Pediatric Neurology 104 (2020) 13–18

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Topical Review

Exercise Training as Part of Musculoskeletal Management for Congenital Myopathy: Where Are We Now?

Alena Adaikina, MSc [a, *], Paul L. Hofman, MD [a], Gina L. O'Grady, FRACP, PhD [b], Silmara Gusso, PhD [c]

[a] Liggins Institute, University of Auckland, Auckland, New Zealand
[b] Paediatric Neurology Department, Starship Children's Hospital, Auckland, New Zealand
[c] Department of Exercise Sciences, University of Auckland, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 25 June 2019
Accepted 22 October 2019
Available online 29 November 2019

Keywords:
Congenital myopathy
Neuromuscular disorders
Vibration therapy
Aerobic exercises
Strength training

ABSTRACT

Congenital myopathy is a heterogeneous group of muscle disorders characterized by muscle weakness and hypotonia. This condition is associated with a range of skeletal, respiratory, and ophthalmologic complications and requires a multidisciplinary therapeutic approach aimed at maximizing the function and independence of patients. One promising direction for therapeutic intervention is physical exercise rehabilitation, given its demonstrated ability to promote muscle and bone health of patients with a variety of neuromuscular conditions. However, there are few data to assist health care professionals identify the optimal physical activity levels and exercise type, including the intensity, frequency, and duration. This lack of empirical evidence is particularly problematic given the fact that inappropriate exercise modes can potentially cause muscle damage in patients with congenital myopathy. In this article, we discuss the rationale behind the incorporation of two types of physical exercises, strength and aerobic training, into the clinical care of patients with congenital myopathy. Given the paucity of literature on the management of congenital myopathy, we review the results of published research on the treatment of both congenital myopathy and other neuromuscular diseases that could provide helpful insights into the physical rehabilitation of patients with congenital myopathy. We also discuss the potential benefits of vibration therapy, which has been studied in patients with other neuromuscular disorders over the last two decades. We conclude by proposing directions for future research on physical rehabilitation of patients with congenital myopathy.

Introduction

Congenital myopathy (CM) is a heterogeneous group of genetic muscle disorders characterized by muscle weakness, hypotonia, and gross motor delay, and is associated with complications that may include respiratory insufficiency, bulbar weakness, ophthalmoplegia, skeletal malformations (scoliosis, hip subluxation or dislocation, foot deformities, and contractures), and malignant hyperthermia.[1] The estimated prevalence of CM is 1.37 of 100,000 to 5.0 of 100,000 depending on the country and population cohort (pediatric or adult).[2,3] However, the true prevalence of CM is likely higher due to undiagnosed patients with mild clinical symptoms and nonspecific histologic features.[1,4] The classification, based on muscle biopsy, divides CM into the following five broad types: core myopathy, centronuclear myopathy, nemaline myopathy, myosin storage (or hyaline body) myopathy, and congenital fiber-type disproportion myopathy.[1] Genetic classification is based on genes implicated. To date, mutations in more than 32 genes have been identified in CMs, the most commonly affected gene being ryanodine receptor 1.[5]

The key clinical characteristics of musculoskeletal involvement in patients with CM include nonprogressive or slowly progressive muscle weakness and hypotonia, which are often present at birth or in infancy. Muscle weakness is observed in axial and proximal limbs, affecting the walking ability and causing developmental

Conflict of interests: The authors declare no conflicts of interest regarding the publication of the article.

Funding: A.A. and S.G. were funded by grants from the Jubilee Crippled Children Foundation Trust.

* Communications should be addressed to: Adaikina; Liggins Institute; University of Auckland; 85 Park Road, Building 505, Level 2, Grafton, Auckland 1018, New Zealand.

E-mail address: a.adaikina@auckland.ac.nz (A. Adaikina).

https://doi.org/10.1016/j.pediatrneurol.2019.10.008
0887-8994/

delays in motor skills in 71% CM cases.[6] Patients variably have involvement of distal, facial, and respiratory muscles. The severity of the clinical manifestations and the location of the muscles affected depend on the type of CM and genetic cause.[4,7,8] A number of studies have connected CM to a higher risk of developing osteopenia[9,10] and bone fractures,[11,12] although the prevalence and character of bone density changes and related complications have not been accessed precisely for patients with CM.

To improve the health of patients with CM, several therapeutic approaches have been used, including supplementing vitamin D, calcium, and bisphosphonates for bone health,[10] as well as L-tyrosine,[13] salbutamol,[14] pyridostigmine,[15] myostatin inhibition treatment,[16] antioxidant therapy,[17] and acetazolamide[18] to assist for muscle strength and function. However, data on the effectiveness of most of these therapies are scant, and more research is needed to explore the effectiveness of these medications.

