Exercise therapy for muscle and lower motor neuron diseases

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Muscle and lower motor neuron diseases share a common denominator of perturbed muscle function, most often related to wasting and weakness of muscles. This leads to a number of challenges, such as restricted mobility and respiratory difficulties. Currently there is no cure for these diseases. The purpose of this review is to present research that examines the effects of exercise in muscle and lower motor neuron diseases. Evidence indicates that moderate intensity aerobic- and strength exercise is advantageous for patients with muscle diseases, without causing harmful exercise-induced muscle damage. On the contrary, motor neuron diseases show a rather blunted response from exercise training. High-intensity training is a modality that seems safe and a promising exercise method, which may circumvent neural fatigue and provide effect to patients with motor neuron disease. Although we have come far in changing the view on exercise therapy in neuromuscular diseases to a positive one, much knowledge is still needed on what dose of time, intensity and duration should be implemented for different disease and how we should provide exercise therapy to very weak, non-ambulatory and wheelchair bound patients.

Key words: muscle disease, motor neuron disease, exercise

Background

Muscle and lower motor neuron diseases encompass a large number of conditions with a common denominator of muscle weakness and wasting in most cases, which may lead to a number of challenges, such as fatigue, restricted mobility, and respiratory difficulties that impact a person’s quality of life (1). Currently, treatment options for these diseases are scarce, and patients rely on supportive disease management that may contribute to enhance quality of life by improving physical function and possibly stabilizing or slowing down disease progression.

For a long time, physical exercise was considered deleterious for patients with muscle diseases, the notion being that contractions in the pathological muscle would accelerate the disease process. This notion was supported by experiments in the mdx mouse model of Duchenne muscular dystrophy that showed signs of damage after exercise. However, the types of exercise used were highly unphysiological as they involved eccentric exercise and electrical stimulation of muscle (2, 3) types of exercise that would also induce muscle damage in a healthy individual.

Exercise is physical activity that is planned, structured, and repetitive for the purpose of conditioning any part of the body. The general population is encouraged to exercise because of its great health benefits, and its importance as a means of physical rehabilitation is also widely acknowledged (4). Lack of exercise, regardless of condition, leads to a variety of changes in the body. The heart’s ability to pump blood efficiently, aerobic capacity, and muscles’ capacity to process oxygen declines, which ultimately leads to decreased endurance, muscle weakness, and fatigue (4), as well as numerous lifestyle-related diseases. Patients with muscle and lower motor neuron diseases are more prone to developing disorders associated with a sedentary lifestyle, such as obesity and metabolic syndrome due to restricted mobility (5-7). Currently there are no specific guidelines about the type or intensity of exercise recommended to these patients. One of the challenges health care professionals often face is the question of how much, and what type of exercise should patients engage in. Nonetheless, the body of evidence favoring exercise training in patients with muscle and lower motor neuron diseases has increased substantially in the last two decades, and the purpose of this review is to present the current evidence for physical conditioning in these disease groups.

Methods

A literature search on PubMed, using key words “Limb girdle muscular dystrophy”, “Becker muscular...
dystrophy”, “fascioscapulohumeral muscular dystrophy”,
“myotonic muscular dystrophy”, “McArdle disease”,
“Pompe disease”, “mitochondrial myopathy”, “spinal
and bulbar muscular atrophy”, “spinal muscular atrophy”
combined with key words “exercise”, “training”, “physical
activity”, “resistance training”, “resistance exercise”,
“strength training”, “strength exercise”, “aerobic train-
ing”, “aerobic exercise”, “endurance training”, “endur-
ance exercise”, was performed from January 2018 to July
2019. Article selection was based on 1) studies assessing
the effects of exercise on humans with these diseases,
2) articles that included a well described diagnosis of a
muscle or motor neuron disease, and 3) articles that pro-
vided a well-described exercise intervention. We includ-
ed randomized controlled trials (RCT), cohorts, and case
reports. Articles were excluded if they did not include an
exercise intervention, lacked intervention description, or
were animal studies. In addition, articles exclusively fo-
cusing on training of respiratory muscles were also ex-
cluded. Using these inclusion and exclusion criteria’s,
fifty articles were chosen to form the basis for this review.

Experience with exercise training in individuals with muscle and
lower motor neuron diseases

Muscular dystrophies

Limb girdle muscular dystrophy

Aerobic exercise

More than 32 different kinds of Limb girdle muscular
dystrophies (LGMD) are known, and exercise has only
been studied in a few of the disorders. Aerobic exercise
has been studied in smaller cohorts of LGMD2I and LG-
MD2L. Patients with LGMD2L completed a 10-week
moderate aerobic training program (8). The six patients
completing the training experienced improvements in fit-
ness, functional capacity, and lower limb strength. No ad-
verse events were reported. Moderate endurance training
also improved aerobic capacity in 9 patients with LGM-
D2I (9), and patients expressed feeling an improvement
in physical function. There was no significant increase in
training-induced creatine kinase (CK) levels. Moderate
aerobic training seems to provide patients with LGMD
better physical function and appears safe, but longer-term
studies are needed.

Strength exercise

Low- and high-intensity resistance training in patients
with LGMD2A and LGMD2I was found to be generally
well tolerated (10). Two LGMD2A patients were excluded
from the high resistance training group due to training-in-
duced CK elevation. Resistance training could potentially
be a beneficial part of a functional rehabilitation program,
but should be carefully monitored for muscle damage.

