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Literature Review

Response to Resistive Strengthening Exercise Training in Humans with Neuromuscular Disease

ABSTRACT

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The role of strengthening exercise to potentially improve weakness and the functional abilities of persons with neuromuscular diseases is controversial. There are questions about the ability of diseased skeletal muscle to respond to resistance exercise, particularly in light of concerns about weakness induced by exercise. Numerous studies show promising results of strength training, although methodologic issues limit conclusions. This article reviews current knowledge in this area and provides recommendations for future investigations.

Key Words: Myopathy, Neuropathy, Overuse Weakness, Dystrophy

Despite intense interest from patients and clinicians to use exercise to strengthen muscles weakened by neuromuscular disease (NMD), we are far from being able to provide science-based recommendations and precautions. Although many studies report improved strength after resistance training without untoward effects, limitations in subject selection and methodology prevent any meaningful conclusions at this point. This article reviews current knowledge about strengthening exercise in NMD, and provides recommendations for future investigations in this area.

CHALLENGES OF INVESTIGATIONS OF STRENGTH TRAINING IN NMDs

Hereditary NMDs are not static. Weakness progresses at markedly different rates when different diseases are compared and even when individuals with the

same disease, such as Duchenne muscular dystrophy (DMD), are compared. Some DMD boys may be wheelchair dependent at age 8, whereas others are ambulatory until age 14 or 15. Normal growth and development are often not considered in studies involving children. In addition, with relatively rapidly progressive diseases such as DMD and amyotrophic lateral sclerosis, the goal of a strengthening program may be to slow the progression of weakness rather than to gain improvements in strength. Thus, a valid control group of diseased subjects receiving conventional rehabilitative care without exercise training becomes critical.

There is also a practical challenge in organizing a study involving NMD subjects. It has been our experience that persons with these diseases are often highly motivated to participate in strength-training regimens, but they are much less likely to participate if randomized to a nonexercising control group.

The relative rarity of the NMDs, and hence the difficulty of enrolling test subjects with the same NMD, led researchers to group subjects with different NMDs to achieve a sufficient number of subjects. However, the severity and rate of progression of a specific disease markedly affects the exercise response. In addition, it is intuitively obvious that diseases grouped together as NMDs and yet affecting the anterior horn cells, peripheral nerves, or muscles may respond quite differently to resistance exercise.

The affected gene product of a hereditary NMD presents specific problems in evaluating the effect of exercise. Diseases with muscle fiber membrane protein abnormalities may be more vulnerable to exercise injury, particularly with eccentric or lengthening contractions. Even greater delineation of the specific deficient membrane protein may be important. For example, a disorder presenting clinically as limb-girdle syndrome has subtypes with unique

structural protein abnormalities of the muscle cell membrane, each of which may have a different response to exercise.¹

DIFFICULTY IN INTERPRETATION OF PAST STUDIES

Different NMDs, Small Samples. Persons with different NMDs may respond in markedly different ways to strengthening exercise, and it is difficult to generalize for an entire disease population by studying only a few subjects. In many studies, there is broad variability in severity of disease among the patients studied. It is difficult to compare an exercise response in a subject with only mild weakness to one who cannot lift his or her limb against gravity.

Variable Control Groups. In many studies, no control group exists. In others, exercise is performed on one limb while the other is used as a nonexercise control. Crossover effects related to neural control have been well documented in the exercise literature, making this comparison problematic. In addition, several studies use nondiseased exercise control subjects to provide information regarding the ability of a specific strength-training protocol to stimulate a training effect in the able-bodied. A diseased nonexercising control group receiving standard rehabilitation care with subject randomization has rarely been included but would be preferred.

Strength Measurement Method. Earlier strength-training regimens used manual muscle testing to measure strength, but manual muscle testing is insensitive to changes in strength. Other studies have used static (isometric) or dynamic (isotonic/isokinetic) methods of strength measurement, which makes comparison difficult.

