



## Progressive exercise therapy in muscle dystrophy: two case studies in adult patients with DM2 and LGMD2D

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### ABSTRACT

These two case studies aimed to investigate the effect and acceptance of progressive strength training in patients with muscular dystrophy. Case 1 completed a progressive resistance exercise over 12 weeks. The results showed increases in leg extensor strength, hand strength and balance. Furthermore, the anaerobic test showed an increase in the maximum glycolysis rate. Creatine kinase levels were reduced while maintaining low muscle soreness. Case 2 conducted seven weeks of electronically assisted strength training and electromyostimulation. In the course of the training, an increase in the self-contribution of the performance in the execution of movement was observed in the assisted strength training. Furthermore, an increase in the intensity of external stimuli was observed. The creatine kinase showed a reduction with physiological behavior of muscle soreness. The results demonstrate the acceptance and feasibility of progressive exercise protocols used to increase performance in two cases of muscular dystrophy.

**Keywords:** Muscle dystrophy; Resistance exercise; Exercise therapy; Muscle soreness; Creatine kinase

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### How to cite this article:

Nico Nitzsche, Noah Augustin, Michael Klotz, Henry Schulz. Progressive exercise therapy in muscle dystrophy: two case studies in adult patients with DM2 and LGMD2D. Internal Journal of Sports Medicine and Rehabilitation, 2020; 4:17.

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## Introduction

Muscular dystrophy is a general term for diseases of the muscle fibers. This disease leads to a decrease in muscle mass and strength, especially in the pelvic and shoulder girdle muscles. There are more than 30 different forms of muscular dystrophies, which differ in the type of inheritance, the affected body region as well as in the age and development of the disease. The worldwide prevalence of muscular dystrophies is 16.14 [CI: 11.21-23.23) per 100.000 [24].

The myotonic dystrophy (DM) is the most common muscle disease in adults and has a prevalence at 8.26 per 100.000 (CI: 4.99-13.68) [24]. In Germany the incidence is about 1:15 000 newborns and the prevalence at 1:37 000 [27]. Countries like Germany, Finland or Canada show a higher prevalence of DM2 compared to other European countries. Suominen et al. [37] investigated the frequency of the disease in Finland and reported a prevalence of DM2 of 1:1830. The presence of muscular, extramuscular and cerebral symptoms is slightly different, but the frequency and severity of individual symptoms can vary significantly. A combination of progressive muscle weakness, myotonic symptoms, early lens opacity, cardiac arrhythmia and endocrine disorders is clinically indicative for both forms [25,32]. Myotonia is one of the most important muscular symptoms of DM1 and usually occurs in the distal muscle groups (e.g. forearm and lower leg muscles). Furthermore, muscle weakness with muscle atrophy occurs. Those affected can lose 30 to 55% of their maximum strength over a period of nine years. The pattern of progression is characterized by distal to proximal muscles [12]. DM2 is an adult disease and is generally milder and slower progression than DM1. Severe forms are possible in adulthood to mild forms in old age. The disease-related muscular weakness can lead to wheelchair use (~10%) and respiratory failure [42,43]. Muscular symptoms are among the most common complaints. According to Day et al. [8], 82% suffer from muscle weakness, 75% from clinical myotonia

and 56% from muscle pain (myalgia). The characteristic feature is proximal muscle weakness, which usually begins in the head and hip flexors, elbow extensors, hip extensors and finger flexors [8].