Assisted exercise

Scezny-Kaiser et al. (11) performed a treadmill ex-
ercise study using hybrid assistive limb (HAL®) in three
LGMD patients; LGMD2A, LGMD2L, and a LGMD of
unknown subtype. HAL® is a powered exoskeleton and
is used during exercise to enhance physical capabilities
in people with disabilities. Physical endurance improved
and no adverse events were reported. Despite a small sam-
ple size, the results are interesting, and the technology al-
lows health care professionals to train very weak patients.
Anti-gravity training improved functional ability in weak
patients with LGMD2I (12), and enhanced lower limb
strength and walking distance (13). Both studies were safe
and well tolerated and plasma CK levels did not indicate
any exercise-induced muscle damage. Bodyweight-sup-
ported training allows patients to work at a certain per-
centage of bodyweight due to off-lifting of weight by
slings or air pressure making it possible for weak patients
to exercise. However, it is costly and cannot be performed
in patients’ habitual environment.

Other exercise modalities

Effect of electrical stimulation therapy and exer-
cise therapy in patients with LGMD was investigated by
Kılınç et al. (14). In the electrical stimulation therapy
group, stimulation was applied bilaterally on the deltoid
and quadriceps muscles using high voltage-pulsed galv-
ic stimulation with a pulse frequency of 50Hz for optimal
contractions. Duty cycle was set at 5 seconds on and 10
seconds off, during 10 minutes of stimulation of each mus-
cle. The exercise therapy group consisted of bilateral pro-
gressive resistance exercise of the deltoid and quadriceps
muscles. The electrical stimulation therapy group gained
muscle strength and physical function improved. The ex-
ercise therapy group had similar improvements. This study
provides important information on the role of electrical
stimulation therapy and exercise therapy for health care
professionals working in rehabilitation clinics.

Intervention specifications for LGMDs are presented
in Table 1.

Becker muscular dystrophy

Aerobic exercise

Moderate cycle training improves aerobic capacity
and strength in patients with Becker muscular dystrophy
(BMD) after three months of exercise, and these im-
provements are maintained after additional 9 months of
training, without any rise in CK level (15). Enhancement
in muscle strength and physical function after treadmill training were also reported in a case study (16). Interestingly, an elevation in CK level was observed, indicating that rehabilitative intervention should be carefully monitored to avoid harmful exercise-induced side effects despite functional improvement.

**Strength exercise**

In patients with BMD, low- and high-intensity resistance training was generally well tolerated and patients showed an increase in endurance and arm strength (10), without signs of muscle damage.

**Assisted exercise**

Anti-gravity training resulted in improved physical function and functional ability (12), and another study found that bodyweight-supported training improved lower limb strength and walking distance (13). In both studies, exercise was well tolerated and CK levels did not indicate any exercise-induced muscle damage. Intervention specifications for BMD are presented in Table 2.

**Facioscapulohumeral muscular dystrophy**

**Aerobic exercise**

Moderate aerobic exercise improved self-reported changes in activities of daily living (ADL) in a cohort of 8 patients with facioscapulohumeral muscular dystrophy (FSHD) (17). Similar improvements were discovered in a randomized, double-blind, placebo-controlled parallel study where the investigators found improvements in fitness, self-assessed physical capacity, and health (18).

### Table 1. A representation of exercise interventions done in LGMD 2A, LGMD 2L, and LGMD 2I. Number in parenthesis represents the article reference.

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|------------------|
| Cycling N = 6 (8) | 10 weeks | 3 days/week 30 min/session | 70% of VO<sub>2max</sub> | VO<sub>2max</sub>, lower limb strength, 6MWT, 5 x STS, 6SST. |
| Cycling N = 9 (9) | 12 weeks | 50 sessions in total 30 min/session | 65% of VO<sub>2max</sub> | VO<sub>2max</sub>, workload, self-reported physical endurance, lower limb muscle strength, and walking distance. |
| Strength: LOIT N = 6 (10) | 6 months | 3 days/week Twice at home and once at lab | Low intensity Knee extension, Elbow flexion 40% of 1RM, increase with 5% every other week 3 sets x 12-15 reps | Bicep strength and endurance, wrist flexion, extension, and endurance |
| HIT N = 3 | 3 months | 3 days/week at lab | High intensity Knee extension, Elbow flexion Wrist flexion & extension Ankle plantar flexion 70-85% of 1RM 3 x 8-12 reps for 1 month 80-90% of 1RM 3 x 6-10 reps for 2 months 85-92% 3 x 8-4 reps for 3 months | | |
| Control group N = 6 | | | | |
| Treadmill training using HAL® N = 3 (11) | 8 weeks F/U at 6 weeks post intervention | 3 days/week Maximum of 30 minutes/session | Velocity of treadmill was set individually Up to 50% body weight support | 10MWT, 6MWT, and TUG |
Voet et al. examined the effects of moderate aerobic exercise therapy and cognitive behavioral therapy on fatigue, strength, and exercise tolerance. One group underwent cycling and one group underwent cognitive behavioral therapy comprising of 6 modules directed towards insufficient coping with the disease. After a 12-week follow-up, the majority of patients continued their level of activity and the beneficial effects remained (19). This study provides valuable information about the impact of physical activity on fatigue. Fatigue can have a detrimental effect on quality of life, and it is substantial to apply appropriate management. Safety and efficacy of a 6-month home-based exercise program was assessed in a multicenter randomized controlled trial (20). The results showed an improvement in aerobic capacity, strength, and functional capacity. Exercise did not elevate CK levels in any of the presented studies. Health care professionals are encouraged to promote regular exercise compatible with FSHD patients’ daily professional and social life.

