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Founders: Giovanni Nigro and Lucia Ines Comi

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Special Issue
Physical exercise in neuromuscular disorders

Guest Editors

Gabriele Siciliano and Antonio Toscano

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EDITORIAL

The role of exercise in neuromuscular diseases

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Regular physical activity, appropriately dosed in volume and frequency, has a wide-ranging beneficial function on the physical and mental health of humans. In fact, the scientific literature demonstrates, incontrovertibly, that physical exercise can perform a powerful preventive function on numerous serious and often chronic and deadly diseases such as type 2 diabetes, stroke, hypertension, and cancer (and in particular breast and colon cancer), osteoporosis, neurodegenerative diseases, depression and pathological anxiety (1). This silent protective action is accompanied by a significant improvement in the quality of life and the level of self-esteem, a slowing down of cellular muscle ageing processes (sarcopenia) and is associated with a reduction in the risk of cognitive decline and development of dementia. The holistic effect of the benefit of physical activity is demonstrated by the fact that it ends up impacting on human longevity by increasing its average survival, or by postponing the onset of potentially deadly diseases (2).

It is of absolute importance that for all these pathological situations and for others, such as inflammatory diseases, physical activity can also perform a curative function and not only a preventive one. And therefore, the focus of the scientific community, slowly but consistently, moves towards a more adequate use of physical exercise as an additional therapeutic element to the common therapeutic approach, often capable of preventing or delaying pharmacological interventions. In short, many people begin to internalize that the exercise is itself a drug that is often more effective than many and has therapeutic indications that are apparently unrelated to each other. As such, it should be administered by competent personnel who know how to manage, above all, the dose.

Although this premise highlights a fundamental role of physical exercise to prevent and treat a *plethora* of human diseases (1, 3), in neuromuscular diseases populations, notwithstanding the great interest, particularly for prevention of excessive fatigue and maintenance of the patient's quality of life, this indication is still lacking (4). In fact, until now, scientists and clinicians thought that, having these diseases ultimately deal with skeletal muscles, as a precautionary measure it was better to ask the subject not to perform exercise, in order to avoid accelerating the degenerative process or determine exercise-induced muscle damage leading to pain, rhabdomyolysis and myoglobinuria. The attitude to precaution has additional fundamentals in a whole series of knowledge gaps regarding the physiopathology of diseases, how this can intersect with the physiological plastic effects of qualitative and quantitative different physical exercise, the outcome measures to be considered, how to proceed for a highly personalized approach, and the impact of new technologies for monitoring temporal evolution of diseases and approach efficacy.

However, in the presence of a neuromuscular disease, a crucial time ridge for the purpose of establishing the ultimate significance of the level of physical activity for disease progression and evolution is represented by the time of diagnosis. In fact, if, on one hand, it is fundamental to establish whether physical activity turns out to be a factor that can accelerate or decelerate the onset of the clinical symptoms of the disease, on the other, it is also of great importance to establish, once the symptoms begin to manifest, whether regular physical activity may change its natural evolution over time. The existence of this ridge defines the importance of future retrospective and prospective studies, possibly on a large scale. Therefore, considering that diagnose often occurs after the age of 30, it is crucial, first to establish whether early physical activity, of high or moderate intensity, is dangerous or beneficial. Some initial retrospective studies have involved, with opposite results, the limb girdle muscular dystrophy 2I (LGMD2I) and the dysferlinopathies (LGMD2B and Myoshy myopathies). In the first case, the retrospective approach allowed to estab-

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lish how the level of physical activity prior to the diagnosis is not able to negatively impact on the onset of the disease (5). In the second case, instead, in full agreement with the physiological significance of the dysferlin in the cellular repair processes from exercise-induced micro lesions, retrospective studies have shown an increased risk of an early onset of the disease (6).

Both in retrospective and perspective studies quality of exercise should be taken into consideration. As known, two different kinds of exercise paradigms can be distinguished at the extremes of a wide range of possibilities: resistance and endurance. Resistance exercise is based on the repeated application of external loads, followed, in the long run, by changes in muscle size (hypertrophy) leading to changes in muscle strength. Following resistance exercise, phenotypical muscular changes mostly depend on the eccentric components of contractions intrinsically linked to muscle damage, particularly at ultra-microscopical level. Endurance exercise includes low load-long lasting activities followed by increased maximal oxygen consumption, increased capillarization and improvement in cardiovascular fitness.

To date, safety of supervised training, mostly including endurance type paradigms which appear to be well tolerated (7, 8), is widely accepted, but precise guidelines of exercise interventions related to neuromuscular diseases' aetiology are still lacking. Indeed, safety and efficacy of resistance type exercise in myopathies have not been sufficiently investigated (9).

To take stock of the knowledge gaps and necessary scientific developments to ascertain the role of exercise in neuromuscular diseases, last June, the first satellite symposium of the National Congress of the Italian Myology Association (AIM), entirely dedicated to the topic with participation of leading exponents in the field of applied muscle physiology and neurology was held at Mondino Foundation in Pavia (Italy).

In the current special issue of Acta Myologica three papers (10-12) summarize what emerged during the symposium, dealing with fundamental physiological acquisitions, known effects in certain myopathies, and open issues to be addressed, with the aim to stimulate future clarifying investigations.