Given the wide range of clinical manifestations of CM, effective treatment requires a multidisciplinary therapeutic approach, which, depending on the patient's condition, may include medical professionals from neurology, respiratory, orthopedics, gastroenterology, nutrition, and other disciplines.[10] Echoing this point, in 2009, an international committee of medical professionals provided clinicians with diagnostic strategies and care guidelines for patients with CM. In their consensus statement, the committee stressed the need to maximize the function and independence of such patients by promoting physical activity and avoiding inactivity and recommended physical therapy being incorporated in rehabilitation plans for this group of patients.[10] However, the implementation of recommendations for physical activity is complicated by the lack of robust clinical trials involving exercise rehabilitation of patients with CM. As acknowledged by the committee itself, no direct evidence exists that could assist health care professionals in identifying the optimal characteristics of physical rehabilitation interventions for this group of patients.[10] To date, few studies on patients with CM have been conducted,[19-21] and the data available do not provide guidance on the optimal characteristics of a physical rehabilitation program, such as intensity, frequency, and duration. There remains an unmet need for therapeutic approaches to promote bone and muscle health, and many authors have called for continued research in this field.[7,8,10,21] The importance of further research in identifying the optimal characteristics of physical exercise for patients with CM is emphasized by the fact that inappropriately selected intensity, duration, and type of exercises can cause muscle damage[22,23] and thereby exaggerate existing muscle damage in patients with CM.

Here we discuss the rationale behind the incorporation of two types of physical exercises, strength training and aerobic training, into the clinical care of patients with CM. Given the paucity of literature on the management of CM, we review the results of published studies on the treatment of both CM and other neuromuscular diseases that could provide helpful insights into the physical rehabilitation of patients with CM. We also discuss the potential benefits of vibration therapy (VT), which has been studied in patients with other neuromuscular disorders (NMDs) during the last two decades, and review the relevant literature. Finally, we propose directions for future research in the field of physical rehabilitation of patients with CM.

Strength training

Strength training is an exercise modality that is aimed at improving the muscle strength, power, and motor performance and promoting and maintaining good health and fitness level, as well as physical independence.[24] For several decades the effectiveness of strength training has been studied both in healthy individuals and in those with chronic conditions, including NMDs, and has been consistently shown to increase muscle strength, endurance, and function.[19,20,24-26] In addition, a number of studies also demonstrated a positive impact of strength training on bone mineral density.[27,28] For patients with CM, these effects are essential; therefore, studies on the potential benefits of strength training are highly promising.

The effectiveness of strength training has not been specifically studied in patients with CM. Therefore our analysis of the applicability of incorporating strength training into physical rehabilitation and health programs for individuals with CM will be informed by the results of extant research on other NMDs.

Given the importance of intensity in evaluating the efficacy of strength training, we have categorized strength training studies according to this parameter. Studies in which participants underwent low- to moderate-intensity strength training have repeatedly demonstrated improvements of muscle strength without negative effects.[29-31] McCartney and colleagues explored the effects of a nine-week, three-days-a-week dynamic weight training on the leg and arm strength on five participants with facioscapulohumeral muscular dystrophy (FSHD), limb-girdle syndrome, and spinal muscular atrophy (SMA). In this cohort, strength increased by 34% in biceps and by 11% in quadriceps with no muscle damage registered on muscle biopsy or tomography.[30] Similar results were received by Aitkens and colleagues, who examined the effectiveness of a 12-week moderate-resistance program on 27 participants with a variety of NMDs. The results demonstrated a significant increase of isokinetic strength by approximately 20% in quadriceps and 10% in biceps ($P < 0.05$). Participants reported high compliance with exercise sessions (88%) and no symptoms of excessive soreness or fatigue due to training.[29] Kooi and colleagues ran a randomized controlled study on 65 patients with FSHD, wherein participants were assigned to either a control group ($n = 31$) with no training or an intervention group ($n = 34$) that underwent 52 weeks of 30-minute moderate-intensity strength training thrice a week. The authors reported an increase in dynamic muscle strength in elbow flexors ($P < 0.05$). The exercise program was well tolerated with no reported soreness or muscle fatigue.[31]