Different Periods and Types of Strengthening Exercise Programs. Concern about possible weakness induced by exercise (overuse weakness)

led some investigators to be very cautious in exercise protocols, whereas others used maximal strength training. In addition, whereas some programs were highly structured and supervised, others were home-based, where compliance with the protocol was not known. The short duration of most strengthening studies does not allow differentiation between neural training effects *vs.* muscle fiber hypertrophy, which occurs later during an exercise program.²

Lack of Functional Status Measures. Although increased strength is often used to measure the success of an intervention, much less attention is devoted to improvements in function related to activities of daily living, mobility, or avocational interests, which are issues of great importance to patients.

RESPONSE OF RAPIDLY PROGRESSIVE NMDs TO STRENGTHENING EXERCISE

DMD is the prototypical, rapidly progressive NMD, and strengthening studies are limited to this disorder. Only three of the seven DMD reports can be evaluated from the standpoint of this review, but even these are subject to different interpretations. As mentioned above, early reports³⁻⁵ are not particularly useful, since subjective manual muscle testing strength measurements were used, diseases other than DMD were included and not separated out for analysis, or the study lacked a nonexercised control group or opposite limb as a control. One report was primarily a drug study.⁶

Of the remaining three studies, one took into account age, disease progression and severity, and preexercise status, and it separated for analysis the 14 DMD subjects from the slowly progressive NMD, but it primarily used manual muscle testing and a home-based exercise pro-

gram.⁷ The initially stronger muscle groups made gains of >50% over the weight initially lifted, whereas weaker muscle strength gains were generally <50%. These strength gains only occurred during the first 4 mo of the study, followed by a plateau up to 1 yr. Scott et al.,^{8,9} using objective static measurements of strength, also studied the course of DMD in 18 boys with a home-strengthening exercise program. Since muscle strength deteriorated in the exercised subjects and there was no nonexercised control group, it is unclear if the program altered the natural course of the disease. The third study¹⁰ used the nonexercised limb as a control in a supervised program of submaximal resistive exercise using dynamic measurements of strength. However, the sample size was very small ($n = 4$). A modest but statistically insignificant increase in strength occurred that was maintained for several months.

In these three studies, there is no clear indication that resistance exercise increased muscle strength. In the rapidly progressive NMDs, however, a reduction in the progression of weakness would be considered to be a beneficial outcome. Without investigations including natural history control subjects, it is not possible to make any conclusions about the role of exercise in rapidly progressive NMDs.

RESPONSE OF SLOWLY PROGRESSIVE NMDs TO STRENGTHENING EXERCISE

Ten reports have been published that included individuals with slowly progressive NMDs. One was a single case report on hereditary distal myopathy.¹¹ Four studies used a combination of strength training and other therapeutic interventions.^{12–15}

Most of the remaining five studies had substantial methodologic limitations, such as an inadequate num-

ber of subjects or a mixed group with different NMDs, ignoring the natural history of each disease.^{16–20} For the most part, these studies used the opposite nonexercised limb as a control, which may underestimate strength increases due to possible cross-over training effects. Indeed, in these studies, strength gains in the exercised limb were the same or only slightly greater than in the nonexercised limb. Two of these investigations included able-bodied controls in addition to using the opposite limb as a control.^{19,20} Evaluation was by quantitative measurements in all investigations, and a home exercise program was used in all but one study.¹⁸ Exercise periods ranged from 9 wk to 1 yr (most were 9–24 wk) and three to four times per week. Exercise training protocols varied in terms of percentage of one-repetitive maximum and number of sets or repetitions performed.

The most comprehensive and well designed study was by Linderman et al.²¹ The patient samples were adequate, and the results for the two diseases—hereditary motor and sensory neuropathy and myotonic muscular dystrophy—were evaluated separately. Subjects within groups were individually matched by strength and randomly assigned as training or control. The training period was 6 mo. In addition, functional performance and fatigability were assessed, as were changes in muscle fiber membrane permeability as evaluated by serum myoglobin levels. The major criticism would be that only knee extensor strength was measured, since hereditary motor and sensory neuropathy is primarily a distal neuropathy. The myotonic muscular dystrophy subjects demonstrated no strength training effect or improvement in functional performance, but neither the exercise or control group showed signs of deterioration. However, deterioration would not be expected in 6 mo in such a slowly progressive NMD. In the hereditary

motor and sensory neuropathy group, knee torques moderately increased, but timed motor performance and functional ability did not improve. There was no change in myoglobin levels in either group.