Berardinelli and D'Antona report on the main physiological aspects of muscle adaptation to physical exercise with the aim of intersecting the effects of muscle exercise adaptation with the pathophysiology of some neuromuscular diseases of known etiology. The second paper, by Sheikh and Vissing, deals with evidences of efficacy of exercise in muscle and lower motor neuron diseases, highlighting that, although moderate exercise appears to be safe and effective in muscular diseases, efficacy and safety in lower motor neurone diseases is still a matter of debate. The third paper by Voet highlights how the vicious circle of inactivity represents a fundamental element at the base of the progressive deterioration of the neuromuscular function of the patient and how the interruption of this circle can lead to a significant improvement of the cardiometabolic fitness and the quality of life of the patients.

All authors agree that future research must consider an accurate evaluation of the overall impact of exercise, both retrospectively and prospectively, with a focus on quality, intensity, frequency and duration, and a strict consideration of the pathophysiology of diseases and their evolution.

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ORIGINAL ARTICLES

Physiological aspects of muscular adaptations to training translated to neuromuscular diseases

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The high level of complexity underlying the heterogeneous pathophysiology of neuromuscular diseases is a fundamental limiting factor in understanding the role of physical activity in their onset and/or clinical evolution. To overcome this difficulty, it is essential to rely on and deep knowledge of the aetiology and on the physiological adaptations to physical exercise, in order to predict how they can impact on the clinical history of each disease. This paper illustrates the possible strategies of intervention in some neuromuscular disorders, through the analysis of their supposed pathogenic mechanisms. Nevertheless, no clear conclusions can be inferred so far.

Key words: muscle adaptation, exercise, neuromuscular disorders

Introduction

Translation of fundamental physiological aspects of skeletal muscle plasticity to neuromuscular diseases may help overcoming the high degree of complexity residing in the existence of a constellation of conditions that are very different in their pathophysiological origin.

In particular, open questions regard how to link physiological aspects of muscle adaptation to physical exercise, disuse, and aging to the pathophysiology of neuromuscular diseases and their evolution.

Considering the plastic nature of skeletal muscle tissue capable of a wide range of adaptations through qualitative and quantitative variations of cellular protein expression to load and nutrients, the physiological translation should pass through elements of intercorrelations between the cellular structure, from one side, and the its energy disposal, from the other, determined by its use or disuse/non-use, with the *leitmotif* of the aging process on the background, known to correlate with the arising of age-related diseases and consequent increased probability of death.

A fundamental observation from this point of view resides in the positive correlation between activity energy expenditure (AEE), unlike resting metabolic rate (RMR), and longevity, through significant delay of age-related diseases, such as cardiovascular, metabolic diseases, and cancer. As known, the subjects' daily energy consumption includes resting metabolic rate, representing almost 50% of the total expenditure (EE), and AEE, that is the energy consumption due to exercise and daily activities, whereas the thermal effect of meals (TEM) represents a small and constant quote. Of course, the relative proportion of resting and activity expenditure is highly variable between subjects and is strictly linked to their daily habits. A really important finding that may help unraveling the role of energy consumption in longevity is the age-related decline of total energy consumption, reflected by changes in body mass (particularly from birth to 20y) and daily energy consumption (from 2550 kCal/day 18-19y to 2050 kCal/day over 60y WHO/FAO guidelines) (1).

In the large part of the population, the aging process adds to the generally observed reduction in the level of physical activity to determine a progressive decline in several physiological capacities. Therefore, in order to get insight into physiology of aging, it is of major importance to try normalizing this process over the level of physical activity. In other terms, it is mandatory to exclude the impact of physical activity to understand what aging *per se* is. In this sense, a precious help may derive from having a deep look at the ageing processin the so called master athletes (2), who have long lasting commitment to moderate to high intensity physical activity. In these subjects, it can be reasonably considered that the ageing process is, as much as possible, unlinked from inter-subjects variations in the basal level physical activity. That said, in

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master athlete performance inevitably declines with age and the major determinants of this loss are the reduction in the aerobic fitness (mirrored by VO_{2max} decrease) (3) and the concomitant changes in the skeletal muscle functional and structural features, including variations in muscle phenotype (generally a fast-to-slow transition) (4). By comparing the aging process in sedentary subjects and master athletes, it is now clear that the maximum rate of oxygen consumption inevitably declines with age but this change is enormously conditioned by the level of physical activity maintained over time. In fact, an elder active subject may express much higher VO_{2max} than a sedentary young (5). Therefore, being the total energy expenditure and maximal oxygen consumption largely dependent from the basal level of physical activity, from this point of view, a young may be considered elder and *vice versa*.

Considering the organ mass change over time and the relative contribution to total mass of each organ, the skeletal muscle appears as a fundamental contributor of this variation. This phenomenon is highly amplified with age by following an exponential, unlike linear, change due to ageing-associated muscle disuse and is predictable that an earlier exponential change may well represent the age-related variations in the skeletal muscle in presence of neuromuscular diseases, independently from their pathophysiology (6).

A fundamental regulator of skeletal muscle mass and its sensing of applied load and energy status is the so called mechanistic TOR, an atypical protein kinase essential for organism survival which plays the role of a catalytic subunit of two distinct dimer multiprotein complexes termed mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (7). In these complexes mTOR acts as a multieffector protein kinase. Four major inputs regulate mTORC1 by cooperating or antagonizing each other and include nutrients (amino acids and glucose), growth factors, energy status, and mechanical stress.