**Strength exercise**

Strength training in patients with FSHD was examined by van der Kooi et al. in a randomized, double-blind, placebo-controlled trial (21). Training group consisted of 34 patients and a non-training control group consisted of 31 patients. At week 26 during the intervention, albuterol was added. Some improvements in strength were observed in the training group and any training-induced muscle fatigue that occurred lasted less than an hour, and patients were able to carry out their habitual ADL. Of the 34 trained patients, 19 patients complained of neck and shoulder pain after the intervention. Plasma CK levels were not reported. The authors determined the training to be generally well tolerated and found no enhancing effects of albuterol. The number of patients reporting pain in neck and shoulder is great and the tolerability to strength training should be explored further.

**Other exercise modalities**

Andersen et al. (22) investigated the effects of supervised high-intensity training (HIT) in an RCT. Fitness improved and CK measurements did not indicate any muscle damage during and post training. The majority of patients preferred HIT over moderate-intensity training. High-inten-

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|------------------|
| Anti-gravity: N = 3 (12) | 10 weeks of control period | 3 days/week 40 min/session | 70-80% of maximum heart rate (HRmax) Run/walk, jogging, and high knee lift 12 reps of squats and lunges 15-20 reps of calf raise | 6MWT and dynamic balance |
| Bodyweight supported: N = 3 (13) | 10-week control period | 10 weeks of training | 3 days/week 40 min/session | Closed-kinetic-chain strength exercises: squats, calf raises, and lunges Aerobic: Walk/run, jogging in place, or high knee-lift | Closed kinetic chain leg strength and training distance |
| Electrical stimulation N = 11 | 8 weeks | 3 days/week | Shoulder abduction Knee extension 25% 1RM, 2 sets x 10 reps 30% 1RM, 3 sets x 10 reps 35% 1RM, 3 sets x 10 reps 50% 1RM, 3 sets x 10 reps | Strength, VAS, climb 8 steps, 10MWT, dressing with t-shirt, endurance (number of reps per minute), and modified Lawton ADL. |
| Bodyweight supported: N = 3 (13) | 10-week control period | 10 weeks of training | 3 days/week 40 min/session | Closed-kinetic-chain strength exercises: squats, calf raises, and lunges Aerobic: Walk/run, jogging in place, or high knee-lift | Closed kinetic chain leg strength and training distance |
| Electrical stimulation N = 11 | 8 weeks | 3 days/week | Shoulder abduction Knee extension 25% 1RM, 2 sets x 10 reps 30% 1RM, 3 sets x 10 reps 35% 1RM, 3 sets x 10 reps 50% 1RM, 3 sets x 10 reps | Strength, VAS, climb 8 steps, 10MWT, dressing with t-shirt, endurance (number of reps per minute), and modified Lawton ADL. |
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Table 2. A representation of exercise interventions done in BMD. Number in parenthesis represents the article reference.

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|------------------|
| Cycling         | 12 weeks | 50 sessions in total | 65% of VO$_{2\text{max}}$ | VO$_{2\text{max}}$, workload, hip abduction, and ankle plantar flexion and dorsiflexion |
| N = 11          | 12 months | session | | |
| Control group   | F/U      | 30 min/session | | |
| N = 7           | (15)     | | | |
| Treadmill       | 4 weeks  | 3 days/week | 65-80% HR$_{\text{max}}$ | Lower limb strength, TUG, 10MWT, and 6MWT |
| N = 1           | 20 min/session | | | |
| (16)            | | | | |
| Strength:       | 6 months | LOIT 3 days/week | Low intensity: Knee extension, Elbow flexion 40% of 1RM, increase with 5% every other week 3 sets x 12-15 reps | Bicep strength and endurance, wrist flexion, extension, and endurance |
| LOIT N = 2      | Twice at home and once at lab | | | |
| HIT N = 1       | HIT 3 days/week at lab | | | |
| Control group   | 3 months | 3 months | High intensity: Knee extension, Elbow flexion Wrist flexion & extension Ankle plantar flexion 70-85% of 1RM 3 sets x 8-12 reps, month 1 80-90% of 1RM 3 sets x 6-10 reps, month 2 85-92% 3 sets x 8-4 reps, month 3 | | |
| N = 6           | (10)     | | | |
| Anti-gravity:   | 10 weeks | 3 days/week 40 min/session | 70-80% of maximum heart rate (HR$_{\text{max}}$) Run/walk, jogging, and high knee lift 12 reps of squats and lunges 15-20 reps of calf raise | 6MWT and dynamic balance |
| N = 5           | control period | | | |
| N = 5           | 10 weeks of training intervention | | | |
| (12)            | 10 weeks | 10 weeks of training intervention | | | |
| Bodyweight      | 10 weeks | 3 days/week 40 min/session | 70-80% of HR$_{\text{max}}$ Closed-kinetic-chain strength exercises: squats, calf raises, and lunges | Closed kinetic chain leg strength and training distance |
| supported:      | control period | | | |
| N = 5           | 10 weeks of training intervention | | | |
| (13)            | 10 weeks | 10 weeks of training intervention | | | |

University training may be a good option for patients struggling with fatigue. Neuromuscular electrical stimulation (NMES) is passive muscular training that can easily be adapted in the clinic and may be advantageous for very weak patients. Colson et al. (23) studied the safety and efficacy of NMES and found that the treatment was safe and well tolerated. Patients reported a reduction in pain, fatigue, and an increase in functional capacity and strength. In addition, patients expressed feeling a positive effect on ADL. There was no significant CK level elevation during the intervention.