Studies using high-intensity strength training are limited when compared with those using low- to moderate-intensity data.[32-34] Vignos and Watkins investigated the effect of 12-month, 30-minute daily weight lifting on 24 patients with various forms of muscular dystrophies and demonstrated an improvement of muscle strength and function that reached a plateau after four months. Notably, the strongest muscle groups assessed at baseline gained more strength, and the results sustained for over a year in some NMDs.[32] Milner-Brown and Miller supported these findings and reported an increase of isometric strength by 77% in quadriceps and 83% in biceps in 16 participants with different NMDs following 13 months of a high-resistance dynamic exercise program.[34] In another study, 10 patients with NMDs underwent a 12-week exercise program similar to the one implemented in the Aitkens et al. study,[29] except for the high intensity. Although the authors reported an increase in the quadriceps muscle strength, they concluded that the high-intensity resistance training had no advantage over a moderate-resistance program in the NMD population.[33] High-resistance training was tolerated in all studies, and participants did not report any detrimental side effects, although the objective indicators of muscle damage were not evaluated.

To summarize, the available studies have been mostly performed on heterogeneous NMDs, which constrains our ability to generalize their findings to CM. However, low- and moderate-intensity strength exercise programs have been studied more extensively and have had no reported evidence of adverse effects, which provides us with suggestive evidence in favor of

recommending low- and moderate-intensity programs as a more preferable type of strength training in patients with CM to increase muscle strength and function.

Apart from the intensity of training, consideration should be given to the type of strength exercises, which can be classified into eccentric or concentric. Concentric exercises involve shortening of muscle fibers, whereas eccentric actions focus on the active lengthening of muscle fibers. The International Committee on Standard of Care for CM recommends concentric exercises as optimal for patients with CM.[14] This conclusion stems from the findings that eccentric exercises result in muscle damage, which is clinically connected to delayed-onset muscle soreness, transitory muscle weakness up to 24 hours,[22,35-38] and increased serum creatine kinase (CK) in both healthy subjects and patients with NMD.[26,36] For patients with CM, this change could be detrimental, especially given the fact that as of now no data exist on the possibility of muscle repair after damage. Kilmer and colleagues investigated the acute effects of high-intensity eccentric training on muscle damage, as assessed by the level of CK in patients with NMD (n = 14) and healthy (n = 18) subjects. After baseline measurements, all participants performed a bout of intense eccentric contractions, followed by the testing of muscle strength and serum CK three and seven days after the exercise session. As a result, in both groups, the serum level of CK remained high for over seven days.[26] In contrast, after concentric exercises, muscle strength restored to baseline in the next few hours[35,38] and no significant increase in soreness was reported.[22,38] In addition, studies have reported morphologic abnormalities (e.g., myofibrillar disturbances, Z-line streaming, streaming, Z-lines out of register, loss in thick myofilaments) in biopsy analysis after eccentric exercises,[39,40] whereas no changes have been registered after concentric exercises.[39] Taken together, this accumulated evidence suggests that concentric exercises are optimal for patients with CM allowing them to avoid potential detriments from exercising.

Aerobic exercises

Aerobic exercises are widely considered to be beneficial for the improvement and maintenance of health. They not only improve cardiovascular capacity but also reduce the risk of many conditions related to the sedentary lifestyle, including obesity, type 2 diabetes, metabolic syndrome, and stroke among others.[41-43] It has also been shown that aerobic exercises improve muscle strength and tone in the larger muscle groups[44] and bone density when weight bearing is involved.[45] These effects potentially could be highly beneficial for patients with CM.

To date, only one study on the feasibility of using aerobic training in patients with CM has been published,[21] although some studies have included patients with CM when exploring exercise rehabilitation as part of treating neuromuscular conditions.[25,46] Hedermann and colleagues explored the effectiveness of aerobic training on participants with CM in a nonrandomized controlled study. Seven of 16 participants completed 10 weeks of 30-minute moderate-intensity cycle ergometer exercises thrice weekly and demonstrated an increase of VO_{2max} by 14% ($P < 0.001$), whereas in the nonintervention group a tendency to decrease of VO_{2max} was shown (n = 7; $P = 0.083$). Nine of the 16 participants dropped out of the study, with six of them dropping out due to reported fatigue. However, those who completed the study reported decreasing fatigue levels as the training progressed.[21] Florence and Hagberg ran a randomized controlled study that explored the cardiovascular response to a 12-week aerobic-exercise program in a group of adults (age 30.5 ± 9.32) with NMDs, including three participants with CM (nemaline myopathy, central core disease, myotubular myopathy). Participants were assigned to either an exercise (n = 8) or control (n = 4) group; a group with healthy individuals who exercised was also recruited (n = 6). The exercise groups (both NMD and healthy) performed 12 weeks of exercise training on exercise ergometer for 30 minutes thrice a week; the control group continued their usual activities with no changes in their activity regime. As a result of the training, aerobic capacity, assessed by VO_{2max}, significantly increased in both neuromuscular and healthy participants, by about 24% and 16%, respectively ($P < 0.05$). Participants with neuromuscular conditions reported no side effects of the training and demonstrated high compliance to exercise sessions (94% of all sessions were completed).[46] Other findings included no change in the CK level during the intervention[21,46] and no reports from participants of myalgia.[21] Although this suggests that exercising did not cause sarcomeric injury,[21] the small number of participants limits interpreting these findings as definitive evidence. In addition, the studies did not address the entire range of CM types, some of which might respond to exercise intervention differently due to the variation in the muscle lesion pathogenic mechanisms.