In particular, as chemical inhibitors of glycolysis suppress mTORC1 activity, the complex senses the cellular energy of the cell. This phenomenon suggests that changes in energy disposal may promote convergent upstream regulatory signals on mTORC1. As already known, glycolysis and mitochondrial respiration convert nutrients into energy, which is stored in the form of ATP. Glucose loss, inhibition of glycolysis, or mitochondrial respiration cause a significant reduction of the intracellular ATP levels that determines a change in the intracellular ADP/ATP and AMP/ATP ratios. This change is sensed by heterotrimeric complex AMP dependent protein kinase (AMPK) Under nutrient deprivation AMPK transmits stress signals to mTORC1 (8). This process leads mTORC1 inhibition through direct and indirect mechanisms. Importantly, mechanical load and nutrients as branched chain amino acids (BCAA) (9), although first acting at different levels, seem to have a common target on the mTOR biosynthetic pathway controlling protein synthesis. For example, eccentric type exercise is able to activate downstream mTORC1 kinase effector (S6K1) responsible for translation initiation, through changes in the membrane level of phosphatidic acid (PA) (10, 11).

Importantly, with age, mTORC1 possibly increases its basal level of expression and activation (12). This change appears to be paralleled by reduced responsiveness to stimuli (ie, mechanical load, BCAA), partly ascribable to increased expression of negative regulators. In a condition in which mTORC1 responsiveness is blunted, increased loss of muscle mass and concomitant increased insulin resistance appears to contribute to the arising of age-related diseases. Of importance, muscle-specific inactivation of mTOR leads to severe myopathy, resulting in premature death. In fact, mTOR-deficient muscles display metabolic changes including impaired oxidative metabolism, altered mitochondrial regulation, and glycogen accumulation associated with protein kinase B/Akt hyperactivation. Importantly, loss of mTOR exacerbates the myopathic features in both slow oxidative and fast glycolytic muscles. Moreover, mTOR loss leads to reduced muscle dystrophin content thus exerting a control of dystrophin transcription (13).

Physiological muscle adaptations to exercise

Muscle adaptations to exercise include morphofunctional modifications triggered by the repetition of muscular contraction bouts, leading to increased mitochondrial biosynthesis and angiogenesis, fibers hypertrophy and fundamental changes in cell metabolism, including increase lactate tolerance (Tab. 1). These adaptations follow modifications of the expression and the activation a series of subcellular signals and a series, still partially unknown, of pre- and post-transcriptional events. The primitive stimulus (exercise or training) with its quality (strength or endurance) are able to activate a large number of cellular events, in turn responsible for the activation, inhibition or modulation of cross linked signaling routes, implicated in the regulation of transcription and translation. At the center of these routes mTORC1 and peroxisome PGC1α are cross-linked master regulators of the plastic responses due to strength type and endurance type exercise respectively (Fig. 1).

In particular, as regards mitochondrial biogenesis following endurance type exercise of sufficient duration (14), it is possible to identify two major governors of the process: AMPK and PGC1α AMPK regulator is the energy status of the cell defined by the AMP/ATP and Cr/