Limb girdle muscular dystrophy (LGMD) is a disease of the muscle fibers, which is accompanied by paralysis and muscle fading. Six autosomal dominant (LGMD1A-F) and ten autosomal recessive (LGMD2A-J) forms are currently known. In LGMD2D, the SGCA gene, which is responsible for the formation of the protein alpha-sarcoglycan, is affected. LGMD is a rare hereditary disease in Germany and other parts of the world. The prevalence LGMD is estimated by 1.63 per 100.000 (CI:0.94-2.81) [24]. In Europe, the prevalence of LGMD2D is estimated to be 3.9 per million [21]. In Germany, the incidence is estimated at 1:3 080 000 (~0.325 per million)[16]. Typical symptoms are paralysis and muscle atrophy. Especially the proximal, trunk muscles are affected. In the upper arms and thighs, the extensor muscles are affected more than the flexor muscles. In most cases, the thigh muscles are affected first, later the weakness also affects the shoulder muscles. Patients often suffer from low back pain, joint stiffness, joint contractures, and rapid fatigue [10]. Basically, muscular dystrophy shows not only a reduction in muscular performance but also a change in energy metabolism. Fontes-Oliveira, Steinz, Schneiderat, Mulder, and Durbeej [11] found a dysregulated expression of genes in energy production, with a reduction in PFK expression. The lactate concentration at rest and under/after exercise is comparable to that of healthy controls, but also significantly higher [34,41]. Furthermore, studies in patients and animal models show changes in glycolytic enzyme activity in patients with muscular dystrophy. Di Mauro, Angelini, and Catani [9] showed that the glycolytic enzymes PFK and LDH had only about 50% of the activity as in healthy subjects. It could also be shown that at the end of the exercise there were lower pH reductions and lower lactate concentrations compared to healthy controls [22]. This indicates

a lower glycolytic activity in muscles of patients with muscular dystrophies.

### Exercise therapy

Overall, endurance training, upper and lower extremity strength training, balance training, functional and neuromuscular electro stimulation and combined training studies are available for training in muscle dystrophy [1,5,7,14,17,26,30,38,44].

The efficacy of strength training has been demonstrated in patients with DM1 [19,20]. No significant effects on muscle strength, fatigue or functional performance have been found. Few studies show improvements in muscle endurance and an increase in quadriceps strength [19,20]. In a 12-week (3 times per week), progressive training program in 9 patients with DM1 (3 × 10 repetitions, 80% of the 1RM), increases in knee extensor muscles were shown but without significant difference between the pre- and posttest in the isokinetic test [40]. A 6-month strength training program in patients with LGMD at 60% of maximum strength leads to a significant increase in strength and endurance. HIT training can also achieve this effect, although it should be noted that some patients may drop out due to increases in CK. It can be stated that strength training can be safe and effective in LGMD but should always be carefully supervised [35].

The effects of training interventions were largely investigated using DM1 population. A review of 21 studies by Roussel, Morin, Gagnon, and Duchesne [31] summarized various effects of training, such as improved self-perception, increase in maximum strength, increase in aerobic capacity, improvement in respiratory function, stress-induced normalization of electromyographic patterns, slight increase in muscle volume, with increase of type 1 and type 2a fibers. The data show potentially significant effects of training in muscular dystrophy. However, due to the heterogeneity between the studies, it was not possible to identify training parameters for individual practical action. In order to show possible approaches to design a training therapy for muscle strengthening in muscular dystrophy, two case studies will be

presented. The aim of the work was to show the effect of progressive muscle training based on two case studies with different clinical symptoms and severity.

**Case 1** was a 45 year old male patient with DM2 (71 kg, 174 cm). The disease was clinically and molecularly confirmed in 2005 (Universitätsklinikum Magdeburg, Germany). At the time of diagnosis, the patient had been diagnosed with a highly elevated CK value. Through a muscle biopsy and molecular genetic tests, the diagnosis (PROMM) has been confirmed. The patient had been suffering from increasing muscle weakness for 2 years. In the family, DM2 was also confirmed in the mother and the grandmother suffered from cataracts. He reported back pain lumbar with partial radiation into the buttocks and dorsal side of the thighs. In addition, his hands tremble during exertion and he suffers from weakness in his legs when trying to stand up or when climbing stairs. At the time of diagnosis, the test person does not suffer from any muscle pain. However, the muscles of the legs cramp several times a day, especially at rest.

