

# Rehabilitation Management of Neuromuscular Disease: The Role of Exercise Training

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## Abstract

This paper summarizes the current state of knowledge regarding exercise and neuromuscular diseases/disorders (NMDs) and reviews salient studies in the literature. Unfortunately, there is inadequate evidence in much of the NMDs to make specific recommendations regarding exercise prescriptions. This review focuses on the role of exercise in a few of the specific NMDs where most research has taken place and recommends future research directions.

**Key Words:** exercise, neuromuscular disease, muscular dystrophy, rehabilitation, strength training

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## INTRODUCTION

Individuals with neuromuscular diseases (NMDs) are characterized by a progressive weakening and loss of functional skeletal muscles. The disability associated with NMDs depends on the specific type of disease, pathogenesis, extent of clinical involvement, and rate of progression. Although several therapeutic treatments have been proposed for NMDs, with the exception of certain inflammatory and metabolic myopathies, there is currently no effective pharmacologic management. Thus, the primary clinical goal is to maintain strength, function, independence, and quality of life.

An essential tool to maintain and improve strength, increase endurance, improve function, and enhance quality of life in able-bodied individuals is through exercise. Strength training (progressive resistance exercise) increases lean body mass, muscle

protein mass, contractile force, power, and improves physical function.<sup>1-3</sup> The lifting of weights during concentric (muscles shorten during contraction) or eccentric (muscles lengthen during contraction) exercise places stress on the muscle. This stress causes microscopic damage to the myofibers which initiates gene transcriptional and splice mechanisms, protein turnover, and signaling pathways from hormone and cytokine receptors.<sup>3</sup> This process involves a number of proteins that shuttle between sarcomeric and non-sarcomeric localizations and convey signals to the nucleus. Satellite cells, mononuclear, and myogenic progenitor cells that typically exist in a state of quiescence under the basal lamina are activated and fuse to the existing fiber and increasing the number of nuclei in the muscle and provide the machinery for additional contractile proteins. Exercise induces muscle hypertrophy by increasing the DNA content in the myofibrils, which in turn, increases the amount of muscle proteins, especially actin and myosin.<sup>4</sup>

Aerobic endurance training induces physiological adaptations that differ from strength training. Aerobic training that involves the use of large muscle groups for sufficient intensity and duration (30 minutes at 50-85% of VO<sub>2</sub>max) induces adaptations in the heart, peripheral circulation, and skeletal muscle systems. Greater oxygen delivery is achieved by training-induced increases in cardiac output (due to increased stroke volume), capillary density, and vascular conduction. Improved utilization of oxygen by

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trained skeletal muscle is accomplished by mitochondrial biogenesis and increased mitochondrial oxidative enzyme activity that lead to an increased capacity to generate energy through oxidative phosphorylation in trained muscles. In healthy individuals, these adaptations play a major role in improving oxidative capacity ( $\text{VO}_2\text{max}$ ), endurance, and reducing fatigue as shown by the ability to perform submaximal work with less effort for longer duration. Endurance-trained individuals produce lower concentration of blood lactate and lower heart rates than untrained individuals at the same level of submaximal exercise. Cessation of endurance training and resistance training is reversible and leads to partial or marked reductions in the training-induced cardiopulmonary, vascular, and skeletal muscle (deconditioning).

### EXERCISE AND NEUROMUSCULAR DISEASES

One of the primary questions for researchers and clinicians is to determine whether aerobic or progressive resistance exercise training may be helpful in individuals with neuromuscular diseases. The use of exercise has been controversial issue for individuals with NMDs because in the 1970s some limited evidence suggested that exercise training may cause overwork weakness in individuals with NMDs.<sup>5,6</sup> In a postmortem muscle study of a patient with Duchenne muscular dystrophy (DMD), the greatest muscle degeneration occurred in muscles used during sustained physical activity, suggesting possible overwork in these muscles.<sup>7,8</sup> As a result, for many years individuals with NMDs have been warned against performing excessive physical activities that could accelerate their weakness. The weakness, fatigue, poor endurance, and associated functional impairments are the result of both loss of functional muscle fiber and atrophy of disuse secondary to a sedentary lifestyle. The lack of exercise exacerbates the reduction in muscle mass and increased obesity, which contributes to the high prevalence of

metabolic syndrome observed in patients with NMDs.<sup>9</sup>

Although diminished aerobic capacity is rarely the limiting factor in performing daily work tasks, involvement of the cardiac and pulmonary musculature in NMDs may reduce cardiopulmonary fitness, compounding the effects of deconditioning.<sup>10</sup> It is well known that poorly conditioned able-bodied subjects, when compared with conditioned individuals, exhibit decreased muscle strength and endurance, impairment in cardiopulmonary function (lower peak minute ventilation, reduced stroke volume, reduced cardiac output, increased resting heart rate, and higher  $\text{VO}_2$  and higher heart rate at defined submaximal workloads), reduced resting energy expenditure, mitochondrial dysfunction, hormonal dysregulation, decreased lean body mass, increased fat mass, and reduced bone mineral density. In the able-bodied population, an inactive lifestyle increases the risk of coronary heart disease, hypertension, osteoporosis, obesity, metabolic syndrome, and adult-onset diabetes mellitus. It has been shown that aerobic endurance exercise training and strength training can reverse many of the problems associated with inactivity in young, middle-aged, elderly, and physically frail adults.<sup>11</sup>