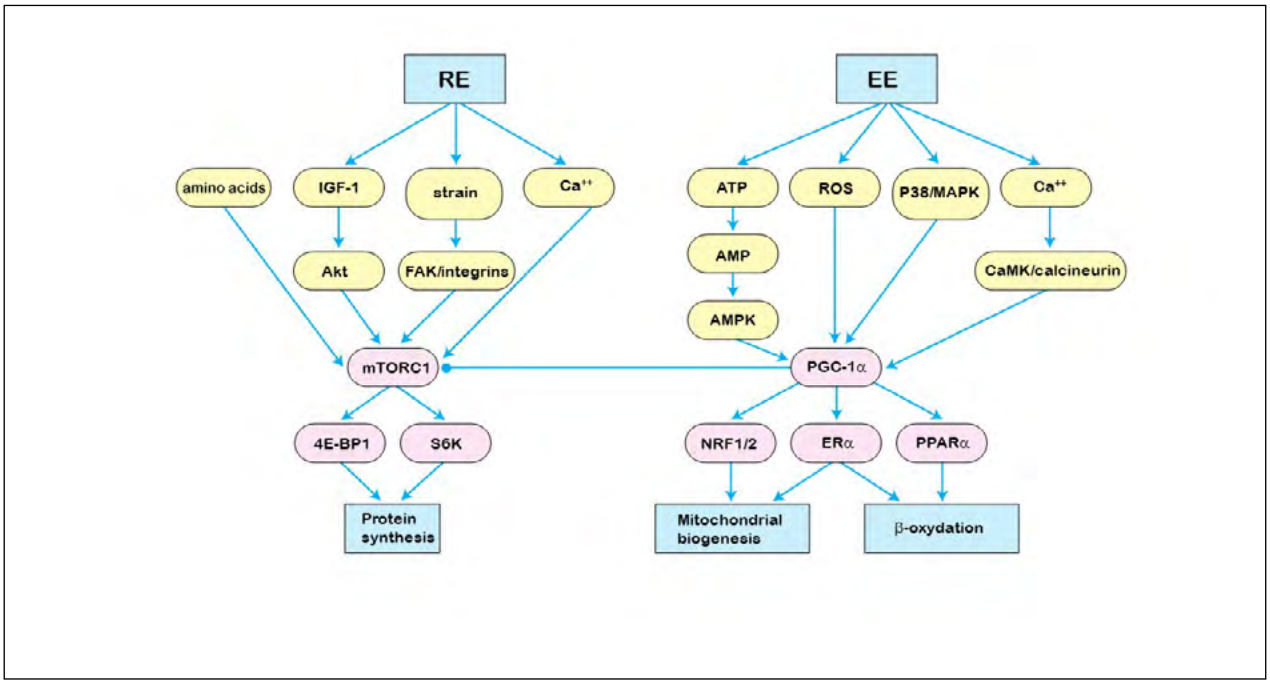

Figure 1. Schematic representation of the sub-cellular signals activated by the endurance (EE) and resistance (RE) exercises. In EE, the activation of the downstream pathways foresees modifications of the energetic availability (ATP), oxidative stress with production of reactive oxygen species (ROS), meccanostresses with p38 / MAPK activation or changes in cellular calcium content (ERα = alpha receptor for estrogens; PPARα = peroxisomal proliferator-activated receptor alpha), leading to PGC-1α mediated mitochondriogenesis and mitochondrial β-oxidation. In RE, Insulin Growth Factor 1 (IGF-1), amino acids, mechanical strain and calcium disposal converge on upstream signals activating mTORC1. Akt = protein kinase B; FAK = Focal Adhesion Kinase; S6K = ribosomal protein 6 kinase; 4E-BP1 = eukaryotic translation initiation factor 4E-binding protein 1. Modified with permission from: Physical Activity. Giuseppe D'Antona. Poletto publisher 2019 (1st edition) (62).

PCr intracellular levels. An increased AMP/ATP ratio due to deprivation of glucose, oxidative stress and exercised induced ATP turnover, leads to acute or chronic AMPK activation. In the first case AMKP hypercactivation determines protein synthesis inhibition and increased lipid oxidation. In the latter it stimulates mitochondrial biogenesis. Endurance exercise is also associated with NAD+ fluctuations within the skeletal muscle fibers. NAD+ is a regulator of the deacetylasisirtuine family (SIRT). An increased NAD+/ NADH ratio due to acute exercise and fasting activates SIRT1 in the cytosol and SIRT3 in the mitochondria. The subsequent deacylation of transcription factors and mitochondrial enzymes is followed by a series of adaptations, which increase mitochondrial oxidative function. This adaptation is particularly significant in the presence of low load or in the recovery time from exercise. On the contrary if the load increases, the lactate production reduces the NAD+/ NADH ratio thus blunting the upregulation of mitochondrial function through this mechanism (15). Considering the final physiological effect of endurance type exercise on mitochondrial biogenesis and oxidative capacity, possible translation of this exercise paradigm regards spinal muscular atrophy.

Spinal muscular atrophy (SMA) is caused by homozygous deletion/mutations in the survival motor neuron 1(*SMN1*) gene with an estimated incidence of 1 in 11,000 live births. It is characterized by motoneurons degeneration in spinal cord and brainstem causing muscle wasting and weakness. In SMA clinical severity ranges from the extremely severe type 1 to the mildest type 3. Approximately 60% of affected infants have a type 1 SMA, with onset of symptoms at 6 months of age or younger, and a median life expectancy of less than 2 years without respiratory and nutritional support. New developmental motor milestones are rarely achieved after diagnosis. The mildest phenotype begins after the acquisition of autonomous ambulation, that is usually preserved till late if the onset was later than 3 ys of age, and gets lost about 10 yrs after the diagnosis if ambulation was acquired by 3 ys of age. Even an adult very mild form has been described, usually called type 4 characterized by adult onset and quite normal motor function. Between the extreme phe-

notypes there is a continuum with variable severity. The different phenotypes share the same molecular defects -a homozygous deletion or mutation in the survival motor neuron 1 which results in decreased expression of the survival motor neuron (SMN) protein and degeneration of motor neurons in the spinal cord and brain stem. A paralogous gene, survival motor neuron 2 (SMN2), also encodes the SMN protein; however, 90 to 95% of the translated protein is truncated and nonfunctional as a result of aberrant splicing. The more the SMN2 copies, the mildest the phenotype, as a general rule. Therefore, modulation of pre-messenger RNA (pre-mRNA) splicing of SMN2 to promote increased production of SMN protein has been shown to be an effective treatment strategy across the disease spectrum of spinal muscular atrophy. In addition to muscle weakness, fatigue is a common complaint in SMA. A possible explanation comes from SMA animal models and post-mortem studies, demonstrating abnormal development and maturation of the neuromuscular junction. Neuromuscular dysfunction has been found also in at least half of the patients with SMA. SMN has a role in myogenesis and normal muscle differentiation requires adequate levels of SMN, supporting the hypothesis that a delay in muscle maturation is one of the primary pathologic components of SMA. The association between normal myogenesis and increased oxidative metabolism has been demonstrated. Deregulated myogenesis and impaired mitochondrial biogenesis seem to be inversely proportional to SMN availability, being more prominent in muscle from patients with SMA-I than in muscle from patients with SMA-III. The reduced mitochondrial content makes SMA muscle unable to sustain muscle fiber maturation and contraction properly, contributing to patient weakness and hypotonia (16). Recent clinical observations reporting an incomplete response to aerobic exercise in patients with SMA also sustain this scenario (17). Considering its slow progression, SMA-III may benefit of endurance exercise training in terms of functional performance and exercise capacity through the amelioration of muscle fibers metabolic function and the interruption of further muscle functional and structural impairment induced by the vicious circle of inactivity (18). It has been shown that this exercise paradigm is able to determine positive effects on post-natal maturation of motor units and physical behavior in mouse models of SMA (19, 20). Although there are several inconsistencies regarding the human studies, particularly in terms of number of subjects enrolled, optimal training frequency, and possible adverse events (21), initial evidence seems to suggest a positive effect of endurance exercise type on maximal oxygen consumption (VO2max) in SMA-III (22). Despite these premises, considering the vulnerability of patients to exercise-induced fatigue, great future attention will be required to identify the correct dose of endurance exercise to be administered.