Improvements in aerobic capacity have also been demonstrated in studies that included participants with other NMDs.[47-49] Andersen et al.[50] explored the effectiveness of eight weeks of a weekly supervised high-intensity training in a randomized controlled study that used 12 patients with FSHD and healthy subjects (n = 6). As a result, patients with FSHD who underwent high-intensity training (n = 6) improved aerobic capacity ($P < 0.01$) and showed no symptoms of muscle damage (pain and CK level); however, muscle strength and mobility did not change. Voet et al.[51] compared the effects of aerobic exercise training (n = 28) and cognitive behavioral therapy (n = 25) with those of usual care (n = 24) on fatigue and pain level, aerobic capacity, muscle strength, and physical activity level in a randomized clinical trial among patients with FSHD. Patients who received 30 minutes of aerobic training thrice weekly during 16 weeks demonstrated improvements in the fatigue level, quadriceps muscle strength, and physical activity level compared with the usual care group, but showed no changes in aerobic capacity. In Wright et al.'s study,[49] 12 weeks of a home-based walking program showed a decrease of the submaximal exercise heart rate ($P = 0.046$) and submaximal exercise systolic blood pressure ($P = 0.019$) in eight patients with various NMDs who trained at 50% to 60% heart rate reserve for 15 to 30 minutes three to four days a week. Another study explored the adaptation to aerobic training of 10 patients with mitochondrial myopathies.[47] Aerobic capacity increased by 20% to 30% ($P < 0.05$) after 14 weeks of training (30 to 40 minutes, three to four times a week) on a stationary bicycle at an intensity of 70% to 80% of the maximal heart rate. Olsen and colleagues obtained similar findings in a study involving a 12-week low-intensity aerobic program in a group of patients with FSHD. Eight participants performed cycle ergometer exercises at 65% of their VO_{2max} five times a week, 45 minutes a day. Seven healthy individuals served as a control group and had a similar intervention. Aerobic capacity increased in both the FSHD and the healthy cohort by 16% ($P < 0.002$) and 13% ($P < 0.02$), respectively. The serum level of CK in participants was stable over the duration of the exercise program.[48] A common finding in all studies involving aerobic training was that the interventions were well tolerated and participants showed high compliance with training sessions.

Finally, animal studies on transgenic mouse models with tropomyosin 3 (TPM3) (Met9Arg) nemaline myopathy showed that four weeks of aerobic training on treadmill caused no muscle damage and led to no changes in the total number of rod-affected fibers in muscle.[52] Another study on similar transgenic mice demonstrated that daily 30-minute high-intensity endurance exercises on a treadmill over 17 days following prolonged

immobilization (28 days) alleviated disuse-induced weakness in nemaline myopathy and helped restore the preimmobilization level of muscle strength.[53] However, these studies were conducted only on models with TPM3 nemaline myopathy; therefore the effects could be specific for this type of CM, and more research in this field is needed to understand the impact of aerobic training on affected muscles.

Vibration therapy

Along with aerobic and strength exercises, VT can potentially be another promising approach of treating patients with CM.[14] VT involves weight-bearing exercises performed on an oscillation platform generating vibration impulses that mechanically stimulate the musculoskeletal system via stimulation of spinal reflexes, leading to changes in muscle length. The resulting activation of muscle spindles elicits a reflex contraction in the homonymous muscle. The vibratory stimulus, therefore, leads to cyclic elongation and contraction of the stimulated muscles. VT has been shown to have a positive impact on muscle strength, tone, and function in patients with NMDs including those with Duchenne muscular dystrophy (DMD),[54,55] mitochondrial disease,[56] SMA,[54] and multiple sclerosis.[57] In addition, VT has been reported to increase bone mineral density in individuals with altered muscle and/or bone health including cerebral palsy,[58] postmenopausal osteoporosis,[59] and adolescent idiopathic scoliosis.[60] The therapy has been shown to be safe, with few adverse effects in all the NMDs treated to date.[54-57]