Intervention specifications for FSHD are presented in Table 3.

Myotonic muscular dystrophy

Aerobic exercise

Ørngreen et al. (24) studied the effects of aerobic training. Twelve of the 17 patients completed the study, five patients discontinued due to low compliance, and nine adhered adequately to the training protocol. Most patients reported beneficial changes in ADL and fitness.
improved after the training. Plasma CK levels did not increase, but one patient reported a worsening of fatigue.

**Strength exercise**
The effect of strength training was first reported in 1993, where modest strength improvements were observed after 12 weeks of exercise (25). Tollbäck et al. (26) also found improvements in strength after training for 12 weeks. Two patients dropped out for personal reasons and one dropped out due to severe back pain. No other adverse events were reported by the authors in the two studies. A study reported in 1995 (27) and another in 1999 (28) that strength training was safe and well tolerated, but no apparent improvements were observed, neither any adverse events nor deterioration was reported. The absence of any prominent changes differs from previous studies (25, 26). One explanation could be that the patients exercised at home, which may influence the validity of their reporting and compliance or the effect of exercise was assessed with unfitting outcome measures.

**Other exercise modalities**
Cudia et al investigated the effects of functional electrical stimulation induced cycling (29) and compared the intervention with strength and aerobic training. Muscle strength and walking distance improved. Improvements were also observed in the strength and aerobic group and no adverse events were reported. Fatigue can limit everyday activities and adherence to exercise in these patients, and a reduction in treatment time, could possibly improve patient compliance.

Patients with myotonic muscular dystrophy (DM) often face challenges with impaired hand function. Aldehag et al. (30) investigated the effects of hand training with a silicone-based resistance putty in a randomized controlled crossover pilot study. Patients improved hand strength and self-perception of occupational performance. Despite a large dropout due to personal reasons, lack of motivation, and fatigue, the study addresses an important issue that hand impairment can have on ADL.

Recently, Okkersen et al assessed the effects of cognitive behavioral therapy with optional graded exercise therapy in patients with severe fatigue in a single-blind, large randomized trial (31). Cognitive behavioral therapy increased patients’ capacity for activity and participation, compared with standard care alone.

**Intervention specifications for DM are presented in Table 4.**

**Glycogen storage disease**

**McArdle disease**

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|-----------------|
| Cycling N = 8   | 12 weeks | 5 days/week 35 min/session | 65% VO_{2max} | VO_{2max}, workload, and ADL |
| Control group N = 7 |          |           |           |                 |
| (17)            |          |           |           |                 |
| Cycling + post exercise protein-carbohydrate supplement N = 18 | 12 weeks 12 months F/U | 3 days/week 15 min/session week 1 20 min/session week 2 30 min/session from week 3 | 70% VO_{2max} | 6MWT, workload, fitness, and SF-36 |
| Cycling + placebo supplement N = 13 |          |           |           |                 |
| Control group N = 10 |          |           |           |                 |
| (18)            |          |           |           |                 |
| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome          |
|----------------|----------|-----------|-----------|---------------------------|
| Cycling        | 16 weeks | 3 days/week (2 days home and 1 day supervised) | 50-65% HRmax, 12-14 RPE (Borg Scale) | Fatigue                   |
| Cognitive-behavioral therapy | 16 weeks | 3 days/week (2 days home and 1 day supervised) | 50-65% HRmax, 12-14 RPE (Borg Scale) | Fatigue                   |
| Usual care     | 16 weeks | 3 days/week (2 days home and 1 day supervised) | 50-65% HRmax, 12-14 RPE (Borg Scale) | Fatigue                   |
| Cycling        | 24 weeks | 3 days/week | 50-65% HRmax | VO₂ max, 6MWT, and fatigue severity scale |
| Control group  | 24 weeks | 3 days/week | 50-65% HRmax | VO₂ max, 6MWT, and fatigue severity scale |
| Strength       | 52 weeks | 3 days/week | 50-65% HRmax | VO₂ max, 6MWT, and fatigue severity scale |
| Control group  | 52 weeks | 3 days/week | 50-65% HRmax | VO₂ max, 6MWT, and fatigue severity scale |
| HIT            | 8 weeks supervised | 21 min/session, including an 8-min warm-up and two sets of 5-min HIT with 3-min break at very low intensity. | Each minute of HIT was performed at three different work intensities: 30 s of easy pedaling (low intensity), 20 s of hard work (middle high intensity), and 10 s of all-out, maximal intensity | VO₂ max and workload |
| Control group  | 8 weeks unsupervised for all. | 21 min/session, including an 8-min warm-up and two sets of 5-min HIT with 3-min break at very low intensity. | Each minute of HIT was performed at three different work intensities: 30 s of easy pedaling (low intensity), 20 s of hard work (middle high intensity), and 10 s of all-out, maximal intensity | VO₂ max and workload |
| NMES           | 5 months | 5 days/week | 50-65% HRmax, 12-14 RPE (Borg Scale) | Pain, fatigue, shoulder flexion strength, knee extension strength, and 6MWT |
| NMES           | 5 months | 5 days/week | 50-65% HRmax, 12-14 RPE (Borg Scale) | Pain, fatigue, shoulder flexion strength, knee extension strength, and 6MWT |
Aerobic exercise

Haller et al. (32) found that patients generally benefitted from moderate aerobic training. However, one patient had elevated CK levels the first two weeks of intervention, which stabilized thereafter, and another patient had elevated CK levels during week 8, possibly due to unusual physical exertion at home, according to author reporting. Aside from the two patients, CK levels remained stable, indicating that exercise did not provoke muscle injury. Porcelli et al. (33) found that home-based aerobic training also increased fitness in patients with McArdle disease. However, patients did not feel any benefits from the exercise nor did the intervention increase their habitual ADL.