Another fundamental adaptation to exercise is related to calcium fluctuations within the sarcoplasm due to bouts repetition. As known, increased activity leads to calcium release at the sarcoplasmic reticulum through ryanodin receptors (RyR) and concomitant activation of calmodulin-dependent protein kinase (CaMK) signaling. **Calpain 3 (CAPN3)** is associated with the muscle triad through its interaction with RyR1. Following calcium release, phosphorylation of CaMK leads to the activation of p38 MAPK, which, in turn, stabilizes the transcriptional co-activator PGC1α, leading to increased transcription of muscle adaptation genes controlled by MEF2, PPAR and, possibly, other transcription factors. CaMK activation also phosphorylates transcriptional inhibitor HDAC, leading to its relocation from the nucleus to the cytoplasm, thus alleviating transcriptional repression. In the absence of CAPN3, as in calpain myopathy (limb girdle muscular dystrophy 2A), the levels of RyR and the amplitude of calcium release are blunted, leading to decreased activation of CaMK. As a result, both branches of downstream events are suppressed determining and the failure to up-regulate transcription of genes necessary for the adaptation to exercise arises.

Mutations in calpain 3 gene leads to autosomal recessive limb girdle muscular dystrophy 2A (LGMD2A), characterized by atrophy and weakness of proximal limb and girdle muscles. LGMD2A is one of the most common subtypes of LGMD worldwide, accounting for 15-40% of LGMD cases. Recently, a *CAPN3* gene heterozygous deletion(c.643_663del21) has been associated with an autosomal dominant transmission pattern in thirteen unrelated European families (23). Clinical features may include a slowly progressive, symmetrical, limb-girdle weakness and selective muscle atrophy (e.g. hip adductors and extensors, and hamstring muscles), with an onset between the ages of 12 and 20. Scapular winging, scoliosis and joint contractures may also be observed. In general, ambulation loss occurs one to three decades after diagnosis; in fact,20% of LGMD2A patients may become wheelchair dependent before their thirties. Respiratory failure in calpainopathy is known to occur in patients with an advanced stage of the disease, particularly after ambulation loss. Early respiratory insufficiency requiring nocturnal non-invasive ventilation (NIV) in a 70-year-old ambulatory man with LGMD2A has recently been described (24). Most studies, with a few exceptions, have reported the lack of cardiac dysfunction in patients with calpainopathy (25). reported that cardiac function in 33 patients was normal on electrocardiogram and echocardiography, with the exception of 2 patients who had atrial fibrillation. In mice, calpain 3 transcripts are expressed during cardiogenesis, although its expression decreases

as the organ matures. The absence in mature cardiomyocytes is a possible explanation for the absence of cardiomyopathy in the majority of patients. A few case reports have suggested cardiac involvement. For example, Okere et al. reported that a 23-year-old patient with calpainopathy had cardiomyopathy (26).

Considering the role of calpain and on the pathophysiology of calpainopathy, a working hypothesis in LGMD2A includes short duration bouts of endurance exercise. Notwithstanding these premises only pilot studies are available on the effects of training in LGMD2A, only focusing on resistance type exercise (27).

When the quality of training includes multi joint bouts heavy exercise, possibly with pyramiding increase of weight load and decrease in repetition number, the fundamental skeletal muscle adaptations consist in increased strength and hypertrophy appearance. It is widely known that, in this case, the hypertrophic plastic response of the muscle mostly depends on muscular damage due to the eccentric components of exercise. In fact, following eccentric contractions, a stereotyped response follows particularly in unaccustomed individuals including functional and biochemical features underpinning the structural alterations that the single muscle fibers sustain (Fig. 2). A fundamental role in muscle repair in presence of eccentric induce muscle damage is attributed to dysferlin.