### OVERVIEW OF THE EXERCISE STUDIES IN NMDS

Unfortunately, the number of studies that have examined the effect of exercise in NMDs is sparse and many of these studies have methodological limitations. The main reason for the lack of good controlled studies is due to the rarity of NMDs. Frequently, researchers grouped subjects with different NMDs to achieve a sufficient number of subjects to obtain statistical significance, even though the severity, rate of progression, and disease type markedly affects the exercise response. There is no reason to believe that diseases affecting the anterior horn cells, peripheral nerves, and/or muscles would respond similarly to exercise training. Nevertheless, these studies

did demonstrate that individuals with NMDs had some beneficial responses to exercise training. In slowly progressive or static NMDs, the goal of resistance exercise is to increase strength, thereby giving the patient increased capacity to perform daily functions. A number of investigations combining patients with slowly progressive NMDs demonstrated modest benefits of strengthening exercise in slowly progressive disorders.<sup>12-15</sup> Other investigators have demonstrated that endurance training improves oxygen uptake or reduced heart rate at a submaximal workload after stationary bicycle training.<sup>16,17</sup> However, there is some evidence that a high-resistance training program offers no additional strength benefits compared with a moderate-resistance strengthening program.<sup>14,18</sup> Whether the strength gains occur through direct hypertrophy of diseased muscle fibers or through reducing the effects of disuse weakness is not known.

Recent Cochrane systematic reviews have determined that there is insufficient evidence to determine whether exercise is beneficial or detrimental for individuals with amyotrophic lateral sclerosis, muscle diseases, and peripheral neuropathies.<sup>19-21</sup> When randomized control studies are scarce, evidenced from nonrandomized and other weaker designs may be relevant. Cup et al<sup>22</sup> performed a systematic review to assess the effect of exercise and physical therapy on all types of NMDs. Only 39 studies met their inclusion/exclusion for internal validity and descriptive criteria. In addition, there has been little uniformity regarding the type of exercise interventions (aerobic, strengthening, or combinations of exercise regimens), duration of exercise, intensity of exercise therapy, initial state of physical activity and fitness, and types of outcome measures. A major weakness is the lack of clearly identified primary and secondary outcome measures. Outcome measures that have been reported include strength, endurance, fatigue, cardio-pulmonary function, functional ability, activities of daily living, anxiety, depression, well-being, and pain, among others.

## REVIEW OF EXERCISE STUDIES IN SPECIFIC NMDs

Tremendous advances have occurred in the past decade in our understanding of the molecular genetic basis and pathophysiology of neuromuscular diseases. Molecular genetic advances have led to the discovery of specific genes for over 100 neuromuscular disorders. A wide range in clinical phenotypes and genetic heterogeneity has been identified within specific syndromes. For example, at least 14 genetically distinct subtypes of Hereditary Motor Sensory Neuropathy have been described, some with undetermined gene loci; 6 genetically distinct subtypes of autosomal recessive limb-girdle muscular dystrophy (LGMD) have been identified, and 2 genetically distinct subtypes of Bethlem myopathy exist. If the individual suffers from a neuromuscular disease, the benefit of and response to exercise may be remarkably different depending upon disease pathogenesis. This paper reviews the known effects of exercise with regard to the specific neuromuscular disorders and their pathogenesis. The evidence-based knowledge of the benefits and contraindications of exercise in different NMDs is limited because the pathogenesis of many diseases has been clarified only recently. In many earlier studies, the diagnostic capabilities were not sufficient to ensure that patients within a study had the same neuromuscular disorder.

### Hereditary Muscular Dystrophies

Muscular dystrophies are a pathogenetically heterogeneous group of hereditary muscle diseases, which present with muscle weakness. Typically, the muscular dystrophies are accompanied by progressive muscle fiber damage, inflammation, necrosis, and regeneration as noted by histopathological evaluation. Most dystrophies are associated with defects in sarcolemmal and extracellular matrix proteins, which bind the contractile elements across the sarcolemma to the extracellular matrix [especially to laminin-2 (merosin) of basal lamina]. These proteins

seem to be essential in maintaining the cytoskeletal framework of the muscle fiber during muscle contraction.<sup>23</sup> Thus, it is conceivable that intensive muscle contractions, particularly when including an eccentric component, may damage the already myopathic muscle to a greater extent than in the able bodied. This is a particular concern in those diseases known to involve structural proteins of the muscle cell, such as Duchenne muscular dystrophy, Becker muscular dystrophy, and many of the limb-girdle syndromes. In animal models of dystrophin-deficient dystrophy, there is increased damage to muscle using eccentric contractions, which particularly stress these cytoskeletal elements.<sup>24-26</sup> Maximal eccentric contractions seem to damage the cytoskeletal framework with myofibrillar disruption, which clinically is associated with transient muscle weakness, elevation of serum creatine kinase, and delayed-onset muscle soreness.<sup>27,28</sup> In NMDs that affect the integrity of the muscle cell membrane, it is possible that eccentric contractions may hasten the progression of muscle degeneration.