### Assessments

Before (pretest), in the middle (6th week) and after the intervention (posttest), motor tests were carried out to determine physical performance. Isokinetic strength tests (motion velocity: 240°s<sup>-1</sup>, 10 reps, CON-TREX® MJ Fa. Physiomed, Schnaittach, Deutschland) were used to determine the performance (peak torque, PT) of the leg extensors and leg flexors as well as anaerobic performance based on the maximal lactate formation rate (vLa<sub>max</sub>). For the determination of vLa<sub>max</sub>, capillary blood samples were taken from the earlobe before, immediately after and up to the ninth minute after the test. The calculation of the vLa<sub>max</sub> was performed according to Mader [23]. The isometric hand strength was determined using a hand dynamometer. Furthermore, the maximum strength (1RM) was determined for all six training exercises. The Y-balance test was performed to measure postural stability (composite reach score: CRS). At intervals of

two weeks, venous blood samples were taken to determine the creatine kinase (CK) value. The training volume load was calculated according to Scott, Duthie, Thornton, & Dascombe [33]. Muscle pain was recorded before and after each training session (Delayed onset muscle soreness: DOMS Scale 1-10).

### Exercise protocol

The training intervention included a progressive resistance training over 12 weeks with 3 exercise sessions per week. At the beginning of each session, the patient warmed up for 5

minutes on a rowing ergometer. Before each exercise, two warming up sets were performed. The following exercises/devices were used: Leg press, chest press, lat pull, butterfly reverse, bicep curls and triceps press on the cable pull through. The pause time between the sets was 2 min. During each unit a trainer supervised the correct execution of the exercises. The training protocol was progressively by increasing the load or the number of repetitions. Figure 1 shows the exercise volume (EV as weekly mean value of the total volume for all exercises) over time.

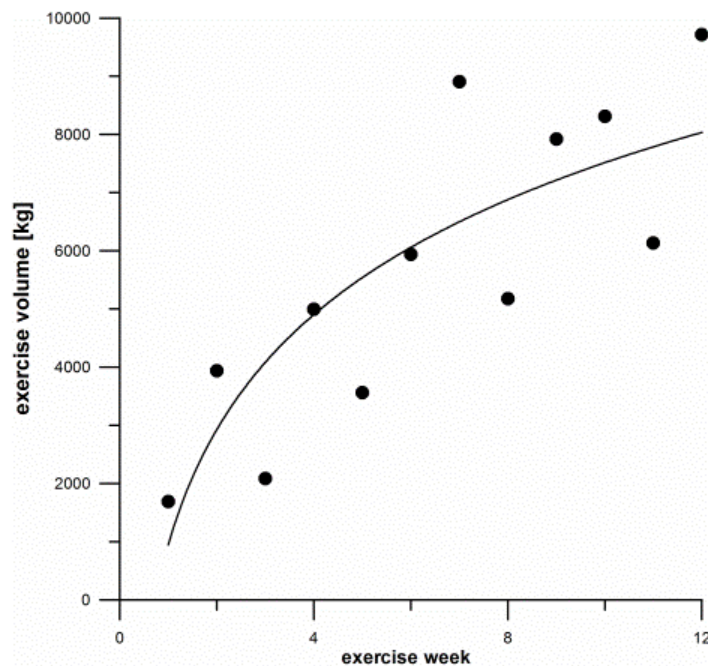


Figure 1: representation of the course of the exercise volume in case 1.

### Results

The patient completed 33 of 36 training sessions (92%). The EV was increased by manipulating load, number of repetitions and number of sets and tended to be flatter towards the end of the intervention. Performance in leg extensors and flexors showed an increase in PT in both legs from pretest to posttest (Figure 2). In the pretest, the CRS of the right leg was approximately 97% and of the left leg approximately 95%. In the posttest, the right leg and the left leg reached to 107%. The difference between the two legs and the posttest decreased. In the pretest the difference was about 2%, in the intermediate test 3.9% and in the posttest only 0.6%. In the pretest and interim test, the hand strength was 78

pounds. In the posttest, the increase was 87.5 pounds (compared to the pretest by 9.5 pounds, about 4.3 kg). The  $vLa_{max}$  increased from  $0.04 \pm 0.02 \text{ mmol l}^{-1}\text{s}^{-1}$  to  $0.13 \pm 0.03 \text{ mmol l}^{-1}\text{s}^{-1}$  in the posttest (3.5-fold increase). The CK decreased continuously from  $15.29 \mu\text{mol l}^{-1}\text{s}^{-1}$  to  $3.96 \mu\text{mol l}^{-1}\text{s}^{-1}$ , until the seventh week of training. From week eight on, the CK increased to  $11.8 \mu\text{mol l}^{-1}\text{s}^{-1}$  (cause given: fall down stairs). The DOMS showed an unchanged value at 1.