The potential impact of VT on muscle damage has been measured by the level of muscle weakness and serum CK in several studies that involved patients with NMD.[54,55] Vry and colleagues reported increased muscle weakness in four of 12 patients with DMD and in two of eight patients with SMA after four weeks of VT, but no complaints about weakness after eight weeks of VT.[54] The serum CK level has been analyzed during VT both in patients with NMD and in a healthy cohort.[54,55,61,62] Myers and colleagues assessed CK levels in four participants with DMD following a four-week VT program thrice a week. All but one participant had stable levels during the training period. One subject had a transient increase in the serum CK during the third week of VT, which, however, returned to the pretraining level within the next training week.[55] Similarly, in Vry et al.'s study,[54] the CK activity in 14 of 22 participants with DMD increased significantly after the first day of training but returned to the norm after four weeks of continuous VT training (nine minutes, thrice a week).[54] In patients with SMA in the same study, the CK level was not elevated. Gojanovic and colleagues reported an increased level of CK within 24, 48, and 96 hours after one bout of 27-minute high-intensity VT in five of 20 volunteers who had no disabilities and/or chronic conditions but led a sedentary lifestyle.[62] At the same time, it should be noted that those studies utilized no control groups and did not consider confounding factors that might have affected the CK level, which prevents us from attributing the resultant changes in CK solely to the VT training. For instance, the serum CK activity in patients with DMD is known to fluctuate during the day and the duration of the disease, as well as to depend on the physical activity level.[63] In addition, in the last two studies participants performed mild-intensity physical exercises (squats, weight shifts, push-ups) on a vibration platform, which might have also contributed to the increased CK levels.

Fatigue level and muscle pain, two other symptoms of CM,[10] also need to be monitored during VT training. Several studies have assessed these parameters and have reported either a stable[55] or a decreased level of their severity,[64] or an insignificant increase in their intensity, which did not lead the participants to terminate participation in the study and declined as the training progressed.[54,65] Alentorn-Geli and team have shown a statistically significant decrease of fatigue ($P = 0.002$) and pain ($P = 0.018$) levels in female patients with fibromyalgia after six weeks of VT in conjunction with traditional exercises ($n = 12$), with no changes in either the control group ($n = 12$) or the group that performed only traditional exercises ($n = 12$).[64] In the Myers et al. study[55] none of the four participants with DMD reported increased fatigue levels during a four-week VT training. Ruck and colleagues reported an interruption of six VT sessions of 937 due to unspecified fatigue, and five sessions due to nonmuscle pain, among 10 children with cerebral palsy over six months of the intervention period. All children completed participation in the study.

Taken together, the findings from available studies on NMDs suggest that VT may benefit patients with CM and therefore is worthy of further scholarly exploration.

Discussion

A properly designed exercise rehabilitation program is widely recognized by health professionals as a way to improve both general health and musculoskeletal status in patients with NMD.[20] However, more studies in the area need to assist in developing specific guidelines for the NMD and CM populations. Aerobic training aims to enhance cardiorespiratory endurance,[19,25,46] whereas strength training, to improve muscle strength, function, and endurance.[19,25] Both exercise modalities, by causing stress and strain on the bone, can potentially improve bone health.[66] Similarly, vibration training has been shown to increase muscle strength and function, thus affecting bone mineral density.[61,67] There are other secondary but equally beneficial effects of exercise or physical training, including improving psychological health and quality of life.[20] These may also have relevance in exercise rehabilitation programs.

NMDs include a wide, heterogeneous group of conditions that differ pathophysiologically, morphologically, and clinically. With such heterogeneity, the potential benefits of physical therapy may differ and may need to be individualized to optimize outcomes. Therefore, although studies treating neuromuscular conditions are beneficial in terms of suggesting directions for future research in patients with CM, their findings cannot be directly applied to these patients.

The low prevalence and the heterogeneity of pathologic features of CM can affect the collection of research-based evidence for treatment efficacy of CM. Possible ways to overcome these limitations could be designing multicenter studies and the use of crossover study design that allows half the sample size required to achieve the same statistical power compared with parallel studies. At the same time, there also remain some concerns about the safety of exercise treatment, although the extant literature reports no major safety issues related to the implementation of exercise programs. Given the lack of evidence-based research on the safety issues associated with physical therapy of patients with CM, we suggest that research on this group of disorders should start with low-intensity, short-term exercise programs, with a gradual increase of the parameters to ensure that both safety and efficacy outcomes are optimized. Another possible way to address this limitation is to expand research on animal models (e.g., transgenic mice) to determine safe exercise training thresholds for this population.