### Dystrophinopathies

Both DMD and Becker muscular dystrophy (BMD) are caused by mutations of the gene that encodes for dystrophin, a protein that forms a structural linkage between the F-actin cytoskeleton and the sarcolemma. Clinical signs of DMD typically usually present with weakness in the neck flexors at less than 2 years of age, delayed onset of walking, and difficulty getting up from the floor (Gower's sign). Quantitative strength testing shows greater than 40% loss of strength by age 6 years, with fairly linear progression from ages 5 to 13 until they lose their ability to ambulate because they cannot contract muscle against gravity.<sup>29</sup> Death typically occurs in the second to fourth decade from cardiac or respiratory failure.

There are 2 principal theories, neither of which is mutually exclusive, have been proposed to explain the pathogenesis of muscles from individuals with dystrophinopathies.

Dystrophin deficiency seems to destabilize the sarcolemma and makes the muscle fibers susceptible to mechanical stress and induces muscle fiber necrosis, fiber loss, and replacement with fibrotic tissue.<sup>30,31</sup>

theory is that disruption of the dystrophin complex downregulates neuronal nitric oxide synthase (nNOS) which disrupts the exercise-induced cell-signaling pathway that regulates blood flow to the muscle and results in functional muscle ischemia.<sup>32</sup> More recent studies have shown that when nNOS is not present at its normal location on the muscle membrane, then blood vessels that supply active muscles do not relax normally and show signs of fatigue.<sup>33</sup> Thus, the pathophysiology of the disease may significantly affect its response to exercise. Exercise, especially exercise that places a large amount of stress on the muscle fibers, such as high-resistive and eccentric exercise, could easily damage skeletal muscle in the dystrophinopathies. Even mild exercise has been implicated in causing functional muscle ischemia and fatigue in dystrophinopathy patients due to disruptions in nNOS signaling.<sup>32,33</sup>

Studies regarding the effect of exercise on skeletal muscles of individuals with DMD have produced conflicting results. Some investigations have demonstrated that low intensity aerobic and resistance exercise maintains or even slightly improves strength in DMD.<sup>34-37</sup> However, others have presented case study evidence that exercise induces weakness in dystrophinopathies. Garrod et al<sup>38</sup> noted that individuals with DMD increase their physical activity after steroid treatment and suggest that this increased exercise places their dystrophin-deficient muscles under greater mechanical stress, which predisposes them to muscle fiber damage and consequent myoglobinuria. A case study of a boy who had both spina bifida and Becker muscular dystrophy revealed that the dystrophic changes in the muscle biopsy were less severe in the lower extremities immobilized by spina bifida than the unaffected upper extremities. The authors suggest that this adds to the evidence that

excessive exercise causes muscle damage in dystrophinopathies and should be restricted.<sup>39</sup>

Studies that have examined the effect of respiratory muscle training on patients with dystrophinopathies have also produced conflicting results depending upon initial muscle strength. Several investigators have reported increased ventilatory strength and endurance after inspiratory and/or expiratory resistance training,<sup>40-44</sup> whereas others have shown no changes.<sup>45,46</sup> Koessler et al<sup>42</sup> demonstrated an improvement in maximum inspiratory pressure and 12-second maximal voluntary ventilation after 24 months of inspiratory muscle training in 18 DMD patients and 9 spinal muscular atrophy patients whose forced vital capacity was greater than 25% predicted. However, inspiratory muscles that are very weak or near their fatigue threshold showed no improvement after respiratory training.<sup>41,47</sup> Sveen et al<sup>48</sup> studied the effect of endurance training (30-minutes of aerobic cycling 3-4 times per week at 65% of their VO<sub>2</sub>max for 12 weeks) on 11 ambulatory patients with mild BMD and 7 matched, healthy subjects. They reported that aerobic endurance training increased VO<sub>2</sub>max by 47%, maximal workload by 80%, and muscle strength by 13-40%, without causing muscle damage as indicated by muscle pathology and increased serum CK. Overall, these results seem to suggest that exercise studies are contraindicated on subjects with dystrophinopathies who have very weak muscles and very susceptible to exercised-induced damage with little gain. Further short-term and long-term studies regarding the effect of endurance exercise and mild resistance exercise is warranted for individuals who still have adequate strength, but these should be monitored with great care to prevent adverse effects from the exercise.