Maté-Munoz et al. (34) examined the acute and chronic responses to exercise in patients with McArdle disease. The acute response consisted of two tests (see Table 5). Ten patients underwent an 8-month long supervised moderate aerobic exercise program to test the chronic exercise response. Most patients chose walking as preferred exercise mode. Both the acute and chronic group showed an increase in fitness and ventilatory threshold. No adverse events or discomfort were reported and CK levels remained stable post exercise.

From the presented studies, it appears that regular exercise may lead to physiological adaptations that increase oxidative and work capacity in patients with McArdle disease.

A case study reported the effects of a 6-week strength training program. The results from the low weight and high repetition training program lowered the patient’s disease severity class (35). The training closely resembles aerobic training intensity, which could explain the benefits obtained from the training. Intervention specifications for McArdle disease are presented in Table 5.

Pompe disease

Combined aerobic and strength exercise

Muscle strength and functional capacity was shown to increase with moderate aerobic and strength exercise training in patients with late-onset Pompe disease receiving enzyme replacement therapy (36). Despite small sample size, the results are encouraging. Van den Berg et al evaluated the safety and efficacy of moderate endurance, strength, and core stability training (37). After 12-weeks, core stability, muscle strength in hip and shoulder, and functional capacity improved. The first week of training, two patients had elevated plasma CK levels, experienced muscle pain, and fatigue. During the second week, CK levels dropped to their normal range, and fatigue and pain diminished greatly. Both patients

Table 4. A representation of exercise interventions done in DM. Number in parenthesis represents the article reference.

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|-----------------|
| Cycling N = 9   | 12 weeks | 5 days/week 35 min/session | 65% of VO\(_{2\text{max}}\) | Self-reported improvements in ADL, VO\(_{2\text{max}}\) and workload |
| Strength N = 27 | 12 weeks | 3 days/week | Knee extension: 30-40% of max, 3 sets x 4-8 reps Elbow flexion 10-20% of max, 3 sets x 4-8 reps Hand grip: 100%, 3 sets x 4 reps | Increase in strength |
| Control group N =14 | 12 weeks | 3 days/week | Knee extension 60-80% of 1RM, 3 x 10 reps | 1RM |
| Strength N = 6  | 12 weeks | 3 days/week | Knee extension and flexion, hip extension and abduction 60-80% of 1RM Week 1-8: 60% of 1RM, 3 sets x 25 reps Week 9-16: 70% of 1RM, 3 sets x 15 reps Week 17-24: 80% of 1RM, 3 sets x 10 reps | Neither positive or negative effects of the training |
continued the training. This study indicates that a combination of aerobic, resistance and core stability training can be performed safely in patients with Pompe disease. However, when combining different modes of exercise, it can be challenging to determine which exercise improved which outcome.

In 2007, a published paper evaluated whether the adherence to nutrition and exercise therapy could slow the deterioration of muscle function (38). Of the 34 patients included, 22 were fully compliant with nutrition and exercise therapy. Patients demonstrated a slowing of their deterioration in muscle function and some showed improvement in their Walton score. Whether continued compliance with nutrition and exercise therapy slows disease progression long term, and if nutrition and exercise therapy can minimize muscle deterioration at symptom onset should be further explored.

Moderate intensity exercise appears to have an adjuvant effect on patients with Pompe disease and regular exercise is recommended.

Other exercise modalities

Side alternating vibration training (SAVT) is mechanical oscillation applied while standing on a vibrating platform. The oscillation is characterized by amplitude and frequency which determine the intensity of the work performed. One patient with Pompe underwent SAVT, and after 15 weeks of SAVT the patient showed an im-
The level of safety of SAVT is questionable and should be the subject for further exploration.

Intervention specifications for Pompe disease are presented in Table 6.

| Exercise mode/N            | Duration | Frequency                      | Intensity               | Improved outcome                        |
|----------------------------|----------|--------------------------------|-------------------------|-----------------------------------------|
| Cycling N = 8              | 14 weeks | Week 1-7: 4 days/week 30 min/session Week 8-14: 4 days/week 40 min/session | 60-70% HRmax            | Oxidative and work capacity             |
| Electromagnetically braked cycling N = 7 | 12 weeks | 4 days/week 60-90 min/session | 65-70% of HRmax         | Aerobic capacity and work load           |
| Acute: Cycling (strictly monitored) N = 46 | Acute: 1 day |                                | 1. Workload increased with 10 Watt/ min until exhaustion, starting at 10 Watt 2. A 12-minute constant-load test at the power output reaching ventilatory threshold on a cycle | Aerobic capacity, peak power output, and ventilatory threshold |
| Control group N = 46      | Chronic: 8 months | 5 days/week 60 min/session | The two tests were separated by a 10-minute active rest period (freewheel pedaling) 75 g sucrose beverage prior to test 60% of HRmax Complex carbs 1 hour before exercise and simple carbs during exercise |                                |
| Chronic: Walking or cycling N = 9 | Acute: 1 day |                                | 1. Workload increased with 10 Watt/ min until exhaustion, starting at 10 Watt 2. A 12-minute constant-load test at the power output reaching ventilatory threshold on a cycle | Aerobic capacity, peak power output, and ventilatory threshold |
| Strength N = 1             | 6 weeks  | 2 days/week Up to 60 min/session | 65-70% of 1RM 10-minute warm-up consisting of 5 minutes of light-intensity dynamic exercise (on a cycle ergometer or rowing ergometer), followed by 5 minutes of mobilization exercisesand body weight exercises (eg, shoulder shrugs and rotations, arm elevations, changing squat stance, walking lunges, push-ups on the wall). Benchpress with free weights, multipower squat, shoulder press, arm curls and elbow extensions with dumbbells, lateral pulldown, abdominal crunches, and low back extensions. 2-3 sets x 10-15 reps | Patient changed to a lower disease severity class |