Conclusion

Although exercise rehabilitation is recommended for the management of CM, there is insufficient evidence on the effectiveness of

different modes and intensities of exercise programs. The existing evidence, however, indicates that exercise training, which includes aerobic, strength and VT, can be of potential benefit for patients with CM.

References

1. North KN, Wang CH, Clarke N, et al. Approach to the diagnosis of congenital myopathies. Neuromuscul Disord. 2014;24:97–116.
2. Amburgey K, McNamara N, Bennett LR, McCormick ME, Acsadi G, Dowling J. Prevalence of congenital myopathies in a representative pediatric United States population. Ann Neurol. 2011;70:662–665.
3. Witting N, Werlauff U, Duno M, Vissing J. Phenotypes, genotypes, and prevalence of congenital myopathies older than 5 years in Denmark. Neurol Genet. 2017;3.
4. Maggi L, Scoto M, Cirak S, et al. Congenital myopathies–clinical features and frequency of individual subtypes diagnosed over a 5-year period in the United Kingdom. Neuromuscul Disord. 2013;23:195–205.
5. Gonorazky HD, Bönnemann CG, Dowling JJ. The genetics of congenital myopathies. Handb Clin Neurol. 2018;148:549–564.
6. Colombo I, Scoto M, Manzur AY, et al. Congenital myopathies: natural history of a large pediatric cohort. Neurology. 2015;84:28–35.
7. Cassandrini D, Trovato R, Rubegni A, et al. Congenital myopathies: clinical phenotypes and new diagnostic tools. Ital J Pediatr. 2017;43:16.
8. Mah JK, Joseph JT. An overview of congenital myopathies. Continuum (Minneap Minn). 2016;22:1932–1953.
9. Crabtree N, Chapman S, Högler W, et al. Vertebral fractures assessment in children: evaluation of DXA imaging versus conventional spine radiography. Bone. 2017;97:168–174.
10. Wang CH, Dowling JJ, North K, et al. Consensus statement on standard of care for congenital myopathies. J Child Neurol. 2012;27:363–382.
11. Abbott M, Jain M, Pferdehirt R, et al. Neonatal fractures as a presenting feature of LMOD3-associated congenital myopathy. Am J Med Genet A. 2017;173:2789–2794.
12. Bharucha-Goebel XD, Santi BM, Medne SL, et al. Severe congenital RYR1-associated myopathy: the expanding clinicopathologic and genetic spectrum. Neurology. 2013;80:1584–1589.
13. Ryan MM, Sy C, Rudge S, et al. Dietary L-tyrosine supplementation in nemaline myopathy. J Child Neurol. 2008;23:609–613.
14. Messina S, Hartley L, Main M, et al. Pilot trial of salbutamol in central core and multi-minicore diseases. Neuropediatrics. 2004;35:262–266.
15. Dowling JJ, Joubert R, Low SE, et al. Myotubular myopathy and the neuromuscular junction: a novel therapeutic approach from mouse models. Dis Models Mech. 2012;5:852–859.
16. Tinklenberg JA, Siebers EM, Beatka MJ, et al. Myostatin inhibition using mRK35 produces skeletal muscle growth and tubular aggregate formation in wild type and Tg ACTA1 D286G nemaline myopathy mice. Hum Mol Genet. 2017;27:638–648.
17. Dowling JJ, Arbogast S, Hur J, et al. Oxidative stress and successful antioxidant treatment in models of RYR1-related myopathy. Brain. 2012;135:1115–1127.
18. Matthews E, Hartley L, Sud R, Hanna M, Muntoni F, Munot P. Acetazolamide can improve symptoms and signs in ion channel-related congenital myopathy. J Neurol Neurosurg Psychiatry. 2019;90:243–245.
19. Anziska Y, Inan S. Exercise in neuromuscular disease. Semin Neurol. 2014;34:542–556.
20. Cup EH, Pieterse AJ, Jessica M, et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil. 2007;88:1452–1464.
21. Hedermann G, Vissing CR, Heje K, Preisler N, Witting N, Vissing J. Aerobic training in patients with congenital myopathy. PLoS One. 2016;11:e0146036.
22. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil. 2002;81:S52–S69.
23. Assumpção C, Lima L, Oliveira F, Greco C, Denadai B. Exercise-induced muscle damage and running economy in humans. ScientificWorldJournal. 2013;2013:189149.
24. Haskell WL, Lee M, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116:1081.
25. Dawes H, Korpershoek N, Freebody J, et al. A pilot randomised controlled trial of a home-based exercise programme aimed at improving endurance and function in adults with neuromuscular disorders. J Neurol Neurosurg Psychiatry. 2006;77:959–962.
26. Kilmer DD, Aitkens SG, Wright NC, McCrory MA. Response to high-intensity eccentric muscle contractions in persons with myopathic disease. Muscle Nerve. 2001;24:1181–1187.
27. Almstedt HC, Canepa JA, Ramirez DA, Shoepe TC. Changes in bone mineral density in response to 24 weeks of resistance training in college-age men and women. J Strength Cond Res. 2011;25:1098–1103.
28. Gomez-Cabello A, Ara I, González-Agüero A, Casajus JA, Vicente-Rodriguez G. Effects of training on bone mass in older adults. Sports Med. 2012;42:301–325.
29. Aitkens SG, McCrory MA, Kilmer DD, Bernauer ED. Moderate resistance exercise program: its effect in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1993;74:711–715.
30. McCartney N, Moroz D, Garner SH, Mccomas AJ. The effects of strength training in patients with selected neuromuscular disorders. Med Sci Sports Exerc. 1988;20:362–368.