### Limb-Girdle Muscular Dystrophies

Currently, at least 17 subtypes of LGMD are recognized.<sup>49,50</sup> Seven have autosomal-dominant inheritance pattern (LGMD type 1, A-E) and 10 with autosomal recessive

inheritance (LGMD type 2, A-J). It is now known that patients with LGMD comprise many distinctly different diseases with specific genetic defects in genes that encode for sarcolemmal, sarcomeric, and sarcoplasmic proteins. The most common LGMDs include LGMD2A (calpainopathy), LGMD2B (dysferlinopathy), and LGMD2C ( $\gamma$ -sarcoglycanopathy), LGMD2D ( $\alpha$ -sarcoglycan-Adhalin), LGMD2E ( $\beta$ -sarcoglycanopathy), LGMD 2F ( $\delta$ -sarcoglycanopathy), and LGMD2I. Mutations in components of the dystrophin-associated glycoprotein complex (DAGC) lead to a loss of sarcolemmal integrity and render muscle fibers more susceptible to exercise-induced damage and the development of hyperCKemia. In addition, the reduction of nNOS levels in the sarcolemma of LGMD subjects alters their cell-signaling response to exercise and makes them more susceptible to fatigue.

Very few studies have examined the effect of exercise in patients with genetically confirmed LGMD. Sveen et al<sup>51</sup> examined the effect of aerobic cycling in 9 adults with mild LGMD2I, which is caused by a defect in fukutin-related protein, a sarcoplasmic enzyme that glycosylates dystroglycan needed for appropriate binding of dystrophin-associated glycoprotein complex to laminin-2. Nine patients with LGMD2I cycled fifty 30-minute sessions at 65% of their maximal oxygen uptake over 12 weeks. The LGMD2I patients reported a 21% increase in VO<sub>2</sub>max and a 27% increase in work capacity, and a self-reported increase in strength and endurance without any evidence of muscle damage as observed by serum CK and muscle biopsy. Yeldan et al<sup>52</sup> reported that progressive resistance exercise improved respiratory function on 17 individuals with genetically confirmed LGMD and 6 with BMD. However, muscle response of respiratory muscles was specific to the training protocol. Deep breathing exercises improved maximal expiratory pressure, whereas inspiratory muscle training improved maximal inspiratory pressure; however, neither regimen significantly altered spirometry results. Bohme and Arnold<sup>53</sup> examined the effect of intensive physical

therapy in 156 patients with LGMD and noted an improvement in functional parameters. Unfortunately, this study did not have adequate genetic characterization of the LGMD. The rarity of individuals with specific LGMDs and the lack of adequate genetic confirmation confound the difficulties in performing studies to determine the effect of exercise in these patients. As is true in the dystrophinopathies, high-resistance exercise training should be avoided in LGMD patients, especially those who are very weak.<sup>54</sup>

### Facioscapulohumeral Dystrophy

Facioscapulohumeral dystrophy (FSHD) was clinically categorized by its characteristic progressive muscular weakness in the facial and shoulder girdle musculature and onset of symptoms often in adolescence or early adulthood. FSHD is an autosomal-dominant disorder resulting from a chromosomal abnormality identified at the 4q35 gene locus that causes reduced DNA fragment size at the telomere region and a epigenetic changes in the chromatin structure.<sup>55,56</sup> As opposed to the other muscular dystrophies, there are few distinctive findings on muscle biopsy.<sup>57</sup>

A randomized clinical trial was performed to assess the effect of progressive resistance strength training (3 times a week for 52 weeks) with and without albuterol in 65 FSHD subjects.<sup>58</sup> No muscle damage was observed as a result of the training. Whereas the isometric strength of the elbow flexors did not increase between the exercised and nonexercised group, the dynamic strength, using the one repetition maximum showed a significantly larger increase in the exercised group. Although the lack of response could be due to the inability of the FSHD group to respond with a normal hypertrophic response to exercise, it is more likely that the lack of response is due to the specificity of the training.<sup>59</sup> To be most effective a training program must be designed to improve the muscle group being exercised and the outcome measures need to be responsive to the prescribed change. Because the weight training performed by van der Kooi utilized

isokinetic exercise, it is not surprising that the training resulted in larger increases in isokinetic strength as compared with isometric strength. Although the elbows responded to the exercise training, the ankle dorsiflexors showed no significant changes as a result of the weight training. The lack of response in the ankle dorsiflexors may be attributed to an ineffective training regimen. However, the authors noted that the dorsiflexors may not have been able to move against gravity and therefore might have been too weak to respond to the training regimen. The amount of weight used for training the dorsiflexors may have been insufficient to cause a training effect. The conflicting responses observed by the various muscles examined by van der Kooi demonstrate the difficulties researchers face in developing an exercise prescription for each of the NMDs. In addition, perhaps the most important outcome is not strength all, but whether the exercise changes function, improves quality of life, and alters future health outcomes. Because aerobic training effects the whole cardiovascular system, effects of training are much easier to delineate. Olsen et al reported that low intensity aerobic cycling at a heart rate corresponding to a work intensity of 65% of  $VO_2$ max for 35 minutes, 5 times a week for 12 weeks significantly increased their maximal oxygen uptake and workload in 8 subjects with FSHD, with no signs of muscle damage. Unlike subjects with sarcolemmal abnormalities, there are no indications that FSHD muscle fibers are more predisposed to mechanical injury than control subjects in the short term.