In the other studies,^{16–20} a moderate increase (10–80%) in strength was observed. An important observation is that strength increases were usually found only when baseline strength was >15% of able-bodied normal control data.¹⁶ In parallel investigations by Aitkens et al.¹⁹ and Kilmer et al.,²⁰ both submaximal and maximal resistive exercise resulted in modest increases in strength in knee extensors, but a slight decrease in elbow flexor strength was observed with the maximal resistance exercise protocol.

RESPONSE OF POSTPOLIO SYNDROME TO STRENGTHENING EXERCISE

Postpolio syndrome occurs in persons who recover function after their initial poliomyelitis, only to experience new symptoms of weakness and fatigue more than 30 yr later. Because there is no evidence of reactivation of the disease with viral-induced degeneration of anterior horn cells, muscle overuse and disuse are presumed to be important causes of the new symptoms. Due to the lengthy gap between the recovery from acute polio and the later development of new weakness, the postpolio syndrome may be considered as a separate NMD.

Twelve studies have been published that include individuals with postpolio syndrome. Three were case reports of a single subject,^{22–24} and several others^{25,26} seemed to represent the same patient sample. As with other strengthening exercise studies in NMD, the postpolio studies have shortcomings in methodology. The number of subjects ranged from 6 to 17. For controls, most studies used

either the opposite limb or some combination of symptomatic *vs.* asymptomatic muscles on the same or opposite side. The terms “fatiguing” and “nonfatiguing” exercise were used, presumably meaning maximal or submaximal resistance training.^{25–27} Other studies used manual muscle testing as the measurement of strength.^{14,15} Exercise periods ranged from 6 wk up to 2 yr, usually 3 days per week, and most were home programs.

Results vary, but all studies report an increase in strength. Spector et al.²⁸ reported a 41–71% increase in dynamic knee and elbow extensor strength, but they reported no change in isometric strength, serum creatine kinase, muscle cross-sectional area by magnetic resonance imaging or in histopathology in a 10-wk study. On the other hand, Fillyaw et al.,²⁷ in a 2-yr investigation, found an increase in static strength. Einarsson et al.^{29–31} observed an increase in both dynamic and static strength, an increase in the fatigue index, and an improvement in activities of daily living during a 6-wk program. Agre et al.^{32,33} reported improvement in strength and endurance, with a greater increase after maximal resistance exercise, during a 12-wk program. Feldman²⁵ and Feldman and Soskolne²⁶ observed increased strength in the “disused” weak muscle and a decrease in the polio-weakened muscle with fatiguing exercise but an increase in strength in both disused and polio-weakened muscles with a nonfatiguing program.

MUSCLE STRENGTHENING IN NMDs WITH ELECTRICAL STIMULATION

Several European studies investigated the effects of low-frequency, long-term electrical stimulation on muscle strength in DMD. In these investigations, maximum voluntary contraction strength increased compared with the unstimulated con-

tralateral muscle. There were no changes in the fatigue index or relaxation time.^{34,35} In a study that grouped various NMDs, Milner-Brown and Miller¹⁴ used a combination of resistance exercise and electrical stimulation. Electrical stimulation alone was ineffective, but by combining both modalities, there was a significant increase in mean maximum force when the initial strength was >15% of normal able-bodied data. There also was increased force in the contralateral control muscle. Despite encouraging preliminary results from these investigations, electrical stimulation to maintain or improve strength in NMD has not gained popularity in North America, possibly due to limitations on insurance coverage for the procedure and lack of knowledge about its application and efficacy.