31. Van Der Kooi LE, Vogels JMO, Van Asseldonk JGPR, et al. Strength training and albuterol in facioscapulohumeral muscular dystrophy. Neurology. 2004;63:702–708.
32. Vignos PJ, Watkins MP. The effect of exercise in muscular dystrophy. JAMA. 1966;197:843–848.
33. Kilmer DD, McCrory MA, Wright NC, Aitkens SG, Bernauer EM. The effect of a high resistance exercise program in slowly progressive neuromuscular disease. Arch Phys Med Rehabil. 1994;75:560–563.
34. Milner-Brown H, Miller R. Muscle strengthening through high-resistance weight training in patients with neuromuscular disorders. Arch Phys Med Rehabil. 1988;69:14–19.
35. Proske U, Morgan DL. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. J Physiol. 2001;537:333–345.
36. Newham D, Jones D, Edwards R. Plasma creatine kinase changes after eccentric and concentric contractions. Muscle Nerve. 1986;9:59–63.
37. Lee J, Goldfarb AH, Rescino MH, Hegde S, Patrick S, Apperson K. Eccentric exercise effect on blood oxidative-stress markers and delayed onset of muscle soreness. Med Sci Sports Exerc. 2002;34:443–448.
38. Newham D, Mills KR, Quigley BM, Edwards RHT. Pain and fatigue after concentric and eccentric muscle contractions. Clin Sci. 1983;64:55–62.
39. Newham D, McPhail G, Mills KR, Edwards RHT. Ultrastructural changes after concentric and eccentric contractions of human muscle. J Neurol Sci. 1983;61:109–122.
40. Stauber W, Clarkson PM, Fritz VK, Evans WJ. Extracellular matrix disruption and pain after eccentric muscle action. J Appl Physiol. 1990;69:868–874.
41. Johnson JL, Slentz CA, Houmard JA, et al. Exercise training Amount and intensity effects on metabolic syndrome (from studies of a Targeted risk Reduction intervention through defined exercise). Am J Cardiol. 2007;100:1759–1766.
42. Colberg SR, Sigal RJ, Fernhall B, et al. Exercise and type 2 diabetes: the American college of Sports medicine and the American diabetes association: Joint position statement. Diabetes Care. 2010;33:e147–e167.
43. Prior PL, Suskin N. Exercise for stroke prevention. Stroke Vasc Neurol. 2018;3:59–68.
44. Sipilä S, Multanen J, Kallinen M, Era P, Suominen H. Effects of strength and endurance training on isometric muscle strength and walking speed in elderly women. Acta Physiol Scand. 1996;156:457–464.
45. Kelley G. Aerobic exercise and lumbar spine bone mineral density in postmenopausal women: a meta-analysis. J Am Geriatr Soc. 1998;46:143–152.
46. Florence JM, Hagberg JM. Effect of training on the exercise responses of neuromuscular disease patients. Med Sci Sports Exerc. 1984;16:460–465.
47. Taivassalo T, Shoubridge EA, Chen J, et al. Aerobic conditioning in patients with mitochondrial myopathies: physiological, biochemical, and genetic effects. Ann Neurol. 2001;50:133–141.
48. Olsen DB, Ørngreen MC, Vissing J. Aerobic training improves exercise performance in facioscapulohumeral muscular dystrophy. Neurology. 2005;64:1064–1066.
49. Wright NC, Kilmer DD, McCrory MA, Aitkens SG, Holcomb BJ, Bernauer EM. Aerobic walking in slowly progressive neuromuscular disease: effect of a 12-week program. Arch Phys Med Rehabil. 1996;77:64–69.
50. Andersen G, Heje K, Buch AE, Vissing J. High-intensity interval training in facioscapulohumeral muscular dystrophy type 1: a randomized clinical trial. J Neurol. 2017;264:1099–1106.
51. Voet N, Bleijenberg G, Hendriks J, et al. Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT. Neurology. 2014;83:1914–1922.
52. Nair-Shalliker V, Kee AJ, Joya JE, Lucas CA, Hoh JF, Hardeman EC. Myofiber adaptational response to exercise in a mouse model of nemaline myopathy. Muscle Nerve. 2004;30:470–480.
53. Kee AJ, Hardeman EC, Joya JE, et al. Muscle weakness in a mouse model of nemaline myopathy can be reversed with exercise and reveals a novel myofiber repair mechanism. Hum Mol Genet. 2004;13:2633–2645.
54. Vry J, Schubert IJ, Semler O, Haug V, Schönau E, Kirschner J. Whole-body vibration training in children with Duchenne muscular dystrophy and spinal muscular atrophy. Eur J Paediatr Neurol. 2014;18:140–149.
55. Myers KA, Ramage B, Khan A, Mah JK. Vibration therapy tolerated in children with Duchenne muscular dystrophy: a pilot study. Pediatr Neurol. 2014;51:126–129.
56. Newell C, Ramage B, Robu I, Shearer J, Khan A. Side alternating vibration training in patients with mitochondrial disease: a pilot study. Arch Physiother. 2017;7:10.
57. Schyns F, Paul L, Finlay K, Ferguson C, Noble E. Vibration therapy in multiple sclerosis: a pilot study exploring its effects on tone, muscle force, sensation and functional performance. Clin Rehabil. 2009;23:771–781.
58. Gusso S, Munns CF, Colle P, et al. Effects of whole-body vibration training on physical function, bone and muscle mass in adolescents and young adults with cerebral palsy. Sci Rep. 2016;6:22518.
59. Ruan X-Y, Jin F-Y, Liu Y-L, Peng Z-L, Sun Y-G. Effects of vibration therapy on bone mineral density in postmenopausal women with osteoporosis. Chin Med J. 2008;121:1155.