The patient reported muscle soreness, stiffness, and aches in legs, twitching while at rest, cramping, and fatigue. Despite the discomfort, her level of activity did not change.

The level of safety of SAVT is questionable and should be the subject for further exploration.

Intervention specifications for Pompe disease are presented in Table 6.
Mitochondrial myopathy

Aerobic exercise

The aspect of training patients with mitochondrial disease is somewhat different from other myopathies in that patients experience a metabolic bottleneck in the mitochondrial respiratory chain function. Taivassalo et al found that aerobic capacity increased with moderate intensity exercise on a treadmill. Fatigue and tolerance to daily activities also improved, and lactate concentration decreased (40). In 6 of the 10 participating patients, CK levels rose slightly, but not to a level indicating significant muscle damage. These findings are in agreement with a study examining the effects of moderate intensity cycling exercise (41). Similar findings were reported by Siciliano et al. (42) (43) showing a decreased lactate concentration, improved SF-36, and improved muscle oxidative metabolism with aerobic training. Jeppesen et al. (44) demonstrated that moderate aerobic training was safe and improved aerobic capacity. No training-induced increases in plasma CK levels were observed. Trenell et al also found beneficial effects from moderate aerobic training including improvement in functional abilities (45). Jeppesen et al. (46) investigated the effects of short- and long-term moderate home-based endurance exercise. Exercise increased oxidative capacity and peak work load. These improvements were sustained after 12 months of exercise. No training-induced CK elevation was observed and patients reported feeling a physical improvement. The effects of moderate intensity cycling and moderate intensity arm strength exercise revealed an increase in functional capacity and muscle strength (47). The training effect was also reflected as improvements in symptoms. To counteract limitations in the oxygen transport pathway, exercise seems to be a promising therapeutic avenue for persons affected by mitochondrial myopathy (48).

Other exercise modalities

The effects of SAVT was considered safe and patients showed some increase in muscle power (49). The presented studies indicate that moderate intensity aerobic exercise is safe and can improve physical capabilities in patients with mitochondrial myopathy.

Intervention specifications for mitochondrial myopathies are presented in Table 7.

Motor neuron diseases

Spinal and bulbar muscular atrophy (SBMA, Kennedy disease)

Aerobic exercise

Moderate aerobic training was examined by Preisler et al. (50). By week 5 of the intervention three patients found it challenging to exercise for 30 minutes due to fatigue or not feeling well recovered in between training sessions. Patients did not experience any change in their daily physical activity, and one patient felt daily physical activity worsened post intervention. Fatigue level increased in seven patients and only one patient experienced improvement. A few patients did feel an increase in endurance, strength, and the distance they were able to walk, while others didn’t experience physical improvements or reported a worsening in endurance, strength, and walking distance. No CK level elevation occurred in seven of the 8 patients, one patient was asked to exercise with a lower frequency.

Other exercise modalities

High-intensity training improved fitness and workload in 8 patients after 8 weeks of training (51). One patient was excluded due to lack of compliance and one patient did not wish to continue for personal reasons. No rise in CK levels occurred after 8 and 16 weeks of training. Self-rated muscle fatigue, muscle pain, and activity level remained the same throughout the training period. Patients expressed an interest in HIT. High-intensity training seems to be a beneficial alternative in comparison to moderate aerobic training, likely because neuronal fatigue due to short duration of exercise is avoided.

Bulbar involvement in patients with SBMA can cause dysphagia and swallowing difficulties. Effects of head lift exercises in swallowing showed an improvement in functional scores for oral dysphagia, indicating that head lifting exercise may factor into improving swallowing (52). Any clinical relevance should be integrated in the clinic with caution, considering the small sample size of the study.

Shrader et al. examined the effects of functional exercise (53). The authors concluded that functional exercise is well tolerated, however, they did not find any functional changes and a modest increase in CK levels was observed.

High-intensity training is recommended in patients with SBMA because it has the best efficacy and is preferred by patients. Intervention specifications for SBMA are presented in Table 8.

Spinal muscular atrophy

Aerobic exercise

Effects of arm cycling in patients with SMA type II showed no adverse events during or after exercise. There was an increase in their cycling distances and durations, but no improvements were observed in Hammersmith Functional Motor Scale (HFMS) (54).