STRENGTHENING EXERCISE RECOMMENDATIONS

Despite considerable methodologic limitations in the literature cited for this review, we can draw two general conclusions about strengthening exercise in NMD:

1. Resistance exercise may be beneficial if the degree of weakness is not severe, and the rate of progression of the disease is relatively slow.
2. High-intensity resistance exercise has no advantage over more moderate programs.

OVERUSE WEAKNESS AND ECCENTRIC CONTRACTIONS

Clinicians have long been concerned about the potential for exercise to hasten the progression of weakness caused by NMD. Although this concern was never validated in prospective studies, a number of case reports exist that document potential

damage (overuse weakness) caused by exercise in patients with various NMD.

In patients recovering from acute polio, a case series from the 1950s reported signs of overuse weakness during both supervised submaximal strengthening and unsupervised community activities.³⁶ In a postmortem muscle study of a patient with DMD, the greatest muscle degeneration occurred in muscles likely to be used during sustained physical activity, suggesting possible overuse in these muscles.³⁷ A pattern of increased weakness in the dominant upper limb subjected to heavy loads during work or with unsupervised weightlifting suggested overuse weakness to several clinicians.³⁸

With recent knowledge about abnormalities in the muscle cell membrane caused by DMD, Becker muscular dystrophy, and the sarcoglycanopathies, there is concern about the potentially damaging effects of eccentric muscle contractions.^{39–41} These concerns are supported by the fact that animal models of dystrophin deficiency demonstrate increased susceptibility to the damaging effects of eccentric contractions when compared with normal animals.^{42–44} 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.^{45,46} In NMDs that affect the integrity of the muscle cell membrane, it is possible that eccentric contractions may hasten the progression of muscle degeneration. The only study testing this hypothesis found that persons with a variety of slowly progressive dystrophies had a similar injury and recovery response compared with an able-bodied control group when exposed to an acute bout of eccentric muscle contractions.⁴⁷ It is premature to make specific recommendations regarding the role of eccentric

muscle actions for muscle strengthening in specific NMD.

CONSIDERATIONS FOR FUTURE STRENGTHENING EXERCISE STUDIES

To draw meaningful conclusions about the effects of strengthening exercise in individuals with NMD, reviewing the limitations of past investigations provides a basis for recommendations for future studies.

1. In designing exercise protocols, subjects with different diseases should not be grouped together for statistical analyses.
2. Comparisons should be made with matched control subjects having the same NMD, rather than using the contralateral limb, nonexercised muscles in the same limb, or able-bodied subjects.
3. Matching of subjects should consider the severity of weakness and relative activity level (active *vs.* sedentary).
4. Only quantitative measurements should be used to assess changes in strength.
5. Evaluations of functional performance should be used. These should include quantitative measures such as timed motor performance and subjective evaluations of activities of daily living.
6. Home-based programs should be carefully supervised and include information regarding adherence to the protocol.
7. The type of exercise training (static/dynamic, concentric/eccentric), the intensity of training, the rate of progression of intensity, and the duration should be precisely defined.
8. To separate the effects of neural adaptation from muscle fiber hypertrophy, the duration of exercise training should be longer than 12 wk.