60. Lam T, Ng BKW, Cheung LWH, Lee KM, Qin L, Cheng JCY. Effect of whole body vibration (WBV) therapy on bone density and bone quality in osteopenic girls with adolescent idiopathic scoliosis: a randomized, controlled trial. Osteoporos Int. 2013;24:1623–1636.
61. Söderpalm A, Kroksmark AK, Magnusson P, Karlsson J, Tulinius M, Swolin-Eide D. Whole body vibration therapy in patients with Duchenne muscular dystrophy—a prospective observational study. J Musculoskelet Neuronal Interact. 2013;13:13–18.
62. Gojanovic B, Feihl F, Liaudet L, Gremion G, Waeber B. Whole-body vibration training elevates creatine kinase levels in sedentary subjects. Swiss Med Wkly. 2011;141.
63. Jackson M, Round JM, Newham DJ, Edwards RHT. An examination of some factors influencing creatine kinase in the blood of patients with muscular dystrophy. Muscle Nerve. 1987;10:15–21.
64. Alentorn-Geli E, Padilla J, Moras G, Haro CL, Fernández-Solà J. Six weeks of whole-body vibration exercise improves pain and fatigue in women with fibromyalgia. J Altern Complement Med. 2008;14:975–981.
65. Ruck J, Chabot G, Rauch F. Vibration treatment in cerebral palsy: a randomized controlled pilot study. J Musculoskelet Neuronal Interact. 2010; 10:77.
66. Moreira LDF, Oliveira ML, Lirani-Galvão AP, Marin-Mio RV, Santos RND, Lazaretti-Castro M. Physical exercise and osteoporosis: effects of different types of exercises on bone and physical function of postmenopausal women. Arq Bras Endocrinol Metabol. 2014;58:514–522.
67. Matute-Llorente A, Gonzalez-Aguero A, Gomez-Cabello A, Vicente-Rodriguez G, Casajus Mallen JA. Effect of whole-body vibration therapy on health-related physical fitness in children and adolescents with disabilities: a systematic review. J Adolesc Health. 2014;54:385–396.