***DYSF* gene**, on Chromosome 2p13.2, encodes a protein called "dysferlin," the muscle-specific member of a class of homologous proteins termed "ferlins". Diseases related to mutation in *DYSF* Gene -Dysferlinopathies- are characterized by a selective and progressive involvement of proximal and/or distal muscles of the limb girdles, usually transmitted in autosomal recessive mode. The age at onset of muscle weakness varies widely (from congenital 14 to 73 years), but usually occurs in the teenage years or early adulthood (on average 15-27 years) (28). Serum creatine kinase (CK) levels are usually elevated (10-100 times normal values) from the early asymptomatic stage of the disease. HyperCKemia characterizes all clinical phenotypes of dysferlinopathy and is a hallmark of the disease. Three main phenotypes are usually associated with *dysferlin* gene mutations: limb girdle muscle dystrophy type 2B (LGMD2B), Miyoshi distal myopathy (MM) and distal myopathy with Anterior Tibialis onset (DMAT). Links between mutation type, location and phenotype are not straight forward. Dysferlin is responsible for plasma membrane repair, vesicle fusion and membrane trafficking. Not only does dysferlin widely exist in cell membranes of skeletal and cardiac muscles, it also exists in the membranes of non-myofiber cells, such as monocytes. The ferlin protein group to which dysferlin belongs all have Ca2+sensitive C2 domains. It has been demonstrated that an influx of Ca2+through the site of membrane injury triggers dysferlin-mediated membrane repair. Patients with mutations in the dysferlin gene often have impaired membrane resealing following mechanical or chemical stress, causing an influx

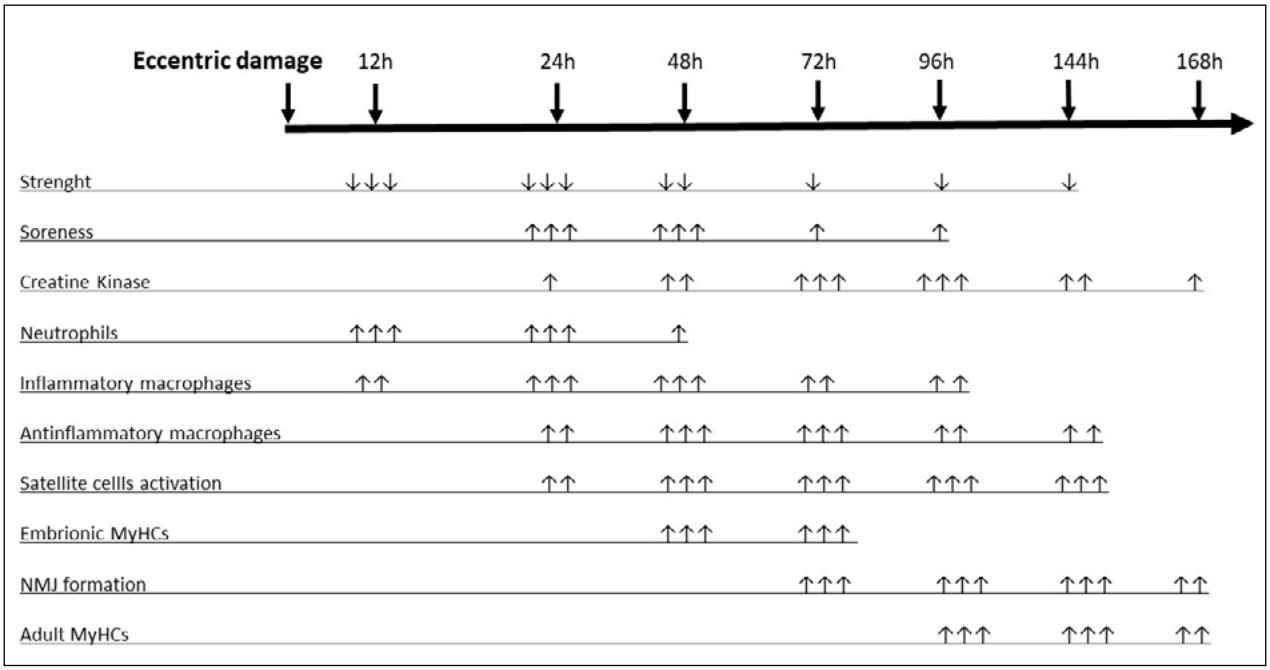

Figure 2. Stereotyped time course of muscular changes following eccentric exercise damage. MyHC = Myosin Heavy Chain; NMJ = neuromuscular junction; ↑ or ↓ = slight change; ↑↑ or ↓↓ = moderate change; ↑↑↑ or ↓↓↓ = large change.

of Ca2+. This is particularly relevant in muscle where mechanical stress due to muscle contraction is quite common and Ca2+ regulation is highly important. Furthermore, two reports have been published documenting mitochondrial abnormalities in patients with dysferlin mutations (29,30). The first report demonstrated accumulation of subsarcolemmal mitochondria in some patients' muscle fibers including one patient with ragged red fibers and paracrystalline mitochondrial inclusions. More recently up to 10% of muscle fibers were reported to be cytochrome *c* oxidase (COX or complex IV) deficient, and some of these fibers have increased mtDNA copy number. In the same study, a reduced complex IV and complex III levels were observed in some patients, while others showed a significant down-regulation of complex I and complex IV activities and only a mild reduction of complex III.

In 2016, Vincent et al. published a work regarding mitochondrial function in dysferlinopathies (30). The authors analyzed skeletal muscle biopsies for eight patients by quadruple immunofluorescent assay to assess oxidative phosphorylation protein abundance and Long-range PCR in single muscle fibers to look for presence of clonally expanded large-scale mitochondrial DNA rearrangements in patients' skeletal muscle. They reported higher complex I and complexIV deficiency in patients than age matched controls but patients do not have rearrangements of the mtDNA. So, they hypothesized that respiratory chain deficiency could be the results of an increased cytosolic Ca2+ concentration (due to a membrane resealing defect) causing mitochondrial aberrations. Considering the crucial role of dysferlin in muscle repair to eccentric mechanical strain and possible translation regards dysferlin myopathies such as LGMD2B and Miyoshi myopathy due to dysferlin gene mutations. In fact, in dysferlinopathy it has been proposed that severity of the dystrophic process mainly depends on type of exercise (concentric/isometric and eccentric) instead of overload. Therefore, a working hypothesis in this neuromuscular disease include bouts of concentric exercise with abolishment of the eccentric components. To date, no studies have analyzed such a training paradigm in dysferlinopathy.