Effects of home-based cycling was investigated by Madsen et al in 8 ambulatory patients with SMA type III (55). One patient discontinued the intervention due to
Table 6. A representation of exercise interventions done in Pompe disease. Number in parenthesis represents the article reference.

| Exercise mode/N                                      | Duration | Frequency       | Intensity                                      | Improved outcome                                                                 |
|------------------------------------------------------|----------|-----------------|------------------------------------------------|----------------------------------------------------------------------------------|
| Cycling and Strength  
N = 5 (36)                                        | 20 weeks | 3 days/week     | 10-15 min/session (week 1-3) 30 min/session (week 4-20) | Week 1-3: Cycling at level 1-2  
Strength: ¼ squat, leg curl, knee raise, push-ups against a wall, back extensions, as well as sit ups, ¼ overhead press, elbow extensions and elbow curl  
50% of 1RM, 2 sets x 10 reps  
Week 4-20: Cycling at level 2-4  
50% of 1RM, 3 sets x 10 reps | Strength increased and 6MWT |
| Cycling, strength, and core stability  
N = 23 (37)                                         | 12 weeks | 3 days/week     | 60% of VO_{2max}  
70% of 4RM  
One session consisted of:  
5 minutes warm up  
15 minutes cycling  
Shoulder extension, flexion and abduction, elbow flexion, knee extension and flexion, hip flexion, abduction and adduction: 3 sets x 15-20 reps  
15 minutes cycling  
3 x 30 seconds: Abdominal bridge, side bridge, back bridge | Climb 4 steps, muscle, strength in shoulder abductors and hip flexors, 6MWT, rise from supine to standing, workload, VO_{2max}, ventilatory threshold, and core stability |
| High-protein and low-carbohydrate nutrition and exercise therapy  
Treadmill and upper body ergometer  
N = 34 (22 complied with nutrition and exercise therapy) (38) | 2y-10y   | Daily           | Not exceed RPE of 11–12                           | Slowing of deterioration in muscle function |
| SAVT  
N = 1 (39)                                          | 15 weeks | One cycle: 60 seconds vibration-on 60 seconds vibration-off | Vibration frequency 5 Hz, progressing to 20 Hz by week 11, and continuing at 20 Hz to week 15  
Starting with two cycles initially, progressing to four cycles by week 11 and continuing with four cycles to week 15. | Improved strength and 6MWT |
Table 7. A representation of exercise interventions done in Mitochondrial myopathy. Number in parenthesis represents the reference.

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|-----------------|
| Treadmill N = 10 | 8 weeks  | 3-4 days/week 20-30 min/session | 60-80% HRmax Not exceed 15 RPE | Aerobic capacity, lactate concentrations decreased, fatigue decreased, and tolerance to daily activities |
| Cycling N = 8 | 14 weeks 49 sessions | Week 1-7: 3 days/week 30 min/session Week 8-14 4 days/week 40 min/session | 70-80% HRmax | SF-36 and aerobic peak capacity |
| Cycling N = 7 | 10 weeks | Week 1-5: 30 min/session Week 6-10: 45 min/session | Max 70% HRmax 60-70 revolution (paddling)/min Max 70% of predicted normal maximum power output | Partially reverting oxidative stress |
| Cycling N = 12 | 10 weeks | Week 1-5: Every other day 30 min/session Week 6-10: Every other day 45 min/session | Max 70% HRmax 60-70 revolution (paddling)/min 60-70% of predicted normal maximum power output | Lactate concentration and muscle oxidative metabolism |
| Cycling N = 20 | 12 weeks | 50 sessions in total 30 min/session | 65-75% HRmax | Oxidative capacity, VO_{2max} and workload |
| Cycling N = 10 | 12 weeks | 3 days/week 30 min/session | 70-80% HRmax | Mitochondrial function and functional ability |
| Cycling N = 4 | Initial: 12 weeks Deconditioning: 3-12 months Second training phase: 12 months | 5 days/week 3 days/week 30 min/session | 70% of VO_{2max} | Oxidative capacity and workload |
severe fatigue and one patient due to difficulty using the cycle independently. Among the remaining patients, the authors found that the exercise was safe. However, patients reported either no change or an increase in fatigue, and no improvements in physical function.

**Strength exercise**

Submaximal resistance training is found to be well tolerated with some strength improvements with no study-related adverse events occurred (56).

**Combined aerobic and strength**

Moderate intensity cycling and strengthening exercise was well tolerated among all patients participating in a single blind randomized controlled clinical (57). The authors reported a large number of falls among the patients, potentially related to fatigue following training. Reporting of muscle soreness and low back pain was also documented. The most notable change was an increase in oxidative capacity. No harmful impact was observed on motor function, strength, and fatigue.

In a recent Cochrane review the authors conclude that it is uncertain whether combined strength and aerobic exercise is beneficial or harmful in people with SMA (58). Further research is needed to understand the rather blunted response from exercise. High-intensity training could be a better exercise modality in SMA patients, as it has been shown to be in SBMA. Intervention specifications for SMA are presented in Table 9.

**Conclusions**

There is considerable amount of evidence indicating that moderate intensity aerobic- and strength exercise is advantageous for patients with muscle diseases, without causing harmful muscle damage. Exercise should be planned carefully and be well monitored, and should be performed within the patients’ limitations. Extreme fatigue and muscle pain, during or after exercise is indicative of negative response to exercise, and intensity and frequency should be reconsidered.

In contrast, motor neuron diseases show different outcomes from exercise. Exercise has a rather blunted response in these patients. One possible explanation could
be that they reach a level of fatigue quicker due to larger motor units that need to fire more frequently, which may cause a neural fatigue, which these patients experience after long-lasting exercise. In these patients, high-intensity training seems safe and may be a promising exercise method which allows the patient to train effectively.