**Case 2** was a 25 years old male patient with LGMD2D (90 kg, 172 cm). The disease was clinically confirmed in 1999 (Universitätsklinikum Leipzig, Germany). At the time of diagnosis, the patient had been diagnosed with a highly elevated CK value due to mononucleosis.

Through a muscle biopsy and molecular genetic tests, the diagnosis of  $\alpha$ -Sarcoglycanopathy could be made (Muscle dystrophy also confirmed at grandmother, since she was 34 Years old). Since 2009 the patient is wheelchair-bound and needs help with the transfer. Since

2013 he has been completely unable to walk and pain is felt in the lumbar, sciatic, ankle and shoulder-neck areas. A voluntary maximum contraction of the muscles is possible, not always visible, but mostly palpable.

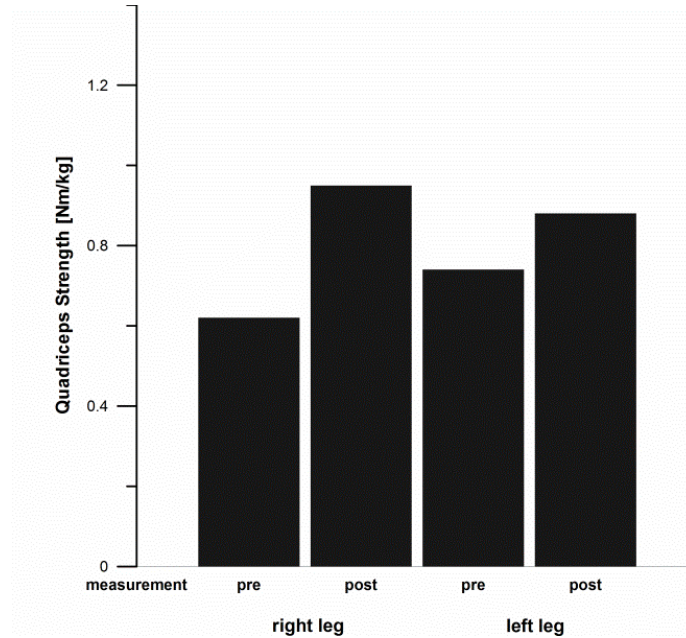


Figure 2: Strength of the knee extensors in the isokinetic test in case 1.

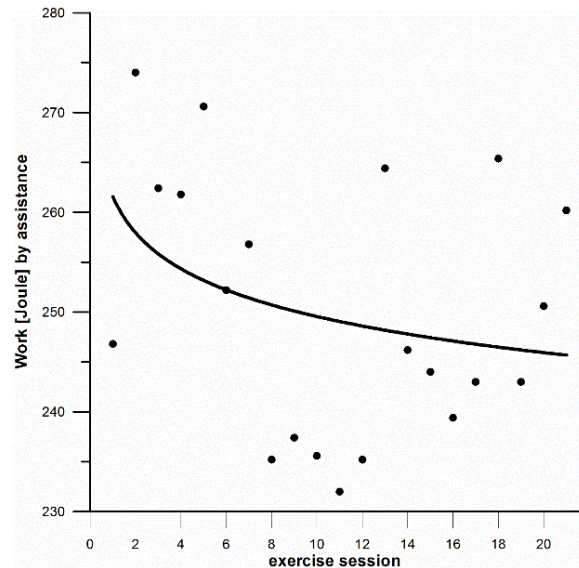


Figure 3: Work by assisted strength training dynamometer at every exercise session in case 2.