Another fundamental knowledge for translation regards muscle energy disposal and biochemical handling during rest and exercise. It is known that fluctuations in energy pool utilization mostly depends on duration and percentage of the maximal sustainable load that is the exercise intensity (Fig. 3).

From this point of view, possible translation examples include mcArdle disease and CPT2 deficiency.

The myopathic form of carnitine palmitoyltransferase 2 (CPT2) deficiency, is an inherited metabolic disorder that affects mitochondrial oxidation of long chain fatty acids (LCFA).

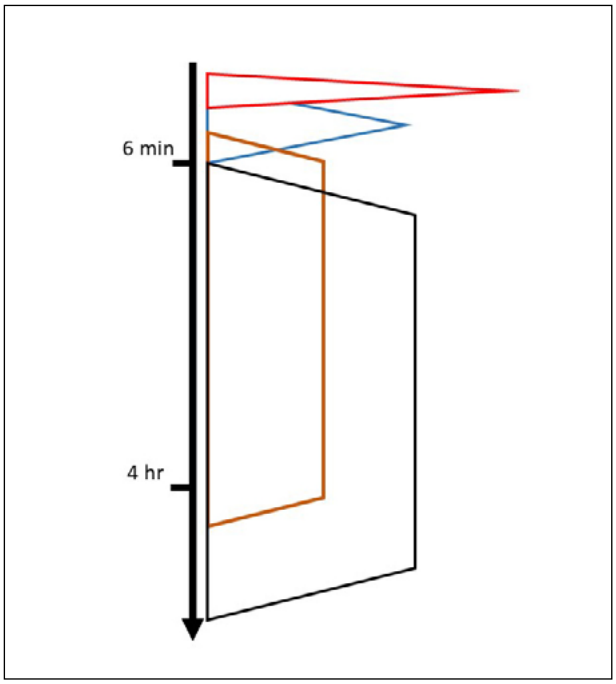

Figure 3. Schematic representation of the cellular energy handling *versus* time of exercise. From the top red: free ATP and phosphocreatine/creatine system, blue: anaerobic glycolysis (muscular glycogen), brown: aerobic oxidation (muscular glycogen, plasma glucose, liver glycogen), black: aerobic oxidation (adipose tissue triglycerides, plasma free fatty acids).

CPT (carnitine palmitoyltransferase) II muscle deficiency is the most common form of muscle fatty acid metabolism disorders, inherited as autosomal recessive condition. It is one of the possible phenotypes related to mutation in the CPT system, consisting of two enzymes (CPT I and CPT II), involved in the transport of long-chain fatty acids into the mitochondrial compartment. The enzymes are located in the outer (CPT I) and inner mitochondrial membrane (CPT II) (31).

Three phenotypes of CPT II deficiency are known: a lethal neonatal form, a severe infantile hepatocardiomuscular form, and a mild myopathic form (32). It has also been reported an antenatal onset of CPT2 in a small subset of patients causing malformations including brain dysgenesis and neuronal migration defects (33). Muscle CPT II deficiency is the most frequent type of CPT II deficiency. Clinical features of the mild myopathic form are muscle weakness, myalgia, pain and rhabdomyolysis, possibly causing renal failure. Joshi et al. (2014) (34) showed that the manifestation of clinical symptoms occurred more frequently during infancy (one to 12 years old) than during adolescence (13-22 years old) and adulthood (> 22 years old). Trigger factors are prolonged exer-

cise, fasting, infections, fever and exposure to cold (34).

In muscle CPT II deficiency, symptoms occur only intermittently. Lipid accumulation in muscle fibers can be detected (34). In approximately 90% of the patients the molecular basis is a p. S113L mutation in homozygous or heterozygous state with an allele frequency of 60-70% and more than 60 mostly private mutations (35). The normal protein content and enzyme activity allow a normal function of the CPT system in situations without stress on the fatty acid metabolism (36).

The biochemical consequences of the disease-causing mutations are still discussed controversially.

In former studies, CPT activities in muscles of patients with CPT II deficiency ranged from not detectable (38, 39) up to normal (41, 42). It is known that CPT I but not CPT II is sensitive to inhibition by malonyl-CoA. Trevisan et al. showed an almost complete inhibition of total CPT activity in patients by malonyl-CoA (43). So, it was inferred that the normal malonyl-CoA-insensitive CPT II activity is deficient. Due to the demonstration that total CPT activity is normal under optimal assay conditions but abnormal when inhibited by malonyl-CoA, palmitoylcarnitine, carnitine and Trition-X100 (non-ionic surfactant), the hypothesis raised of an abnormally regulated enzyme with a normal total CPT II concentration. CPT II with the S113L mutation, is most vulnerable to inhibition when it is most needed (44).