REFERENCES

1. Brown RH: Dystrophin-associated proteins and the muscular dystrophies. *Ann Rev Med* 1997;48:457–66
2. Moritani T, DeVries HA: Neural factors versus hypertrophy in the time course of muscle strength gains. *Am J Phys Med* 1979;58:115–30
3. Abramson AS, Rogoff J: An approach to the rehabilitation of children with muscular dystrophy: Physical treatment in muscular dystrophy, in *Proceedings 1st and 2nd Medical Conferences*, New York, Muscular Dystrophy Association of America, 1952, pp 123–5
4. Hoberman M: Physical medicine and rehabilitation: Its value and limitations in progressive muscular dystrophy. *Am J Phys Med* 1955;34:109–15
5. Wratney MJ: Physical therapy for muscular dystrophy children. *Phys Ther Rev* 1958;38:26–32
6. Fowler WM Jr, Pearson CM, Egstrom GH, et al: Ineffective treatment of muscular dystrophy with an anabolic steroid and other measures. *N Engl J Med* 1965;272:875–82
7. Vignos PJ Jr, Watkins MP: The effect of exercise in muscular dystrophy. *JAMA* 1966;197:843–8
8. Scott OM, Hyde SA, Goddard C, et al: Effect of exercise in Duchenne muscular dystrophy. *Physiotherapy* 1981;67:174–6
9. Dubowitz V, Hyde SA, Scott OM, et al: Controlled trial of exercise in Duchenne muscular dystrophy, in Serratrice G (ed): *Neuromuscular Diseases*. New York, Raven Press, 1984, pp 571–5
10. de Lateur BJ, Giaconi RM: Effect on maximal strength of submaximal exercise in Duchenne muscular dystrophy. *Am J Phys Med* 1979;58:26–36
11. Erwin JH, Keller C, Anderson S, et al: Hand and wrist strengthening exercises during rehabilitation of a patient with hereditary distal myopathy. *Arch Phys Med Rehabil* 1991;72:701–2
12. Moon JH, Na YM, Kang SW, et al: The changes in muscle strength and relaxation time after a comprehensive rehabilitation program for patients with myotonic dystrophy. *Yonsei Med J* 1996;37:237–42
13. Na YM, Lee HS, Moon JH, et al: The effect of home exercise program for patients with myotonic dystrophy. *J Korean Rehabil Med* 1996;20:33–8
14. Milner-Brown HS, Miller RG: Muscle strengthening through electric stimulation combined with low resistance weights in patients with neuromuscular disorders. *Arch Phys Med Rehabil* 1988;69:20–4
15. Milner-Brown HS, Miller RG: Myotonic dystrophy: Quantification of muscle weakness and myotonia and the effect of amitriptyline and exercise. *Arch Phys Med Rehabil* 1990;71:983–7
16. Milner-Brown HS, Miller RG: Muscle strengthening through high-resistance weight training in patients with neuromuscular disorders. *Arch Phys Med Rehabil* 1988;69:14–9
17. Mielke U, Leinritz, Holzer H, et al: Dynamic muscular training in neuromuscular disease. *J Neurol Sci* 1990;S98:388
18. McCartney N, Moroz D, Garner SH, et al: The effects of strength training in patients with selected neuromuscular disorders. *Med Sci Sports Exerc* 1988;20:362–8
19. Aitkens SG, McCrory MA, Kilmer DD, et al: Moderate resistance exercise program: Its effect in slowly progressive neuromuscular disease. *Arch Phys Med Rehabil* 1993;74:711–5
20. Kilmer DD, McCrory MA, Wright NC, et al: The effect of a high resistance exercise program in slowly progressive neuromuscular disease. *Arch Phys Med Rehabil* 1994;75:560–3
21. Linderman D, Leffers P, Spaans F, et al: Strength training in patients with myotonic dystrophy and hereditary motor and sensory neuropathy: A randomized clinical trial. *Arch Phys Med Rehabil* 1995;76:612–20
22. Twist JF, Ma DM: Physical therapy management of the patient with post-polio syndrome: A case report. *Phys Ther* 1986;66:1403
23. Gross M, Schuck C: Exercise programs for patients with post-polio syndrome: A case report. *Phys Ther* 1989;69:72
24. Milner-Brown HS: Muscle strengthening in a post-polio subject through a high-resistance weight-training program. *Arch Phys Med Rehabil* 1993;74:1165–7
25. Feldman RM: The use of strengthening exercises in post-polio sequelae: Methods and results. *Orthopedics* 1985;8:889–90
26. Feldman RM, Soskolne CL: The use of non-fatiguing strengthening exercises in post-polio syndrome, in Halstead LS, Wiechers DO (eds): *Research and Clinical Aspects of the Late Effects of Poliomyelitis*