### Myotonic Muscular Dystrophy

There are 2 subtypes of myotonic muscular dystrophy, DM1 and DM2 (Dystrophia Myotonica types 1 and 2). DM1 is caused by abnormal expansion of the CTG trinucleotide repeats in the Dystrophia Myotonica Protein Kinase gene on chromosome 19q13.3, whereas DM2 is caused by an abnormal expansion of the CCTG repeats in the Zinc Finger protein 9 gene on chromosome

3q21.<sup>61-63</sup> The expansion of the gene is thought to trigger an RNA-mediated process that creates a toxic RNA that modulates other transcripts, including the chloride channel.<sup>64</sup> As a result DM1 and DM2 are multisystem disorders affecting skeletal muscle, smooth muscle, myocardium, brain, and ocular structures. As opposed to the dystrophinopathies and sarcoglycanopathies, which are characterized as being necrotic muscle diseases with regeneration, in myotonic muscular dystrophy necrosis is rare, and atrophy leads to the progressive reduction in muscle mass.<sup>57</sup>

Moderate-resistance exercise and aerobic training have been shown to be safe in patients with myotonic muscular dystrophy, although the benefits of these exercise programs are mixed. Lindeman et al<sup>65</sup> and Tollback et al<sup>66</sup> found few significant effects of progressive resistance exercise in a group of clinically diagnosed ambulatory subjects with myotonic dystrophy. Aldehag et al<sup>67</sup> reported that progressive resistance exercise of hand function 3 times per week for 12 weeks significantly increased motor function and self-rated occupational performance in 5 patients with DM1. Wenneberg et al<sup>68</sup> performed a randomized controlled trial to assess the effect of 3 months of Qigong, a complementary exercise program in individuals with clinically diagnosed myotonic muscular dystrophy. They reported that there was an increase in coping skills and no decline in self-assessed general health in the exercise group, which was significantly different than the control group, which showed a significant reduction in general health and no changes in coping skills. Orngreen et al<sup>69</sup> reported that 12 weeks of aerobic training (fifty, 35-minute cycling sessions at a heart rate corresponding to 65% of VO<sub>2</sub>max) is safe and can improve fitness effectively in patients with DM1. After the training regimen, the DM1 group increased VO<sub>2</sub>max by 14% and workload by 11%. The subjects had a self-reported increase in strength, endurance, and walking, without any muscle damage as observed by serum creatine kinase or muscle pathology.

## METABOLIC AND MITOCHONDRIAL MYOPATHIES

*McArdle disease (glycogen storage disease type V)* results from absence of muscle glycolytic enzyme, myophosphorylase. This enzyme deficiency results in muscle's inability to breakdown glycogen for energy (ATP) generation during anaerobic metabolism. In addition, lack of myophosphorylase also impacts energy generation during aerobic metabolism due to decreased substrate generation (pyruvate) for the tricarboxylic acid cycle. Glycogen is the most important source of energy for the muscle during early exercise and at high exercise intensities. The decrease in oxidative capacity of McArdle disease muscle is at less than half of normal muscle in the first few minutes of moderate exercise, and a more vigorous activity triggers muscle cramps, pain, and myoglobinuria. Because of the risk for severe and potentially dangerous rhabdomyolysis associated with exercise, many patients with McArdle disease have traditionally been advised to avoid exercise. However, sedentary and inactive lifestyle for these patients often results in deconditioning. This can further complicate and worsen the disease by decreasing their cardiovascular and circulatory capacity. With deconditioning and decline in circulatory capacity, the delivery of much needed blood borne energy fuels such as glucose and free fatty acids to muscle becomes impaired, at a time when muscle energy imbalance is compounded by blockage of glycogen breakdown and muscle critically depends on blood borne energy sources for metabolism. Research has also shown that deconditioning reduces levels of muscle mitochondria and mitochondrial enzymes that are necessary for metabolizing energy sources. Thus, avoidance of physical activity and adoption of inactive lifestyle in McArdle disease for fear of muscle injury may result in a downward spiral of decreased exercise tolerance and aerobic capacity, which in turn, further lowers the threshold of physical activity producing muscle injury and cramps.