### Assessments

Due to the limited mobility of the patient, no motor tests are performed. However, the performances recorded during the isokinetic training were used to assess the performance development. CK values were determined before the start of the training program, at weekly intervals and at the end of the

intervention. Furthermore, a scale of muscle soreness (DOMS) before and several times after the training session (VAS 1-10) and the McGill Pain Questionnaire were used daily.

### Exercise protocol

The patient performed three times per week an electronically supported training of the knee extensors (right leg) over seven weeks (CON-

TREX® MJ Fa. Physiomed, Schnaittach, Germany). Due to the inability to extend the leg against gravity, five sets with thirty passive-assisted repetitions were performed. In this mode, the patient had the opportunity to contract during each movement cycle. The work (Joule) and torque (Nm) performed by the patient was displayed as feedback. From the third week of

training (six sessions were performed), additional EMS training (50 Hz, 300  $\mu$ s, 10 sets with 15 contractions per set, contraction time 2 s, 2 s rest) was performed on the right M. rectus femoris. The adjustment of the current intensity (mA) was based on the subjective perception of the patient.

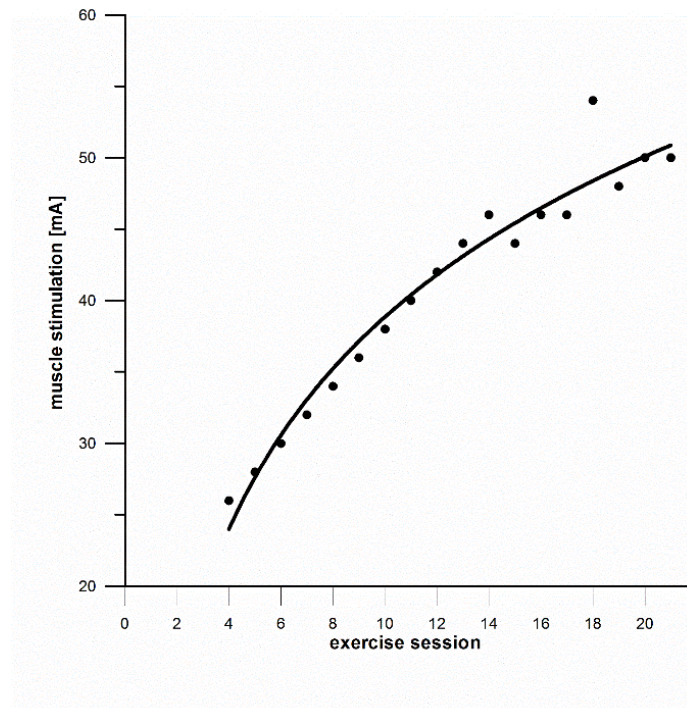


Figure 4: Progression of electrical muscle stimulation in case 2.

## Results

The patient underwent 21 training sessions and showed a high level of motivation over the duration of the intervention and subjectively assessed general well-being as improved. The work performed by the training equipment during electronically supported training showed a decreasing tendency over the training units (Fig.3). This indicates that the patient was doing more work and was therefore more active in the movement cycle. In terms of EMS training, the applied voltage was increased from 26 mA to 46 mA until the seventh week of training (Fig.4). Prior to the intervention, the CK value was  $13.33 \mu\text{mol l}^{-1}\text{s}^{-1}$  and showed a continuous decrease to  $7.64 \mu\text{mol l}^{-1}\text{s}^{-1}$  until the seventh week of training. At week seven on, an increase to  $10.66 \mu\text{mol l}^{-1}\text{s}^{-1}$  was observed. The values of DOMS showed before training sessions  $1.1 \pm 0.7$ , immediately

after training session  $5.4 \pm 0.9$ ,  $6.0 \pm 1.4$  hours after training a value of  $5.4 \pm 1.1$  and after  $20.5 \pm 1.2$  hours the DOMS was decreased at  $3.1 \pm 1.1$ . The McGill Pain Questionnaire values showed  $1.1 \pm 0.3$  in the overall pain assessment.