- Birth Defects: Original Article Series*. White Plains, New York, March of Dimes Birth Defects Foundation, 1987, vol 23, No 4, pp 335–41
27. Fillyaw MJ, Badger GJ, Goodwin GD, et al: The effects of long-term non-fatiguing resistance exercise in subjects with post-polio syndrome. *Orthopedics* 1991; 14:1253–6
28. Spector SA, Gordon PL, Fenerstein IM, et al: Strength gains without muscle injury after strength training in patients with postpolio muscular atrophy. *Muscle Nerve* 1996;19:1282–90
29. Einarsson G, Grimby G: Strengthening exercise program in post-polio subjects, in Halstead LS, Wiechers DO (eds): *Research and Clinical Aspects of the Late Effects of Poliomyelitis. Second Research Symposium on the Late Effects of Poliomyelitis. Birth Defects: Original Article Series*. White Plains, New York, March of Dimes Birth Defects Foundation, 1987, vol 23, No 4, pp 275–83
30. Einarsson G: Muscle adaptation and disability in late poliomyelitis. *Scand J Rehabil Med Suppl* 1991;25:1–76
31. Einarsson G: Muscle conditioning in late poliomyelitis. *Arch Phys Med Rehabil* 1991;72:11–4
32. Agre JC, Rodriguez AA, Franke TM, et al: Low-intensity, alternate-day exercise improves muscle performance without apparent adverse effect in postpolio patients. *Am J Phys Med* 1996;75:50–8
33. Agre JC, Rodriguez AA, Franke TM: Strength, endurance, and work capacity after muscle strengthening exercise in postpolio subjects. *Arch Phys Med Rehabil* 1997;78:681–6
34. Scott OM, Vrbova G, Hyde SA, et al: Responses of muscles of patients with Duchenne muscular dystrophy to chronic electrical stimulation. *J Neurol Neurosurg Psychiatry* 1986;49:1427–34
35. Zupan A, Gregoric M, Valencic V, et al: Effects of electrical stimulation of muscles of children with Duchenne and Becker muscular dystrophy. *Neuropediatrics* 1993;24:189–92
36. Bennett RL, Knowlton GC: Overwork weakness in partially denervated skeletal muscle. *Clin Orthop* 1958;12:22–9
37. Bonsett CA: Pseudohypertrophic muscular dystrophy: Distribution of degenerative features as revealed by anatomic study. *Neurology* 1963;13:728–38
38. Johnson EW, Braddom R: Over-work weakness in facioscapulohumeral dystrophy. *Arch Phys Med Rehabil* 1971;52:333–6
39. Hutter OF: The membrane hypothesis of Duchenne muscular dystrophy: Quest for functional evidence. *J Inher Metab Dis* 1992;15:565–77
40. Petrof BJ: The molecular basis of activity-induced muscle injury in Duchenne muscular dystrophy. *Mol Cell Biochem* 1998;179:111–23
41. Porter JD: Extraocular muscle sparing in muscular dystrophy: A critical evaluation of potential protective mechanisms. *Neuromuscul Disord* 1998;8:198–203
42. Franco A Jr, Lansman JB: Calcium entry through stretch-inactivated ion channels in mdx myotubes. *Nature* 1990; 344:670–3
43. Stedman HH, Sweeney HL, Shrager JB, et al: The mdx mouse diaphragm reproduces the degenerative changes of Duchenne muscular dystrophy. *Nature* 1991;352:536–39
44. Turner PR, Fong PY, Denetclaw WF, et al: Increased calcium influx in dystrophic muscle. *J Cell Biol* 1991;115: 1701–12
45. Clarkson PM, Nosaka K, Braun B: Muscle function after exercise-induced muscle damage and rapid adaptation. *Med Sci Sports Exerc* 1992;24:512–20
46. Friden J, Lieber RL: Structural and mechanical basis of exercise-induced muscle injury. *Med Sci Sports Exerc* 1992;24:521–30
47. Kilmer DD, Aitkens SG, Wright NC, et al: Response to high-intensity eccentric muscle contractions in persons with myopathic disease. *Muscle Nerve* 2001; 24:1181–7