Given these issues, recent studies have looked into whether exercise training and aerobic conditioning can help in ameliorating the symptoms of McArdle disease. Haller et al have demonstrated the beneficial effects of a moderate-intensity aerobic exercise program in improving average work capacity (36%), oxygen uptake (14%), cardiac output (15%), and citrate synthase and beta-hydroxyacyl coenzyme A dehydrogenase enzyme levels (80% and 62%, respectively) without causing pain or cramping or increase in serum creatine kinase level.<sup>70</sup> The exercise regimen entailed cycle ergometer for 30–40 minutes/d, 4 days/wk, for 14 weeks, at an intensity of approximately 60–70% maximal heart rate. The investigators found that moderate aerobic exercise is well tolerated and when performed regularly, leads to adaptations that substantially increase oxidative and work capacity in patients with McArdle disease. Favorable response was also noted in a similar but longer 8-month aerobic exercise training program study.<sup>71</sup> Other case reports and studies also support the benefit of moderate-intensity aerobic exercise and activity program in McArdle disease patients to improve exercise tolerance, work capacity, and overall health status.<sup>72–74</sup> The beneficial effects of the exercise program are thought to occur through increasing cardiovascular fitness and improving circulatory delivery capacity, and increased mitochondrial enzyme level and improved metabolic efficiency.

*Mitochondrial myopathies* are a heterogeneous group of metabolic muscle disorders associated with abnormal structure and function of mitochondria. Brain and skeletal muscles are particularly susceptible to mitochondrial dysfunction due to their high requirement for oxidative energy metabolism. Mitochondrial myopathies often begin with fatigue, exercise intolerance, or muscle weakness during physical activity and their symptoms range from mild to disabling.

Therapeutic exercise has been suggested as a means to improve muscle oxidative capacity and reduce the proportion of mutant mtDNA in patients with mitochondrial

myopathies.<sup>75–80</sup> Because resistance exercise is known to serve as stimulus for satellite cell induction within skeletal muscle, a series of experiments have been performed to determine whether it would lead to a shifting of normal mitochondrial genes from satellite cells to mature muscle, lowering the level of mutant mtDNA and improving oxidative capacity.<sup>79–80</sup> Murphy et al<sup>81</sup> showed that 12 weeks of progressive overload resistance training caused myofiber damage and regeneration, increased neural cell adhesion molecule-positive satellite cells, improved muscle oxidative capacity and increased muscle strength in 8 subjects with large-scale mtDNA mutations. Further work is needed to optimize the training effect and gene-shifting from mutant to wild-type mtDNA and to determine whether the training translates into long-term improvement.

Endurance training has also been hypothesized to induce mitochondrial biogenesis and capacity for oxidative phosphorylation and improve function of individuals with mitochondrial myopathies. In 1996, Taivassalo et al<sup>75</sup> presented a case study that demonstrated that aerobic training could improve exercise capacity and reverse the effects of deconditioning in a patient with a nuclear mutation causing cytochrome oxidase deficiency. Subsequent studies by these authors have shown that that mild endurance exercise (30 minutes/d, 3–4 times per week for 8–14 weeks at 70% maximal heart rate) significantly increases aerobic capacity, oxygen efficiency, decreases resting heart rate, and decreases lactate in a group of patients with mitochondrial myopathies caused by both nuclear and mtDNA mutations.

ever, it seemed that subjects with nuclear DNA mutations had a greater improvement than that shown by subjects with mtDNA mutations. More recently, studies have examined the effect of endurance training in 8 patients with a single large-scale mtDNA mutation and in 20 patients with a variety of mutations in their mtDNA.<sup>80</sup>

reported significant increases in both physiological and biochemical markers of



mitochondrial function, without any changes in the level of mutant mtDNA.<sup>80,83</sup> They also showed loss of endurance training gains in exercise and mitochondrial capacity after the cessation of training, confirming the maladaptive effects of deconditioning. Overall, the beneficial effects of endurance training have been reported in 8 published reports, with no adverse effects.<sup>76-78,80,82,83-85</sup> However, it must be emphasized that these studies were short term ( $\leq 14$  weeks), had small numbers of subjects ( $\leq 20$ ), and were not randomized controlled trials. Nevertheless, the results are extremely intriguing and warrant further studies of both endurance exercise and resistance exercise in individuals with mitochondrial myopathies.

### Acquired Myopathies

Most exercise studies in patients with acquired myopathies have been conducted in patients with inflammatory myopathies: polymyositis, dermatomyositis, and inclusion body myositis.<sup>86</sup> Until early 1990s, patients with inflammatory myopathies were discouraged from physical activity due to fear of exacerbating muscle inflammation. Although sample sizes are small, more recent work suggests that moderate-intensity resistance exercise may improve strength and function without signs of increased muscle inflammation.<sup>87-89</sup> Response to exercise may vary depending on disease activity, medications, and degree of disability. Patients with stable, chronic inflammatory myopathy may be able to tolerate more intensive strengthening regimens (10 maximal muscle contractions 3 days/wk) without untoward effects.<sup>89</sup> Decreased aerobic capacity compared with controls has been demonstrated in both adult patients with inflammatory myositis<sup>90-92</sup> and juvenile dermatomyositis.<sup>93</sup> A home exercise program consisting of 15 minutes of progressive resistive exercise and a 15-minute walk 5 times per week for 12 weeks did not significantly improve muscle function in patients with inclusion body myositis but found no adverse effects on histopathology and inflammation.<sup>94</sup>