## Discussion

The aim of these two case studies was to show the development of performance in progressive training design. Both patients showed a high level of compliance and acceptance throughout the intervention. Based on the different initial condition of both patients, active resistance training (case 1) and passive-assisted strengthening training (case 2) were used. The results of the isokinetic test (case 1) and the progress of work done in training (case 2) show improvements in performance, which were also subjectively perceived by the patients. The behavior of the exercise volume in case 1 and

the applied intensity of electromyostimulation in case 2 show a possible approach to the training process. The load curves also show that further adjustments were to be expected beyond the intervention period, as no plateau had yet been reached. On the one hand, this is an indication of the patients' adaptability. On the other hand, it shows the feasibility and acceptance of a progressive training protocol. It is quite difficult to assess at what point in time changes in the load should be made. This would require studies that compare different training protocols on the basis of subjective and physiological parameters. Improvements in performance was also shown in other studies on DM1 patients, but the results were not statistically significant [19,20,40]. Effects of physical activity have been studied far less in DM2 patients. However, one case study also showed an improvement in the performance of the DM2-patient [36].

For LGMD the results are in line with Ansved [2] and Sveen et al. [39]. Currently, the course of the CK value was investigated in patients with muscular dystrophies who had constant or decreasing CK values during the intervention [3,38,44]. Since the daily variability of CK according to Gutenbrunner [13] fluctuates around its mean value by 10-15% during everyday activities, the values measured in the course cannot be attributed exclusively to daily fluctuations. Furthermore, the continuous decrease in CK values over the intervention area indicates muscle adaptation, which indicates a decrease in tissue damage. Possibly this can be interpreted as an indicator for the preservation of the musculature.

Due to the reduction of enzymes of the energy metabolism in muscle dystrophy, the activity of glycolysis is slowed down [22]. The anaerobic isokinetic strength test in case 1 showed a 6-fold reduced maximum glycolysis rate at the pretest when compared to healthy subjects [28]. The posttest showed a significant increase in the glycolysis rate. Studies in which multi-week resistance training was performed showed an increase in glycolytic enzymes and the maximum glycolysis rate [15,28].

Muscle pain in muscular dystrophy patients was often not recorded since many subjects had early courses of the disease in which an exact pain evaluation was not focused. The low pain perception in the two cases during the sessions is positive for the acceptance of this training load. Dynamic resistance training is a combination of eccentric and concentric muscle work. Compared to concentric training, eccentric training causes greater muscle damage and thus more severe muscle pain [4]. In case 2 due to the combined form of loading, the perception of pain can be the result of both forms of tension. Training by electrical muscle stimulation in muscular dystrophy (type FSHD; 5x/week for 5 months) led to a reduction of subjectively perceived muscle pain [6]. Intensive resistance Training (e.g. calf lifting until full fatigue), which is associated with significant muscle damage, shows a pain maximum (DOMS) approx. 72 hours after training [29]. In case 2, the pain maximum was observed within approximately 6 hours after training and then decreased. It is assumed that an early onset of the pain maximum after training indicates a low level of muscle damage. In this case, this would indicate an acceptable training load. Particularly, patients with limb girdle dystrophy, who suffered from increasing muscle pain and elevated CK values, were sometimes forced to stop strength training studies [39]. Variations in the distribution of receptor types as well as different pain modulation contribute to increased variability of muscle pain perception between subjects [18].

According to studies, this advanced strength training protocol has positive effects in slowly progressive courses. Further studies, especially on long-term effects, are necessary to establish the treatment method. Currently, most forms of muscular dystrophy are symptomatically treated with physiotherapy [2]. Currently, physiotherapy and speech therapy are mainly used, little weight training and far too few therapy units (usually 2 per week). The results show that improvements in muscle function are possible even with long-term disease. These applied training weeks are only a small sample of the potential

development. Despite the illness, the muscles are resilient and can adapt and promote the patients' independence. Such training can be better controlled by regular CK monitoring and can allow for stress control in individual cases.

### Conclusion

The results demonstrate the acceptance and feasibility of the training protocols used to increase performance in two cases of muscular dystrophy. This allows an insight into the possible design of a training therapy with such patients. It is desirable that future training studies with several patients under progressive load show the development of performance.

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