The presented studies include ambulatory patients. In recent years, a few studies have explored the effects of exercise using assisted devices. The effects of exercise using assistive devices should be further explored in very weak and non-ambulatory and wheelchair bound patients.

In addition, it is imperative to set a goal for the exercise in order to obtain clinical relevance, and also determine the appropriateness of training in isolated muscle groups vs. whole-body. Future research should direct the focus on determining duration, frequency, and intensity in order to create an exercise guideline that clinicians and patients can use.

One of the challenges in studying exercise in muscle and lower motor neuron diseases is that the diseases are rare and heterogeneous and one type of exercise may not work for everyone. Furthermore, it can be difficult to recruit a sufficient number of subjects for RCTs and examine the long-term effects of exercise, because of the rareness of the diseases. Lastly, quality of life and social aspects of exercise, as well as motivation and compliance needs more emphasis in trials on exercise therapy in muscle and motor neuron diseases.

Table 8. A representation of exercise interventions done in SMBA. Number in parenthesis represents the article reference.

| Exercise mode/N | Duration | Frequency | Intensity       | Improved outcome                                      |
|-----------------|----------|-----------|-----------------|-------------------------------------------------------|
| Cycling N=8     | 12 weeks | Week 1-2: 2 days/week | 65-70% VO$_{2\text{max}}$ | Workload and citrate synthase                         |
|                 |          | Week 3-4: 3 days/week |                |                                                       |
|                 |          | Week 5-12: 5 days/week |                |                                                       |
|                 |          | 30 min/session |                |                                                       |
| Cycling N=8     | 8 weeks of HIT and 8 weeks of self-training | 3 days/week | 2×5-min exercise periods with 1-min cyclic blocks of intermittent maximal intensity | VO$_{2\text{max}}$, workload, and 6MWT |
| Head lift (Shaker exercise) N=6 | 6 weeks | 6 times a day for 6 weeks | Component 1: 1 min isometric, 1 min rest x 3 Component 2: 30 seconds of isokinetic | Functional scores for oral dysphagia |
| Functional exercise N=24 | 12 weeks | Week 1+2: 2 days/week | Trunk sit back, STS, standing squat with theraband row, standing lunge with theraband, forward reach, double limb heel raise, and wall pushup | No functional changes |
| Stretching N=26 |          | Week 3 - 12: 3 days/week | Week 1+2: 1 set x max reps at 50-70% of 1RM |                                                       |
|                 |          | Weeks 4-6: 3 days/week | Week 3 - 12: 1 set x max reps at 50-70% of 1RM |                                                       |
|                 |          | Week 7-12: 3 days/week | Weeks 4-6: 2 sets x max reps at 50-70% of 1RM |                                                       |
|                 |          |                  | Week 7-12: 3 sets x max reps at 50-70% of 1RM |                                                       |
Conflict of interest

The Authors declare to have no conflict of interest.

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Table 9. A representation of exercise interventions done in SMA. Number in parenthesis represents the article reference.

| Exercise mode/N | Duration | Frequency | Intensity | Improved outcome |
|-----------------|----------|-----------|-----------|------------------|
| Arm cycle       | 12 weeks | 3 days/week, 30 min/session | 60% HRmax | Cycling distances and durations |
| Cycling N = 6   | 12 weeks | 2-4 days/week (gradual increase), 30 min/session | 65-70% of VO2max, 60-75% max HR | Aerobic capacity |
| Control group N = 9 |         |           |           |                   |
| Home based strength training N = 9 | 12 weeks | 3 days per week, 45-60 min/session | 2 sets x 15 reps | Some improvement in upper limb strength |
| Home based cycling and strengthening N = 9 | 1 month lead in period, 6 months - intervention, 12 month - all exercised | Cycling, 5 days/week, 30 min/session | Exercise regimen was structured based on participant performance on the exercise tolerance test and strength assessments | Exercise ability increased slowly and VO2max |
| Control group N = 7 |         |           |           |                   |

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**Abbreviations**

ADL = Activities of Daily Living  
BMD = Becker muscular dystrophy  
CK = Creatine Kinase  
DM = Myotonic muscular dystrophy  
DMD = Duchenne muscular dystrophy  
F/U = Follow-up  
FSHD = Facioscapulohumeral muscular dystrophy  
HFMS = Hammersmith Functional Motor Scale  
HIT = High Intensity Training  
HR = Heart rate  
LGMD = Limb-girdle muscular dystrophy  
LOIT = Low Intensity Training  
Min = Minutes  
MRC = Medical Research Council  
NHP = Nottingham Health Profile  
NMES = Neuromuscular Electrical Stimulation  
RCT = Randomized Controlled Trial  
Reps = Repetitions  
RPE = Rate of Perceived Exertion  
SAVT = Side Alternating Vibration Training  
SBMA = Spinal and Bulbar Muscular Atrophy  
SF-36 = 36 Item Short Form Survey  
SMA = Spinal Muscle Atrophy  
SST = Stair Step Test  
STS = Sit-to-Stand  
TUG = Timed Up and Go  
UC = Usual Care  
VAS = Visual Analog Scale  
VO2max = Maximum volume oxygen consumption  
6MWT = Six-Minute Walk Test  
1RM = One-repetition maximum  
10MWT = 10 Meter Walk Test

**How to cite this article**: Sheikh AM, Vissing J. Exercise therapy for muscle and lower motor neuron diseases. Acta Myol 2019;38:215-32.

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