### Motor Neuron Disease

Most exercise studies of patients with motor neuron diseases have been performed on patients with amyotrophic lateral sclerosis (ALS). ALS is a fatal progressive degenerative disease of the upper and lower motor neuron. The majority of ALS cases are sporadic, about 10% are inherited as an autosomal dominant trait. Although the pathogenesis of ALS has not been delineated, approximately 20% of the patients with hereditary ALS subjects have a defect in the gene encoding copper-zinc superoxide dismutase.<sup>95</sup> Evidence from studies of exercise on superoxide dismutase-deficient transgenic mice suggests that endurance exercise training at moderate intensities slows disease progression, and increases lifespan<sup>96-98</sup>, whereas high-intensity exercise showed no improvement<sup>99</sup> or hastened symptoms and death.<sup>100</sup> Exercise has been shown to induce changes in motor neuron morphology, muscle-nerve interaction, glial activation, and altering levels of gene expression of antiapoptotic proteins and neurotrophic factors in active tissue in these mice.<sup>101</sup>

However, not enough studies have been performed to determine whether the beneficial effect of exercise observed in these transgenic mice occurs in humans. A randomized control trial examined the effects of a twice-daily exercise program of moderate load endurance exercise versus usual activities in 25 people with ALS. ALS subjects performing the exercise showed less deterioration on the ALS functional rating scale and Asworth scales after 3 months of exercise, but there was no significant difference at 6 months. Too many patients dropped out to evaluate the effect of 9 and 12 months. Bello-Haas et al<sup>102</sup> randomly assigned 27 ALS subjects with forced vital capacity  $>90\%$  predicted to a daily resistance exercise and stretching program or usual care. After 6 months, 8 subjects randomized to exercise had significantly higher ALS functional rating scale scores, Medical Outcomes Study 36-Item Short Form Survey Instrument functional subscale scores and greater maximum voluntary

isometric contraction scores than those 10 subjects in the nonexercise group. One non-randomized study found that 8 ALS subjects who performed aerobic exercise to an aerobic threshold on treadmills coupled with non-invasive BiPap ventilation for 1 year improved their functional independent mobility and lowered the rate in decline of respiratory function and muscle strength as compared with a control group of 12 ALS subjects.<sup>103</sup> After analyzing the results of these studies, a Cochrane review determined that the small number of randomized controlled trials combined with the small sample sizes in the trials that have been performed preclude determination as to the benefits of exercise for individuals with ALS.<sup>19</sup>

### Post-polio Syndrome

Halsted first described Post-polio Syndrome (PPS) as a condition that affects individuals who had a confirmed case of polio, had partial or fairly complete neurological and functional recovery after the acute episode, had a period of at least 15 years with neurological and functional stability, gradual or abrupt onset of new muscle weakness, muscle atrophy, muscle pain, and fatigue that persists for more than 1 year.<sup>104</sup> Before 1996, PPS patients were advised to avoid physical activity and intensive exercise due to concerns about overwork weakness.<sup>105,106</sup> Although a 2006 European Federation of Neurological Society (ENFS) task force evaluated the literature regarding the use of exercise in PPS subjects and determined that both aerobic training and progressive resistance exercise training can benefit individuals with PPS<sup>107</sup> a recent systematic analysis by Cup et al<sup>22</sup> determined that there is insufficient evidence to assess the effectiveness of muscle strengthening exercises, aerobic exercises, or a combination of these exercises in individuals with PPS. The reasons for this difference can be attributed to the methodology the groups used to assess the evidence. The ENFS group used a group consensus to assess the results, whereas Cup et al use a systematic analysis. Because few studies

defined their primary or secondary outcome measures, Cup et al divided the number of variables that showed a statistically significant effect by the number of outcome variable in the study and defined evidence of effectiveness if more than half of the variables showed a significant effect. Three randomized controlled trials<sup>107-109</sup> and 5 studies with other designs<sup>110-114</sup> examined the effect of resistance strengthening with various types, intensities, and durations of exercise training on patients with PPS. Whereas the ENFS concluded that there is Level II and III evidence that progressive resistance training increases strength in PPS, Cup et al<sup>116</sup> reported that most of these studies did not meet the level of evidence required by their analysis. One randomized controlled trial, one clinical controlled trial and 2 other designs<sup>118-120</sup> examined the effect of aerobic training demonstrated that aerobic training improved cardiovascular fitness and functional abilities in individuals with PPS. However, there is disagreement as to whether the methodology and data presented in these studies are adequate to make any conclusions regarding the benefits of aerobic exercise in PPS.

