory does not necessarily be of any functional value to the patient. Therefore, studies are needed in which validated functional tests are included. We have recently performed a randomized controlled training study on approximately 40 DM1 patients. Trunk, upper and lower extremity muscles were exercised with rubberbands at a high-resistance level, 3 × 10 repetitions three times a week for 12 weeks. The muscle function was evaluated using various time scored tests, in which the time to perform specified functional tasks was measured. Preliminary data indicate that muscle function was partly improved after the training period (unpublished observations).

Distal myopathy

Distal myopathies are a group of muscle disorders with different inheritance patterns and variable progression rates and characterized clinically by progressive muscular weakness and atrophy beginning in hands or feet. In the group of hereditary distal myopathies, Welander distal myopathy (WDM) represents a clinically homogenous form with late adult onset characterized by slow progression of distal muscle weakness (Welander 1951). The WDM has been linked to chromosome 2p13, but the mutated gene has not yet been identified (Åhlberg et al. 1999).

Little is known regarding the effects of training in these patients. There is one study in which a 78-year-old man with adult-onset hereditary distal myopathy (WDM) underwent 3 weeks of hand and wrist

isometric and dynamic resistance training with a resulting increase in grip and pinch strength of the hands and an improved hand function (Erwin et al. 1991).

We have recently completed a study on 11 ambulatory patients with WDM who were subjected to 12 weeks high-resistance training of foot plantar flexors. The training, which was supervised and performed 3 times a week with free weights at a load corresponding to 80% of the maximum load that could be performed during one contraction (one repetition maximum; 1RM), resulted in a significant increase of foot plantar flexor strength, as measured by 1RM. There were no signs of increased muscle deterioration as judged from muscle biopsies taken before and after the training (unpublished observations). It was concluded that high-resistance training can be beneficial for this category of patients. However, to clarify this, functional studies are needed in order to establish whether these patients also improve in functional parameters as a result of increased strength. A study on the effects of muscle training on hand muscle strength and hand function in Welander patients is currently on-going in our department and preliminary data reveal that hand function may be improved as a result of training.

OTHER MYOPATHIES

Mitochondrial myopathies

Mitochondrial disorders are a heterogeneous group of disorders which may affect a variety of organs, and the clinical phenotypes are quite variable, but do often include the central nervous system and skeletal and cardiac muscle (Larsson & Clayton 1995, Grossman & Shoubridge 1996). These disorders often show an impaired oxidative phosphorylation as a result of a mutation in the mitochondrial DNA (mtDNA). Usually this mutation coexists with normal wildtype mtDNA in various proportions, so-called heteroplasmy. When the relative amount of mutant vs. wildtype mtDNA exceeds a certain threshold, the oxidative energy metabolism is impaired and the pathological phenotype is expressed (Boulet et al. 1992, Taivassalo et al. 1999a).

It has been reported that short-term moderate-intensity aerobic training can significantly increase aerobic capacity, fatigue resistance and tolerance to daily activities in patients with mitochondrial myopathies (Taivassalo et al. 1998, Taivassalo et al. 1999b).

In a recent report, Taivassalo et al. (1999a) demonstrated that concentric high-resistance exercise of armflexors for a total of 11 days resulted in a 33% increase in wild-type mtDNA, a 43% decrease in proportion of cytochrome c oxidase (COX)-negative muscle fibres and a marked increase in fibre

diameters, especially in COX-positive fibres. The subject was a 59-year-old man with proximal weakness and exercise intolerance caused by a point mutation in tRNA, the mutant mtDNA constituting >90% of total mtDNA in muscle before training. The investigators suggested that the changes were caused by fusion of satellite cells devoid of the mtDNA mutation into existing myofibres in response to overload resistance training. Although, being a case-report, this study implies a new and exciting concept in which training-induced satellite cell activation is used to revert the accumulation of mutant mtDNA. Further studies are needed in order to elucidate if such effects of training are also obtainable in other forms of mitochondrial disorders.

CONCLUSIONS

There is clearly a need for well-designed controlled studies to clarify the role of muscle strength training in patients with various myopathic disorders. From the studies published so far, it seems that high-resistance strength training at submaximal and possibly also at near-maximal levels is beneficial, at least in the short perspective for slowly progressive myopathic disorders. In rapidly progressive myopathies, which are caused by aberrant structural proteins such as DMD, the use of high-resistance training is far more controversial. Increased mechanical stress of the muscle fibres should be avoided and it therefore seems advisable to avoid heavy resistance and eccentric training for these patients, although it has not yet been convincingly shown that these types of training regimens are hazardous for the DMD patient. On the other hand, these patients may benefit from low-resistance training in which mechanical damage is avoided and by which the metabolic and possibly contractile properties are optimized. Several of the reports on training effects in various types of muscle disorders indicate that the gain in muscle function is related to the initial muscle strength. Therefore, if muscle training regimens are to be used, they should commence in the early stages of the disease, at which time there is still a substantial amount of trainable muscle tissue. If training is performed in advanced stages of muscle disease, in which the muscle fibres are replaced by adipose and connective tissue, little positive effects can be expected. In the early stages of the disease, on the other hand, the amount of contractile tissue, which could respond to training, is obviously much higher. It is possible that training should start already at the asymptomatic stage in those disorders where DNA testing enables the detection of asymptomatic carriers within families with a known disorder.

The vast majority of studies published so far have involved limited training and observation periods, i.e.

less than a year. We do not know the long-term effects of training on muscles. Heavy-resistance training and possibly submaximal training may cause damage to the muscle fibres, which can be balanced by the activation of repair mechanisms through satellite cells. Because these cells are considered to have a limited potential for cell divisions, one concern is that the satellite cell pool may be consumed prematurely if the diseased muscle is trained too hard, thereby causing a muscle weakness prematurely. Indeed, an accelerated decline in replicative life-span has been reported for myoblasts obtained from DMD patients (Webster & Blau 1990). On the other hand, the activation of satellite cells may be used therapeutically as indicated by Taivassalo *et al.* (1999a) in their study on mitochondrial myopathy. Thus, studies are needed to further elucidate not only the effects in the short perspective, but also to evaluate the long-term effects of muscle training in the various types of muscle disorders.

Although the use of muscle training in the rehabilitation of patients with muscle disorders seems validated and advisable, at least for the slowly progressive myopathic disorders, the main question still remains largely unanswered: Does muscle training, although resulting in an improvement in muscle performance as measured in the laboratory, lead to an improved functional ability for the patient in his daily life activities? In order to answer this, studies of the effects on muscle strength from strength training programmes have to be supplemented with studies on the functional outcome of different training regimens.

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