### Peripheral Nerve Diseases

Peripheral neuropathies consist of a heterogeneous group of genetic and acquired disorders affecting the peripheral nerves. Most exercise studies of patients with peripheral nerve diseases have been performed on patients with Charcot-Marie-Tooth (CMT) disease.

### CMT DISEASE

CMT encompasses a group of more than 40 clinically and genetically heterogeneous peripheral neuropathies that were initially characterized by their mode of inheritance and their nerve conduction velocities and were labeled as CMT1, CMT2, CMT3, and CMT4<sup>121,122</sup> Because CMT subjects exhibit muscle weakness, fatigue, and deconditioning, 3 studies have examined whether exercise could improve symptoms and quality of life in these patients. Lindeman et al randomized 29 CMT subjects randomized to 24

weeks of progressive resistance exercise of their lower extremity muscles and reported a significant increase in knee torque without adverse effects, but few functional changes as compared with the control group. A home-base progressive strength-training program (3 days/wk for 12 weeks using ankle and wrist weights) was performed by 18 CMT1A and 2 CMT2 patients with and without creatine supplementation.<sup>123</sup> Because there was no significant change as a result of creatine on these subjects, the groups were combined to assess the effect of exercise. Although there are several methodological problems including lack of randomization and lack of a control group, the authors reported that the combined exercise group exhibited improved functional measures, increased tension of the knee and elbow, and increased in type 1 fiber diameter after the exercise training. The third study demonstrated that subjective pain and fatigue,  $\text{VO}_2\text{max}$ , isokinetic knee torque, and functional abilities improved after aerobic cycling training (3 days/wk for 24 weeks at 70% of HRmax) in 4 CMT1A and 4 CMT2 male subjects as compared with their values before training.<sup>124</sup>

## CONCLUSIONS

At this time, there is inadequate evidence from randomized controlled trials with sufficient sample size to make recommendations regarding exercise programs for individuals with NMDs. Nevertheless, there is a potential for aerobic training to improve the cardiopulmonary condition of individuals with NMD, but the level of training and kind of training depends on the type, stage, and severity of the disease. Results from the aerobic studies performed almost uniformly show that individuals who are mildly affected by the disease or who are early on in the course of their disease demonstrate short-term cardiopulmonary improvements that are similar to those seen in persons without NMDs. In these individuals, aerobic exercise may reverse the effects of deconditioning and provide positive health benefits in terms of

reduced adiposity, improved cardiopulmonary status, improved sense of well being, and increased bone mass. More severely involved persons with NMD may be unable to respond positively to either resistive training or aerobic exercise. Unfortunately, not enough information is available to make informed decisions regarding exercise in individuals with more severe impairments. Assessing the effect of progressive resistance exercise is much more difficult as it depends upon the pathogenesis of the disease and the exercise protocol, training target, and outcome measure. However, considerable progress has been made in developing both theory of exercise-induced remodeling and empirical benefits of endurance and resistance exercise in individuals with mitochondrial myopathies. More studies need to be conducted to develop a better theoretical understanding these effects in the other NMDs.

To optimally assess the effect of exercise will require a systematic analysis to determine the functional capabilities of muscles from individuals with NMDs. Grange et al<sup>125</sup> suggest that animal models of the NMDs can be used to determine a comprehensive response to exercise, using time-course studies over a wide range of ages and functional abilities to define the muscle gene expression profiles, biochemical processes, protein expression, and physiologic function before, during and after various exercise training protocols. The information derived from these experiments can then be used to determine the intensity, duration, frequency, and timing of exercise to produce the optimal improvement in function and to assess the functional threshold in which the muscle becomes injured or creates adverse effects. These data should provide helpful information to develop appropriate studies in humans.

The current knowledge regarding the effect of exercise on individuals with NMDs is controversial because the evidence mainly comes from short-term uncontrolled trials, nonrandomized trials, or observational studies with small sample sizes and heterogeneous groups of study subjects. More randomized

controlled studies that examine the effect of exercise on genetically homogeneous groups of individuals that have been randomized to a treatment group or a control group are needed. Investigation should identify the patient's pre-exercise status (disease genotype, age, gender, presence of concomitant diseases, severity of weakness, and physical activity level) and the exercise protocol will need to clearly identify the duration, intensity, frequency, and type of exercise training. Several training protocols will need to be tested to optimize the effect, assessing the timing of the intervention, and to determine the safety efficacy of the training program in both the short and long term. In addition to strength determinations and measures of aerobic performance, outcome variables should include indicators of functional ability, patient satisfaction, and emotional well-being and assessment of chronic disease risk, such as blood pressure, resting heart rate, body mass and adiposity, glucose tolerance, and bone density. Primary and secondary outcome measures should be clearly identified. Multi-center studies should be undertaken to have a sufficient number of subjects with a single disease to give the study significant statistical power.

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