The study of Ørngreen and colleagues (45) about fuel utilization in CPT2 patients showed that they are unable to increase long-chain FAO during long-term, low-intensity cycle exercise, and carriers of single *CPT2* gene mutations also can have impaired fat oxidation during exercise, which may explain milder symptoms of CPT II deficiency in these subjects. The authors demonstrated normal FAO at rest but impaired FAO during exercise in CPT II deficiency patients. Furthermore, they showed that the CPT II patients covered their energy deficit by carbohydrate metabolism, by enhanced muscle glycogenolysis (45).

McArdle disease, or glycogen storage disease type 5 (GSD5), is an autosomal recessive disease, due to myophosphorylase deficiency and represents the commonest muscle glycogenosis (46). The typical clinical picture of McArdle disease consists of acute crises of early fatigue and contractures, occasionally accompanied by rhabdomyolysis and myoglobinuria usually triggered by muscle tasks that predominantly involve (aerobic/anaerobic) glycolysis for ATP production (47, 48). Disease time to onset is usually in the first two decades of life, but it can also occur in infancy with progressive weakness, hypotonia, respiratory distress, and early death (47, 49), and later in adult life, with atypical symptoms, such as pain and tenderness in the masticatory muscles when eating (50) or asymmetrical, slowly progressive, limb weakness and muscle wasting which may remain focal (51). The so-called 'second wind' phenomenon, that is marked improvement in tolerance to dynamic exercise (eg, bicycling at a constant, submaximal wattage) after 6-10 min of exertion, with subsequent disappearance of previous tachycardia, is a unique characteristic of patients with McArdle disease (52). Patients lack the enzyme required to mobilize glucose-1-phosphate from skeletal muscle glycogen myophosphorilase, the only isoform of glycogen phosphorylase expressed in skeletal-muscle tissue. Myophosphorylase catalyzes the breakdown of muscle glycogen into glucose-1-phosphate in muscle fibers, preventing the patients to obtain energy from their muscle glycogen stores (53). Muscle glycolysis is not totally impaired in these patients, because the muscle fibers of McArdle disease patients can still take up glucose from the blood and convert it into glucose-6-phosphate, which then enters glycolysis (53). In McArdle disease, due to

Table 1. Muscular adaptations to endurance and resistance type exercise. Arrows indicate: ↑ minimal change; ↑↑ moderate change; ↑↑↑ large change; ↓ decrease; ↔ no change. Modified with permission from Physical Activity. Giuseppe D'Antona. Poletto publisher 2019 (1st edition) (62).

Muscular adaptation	Endurance exercise	Resistance exercise
Hypertrophy	↔	↑↑↑
Strength	↔↓	↑↑↑
Cross sectional area	↔	↑↑↑
Neural adaptation	↔↑	↑↑↑
Anaerobic capacity	↑	↑↑
Lactate tolerance	↑↑	↔ ↑
Myofibrillar protein synthesis	↔ ↑	↑↑↑
Mitochondrial biogenesis, mitochondrial density, oxidative capacity	↑↑↑	↔↑
Fatigue resistance	↑↑↑	↔ ↑
Capillarization	↑↑↑	↔

the block in glycogenolysis, muscle oxidative phosphorylation (OXPHOS) capacity, is also impaired and skeletal muscle is unable to produce pyruvate (54), causing a marked decrease in skeletal-muscle capacity for ATP synthesis through OXPHOS, and in accumulation of ADP and Pi in muscle fibers. This, in turn, can potentially inhibit the myofibrillar ATPase, the sarcoplasmic reticulum Ca2_ ATPase (SERCA1) and the Na^+-K^+ ATPase reactions, leading to decreased contractility and premature fatigue (55-57). Deficient glycogen dependent ATP supply can result in further downregulation of Na^+-K^+ ATPase in the skeletal muscle fibers of patients and in impaired membrane excitability and muscle cramping (54). The causes for exercise rhabdomyolysis in these patients are not completely understood: either the mechanical stress imposed by large muscle glycogen stores (48), the downregulation of muscle Na^+-K^+pumps (55) (which are responsible for maintaining cellular volume and integrity), or increased oxidative stress (57) have been supposed to be involved. Furthermore, elevated Ca^{2+} levels in the sarcoplasm (owing to the above mentioned downregulation in SERCA1) might activate proteases, phospholipases, and other catabolic enzymes that cause structural damage (58), besides causing muscle fatigue and cramps, Haller and Vissing (59) studied the 'second wind' phenomenon. Either when occurring spontaneously, either when glucose induced, it was due to a substrate-dependent increase in muscle oxidative capacity. Also, by providing glycogen-derived pyruvate a small amount of residual myophophorylase activity normalizes the oxidative deficit of muscle phosphorylase deficiency and may eliminate the 'second wind'. The spontaneous second wind seemed to be related to the lack of fuel that is critical for normal oxidative metabolism and makes muscle oxidative capacity dependent on the changing availability of extramuscular fonts, such as free fatty acids, due to the blocked glycogenolysis. Furthermore, patients with McArdle disease have been reported to be insulin resistant in terms of glucose uptake, glycogen synthase activation, and alterations in fuel oxidation. As a result, the ability of insulin to increase fat and carbohydrate oxidation is limited, and the findings suggest that skeletal muscle glycogen levels play an important role in the regulation of insulin-stimulated glycogen synthase activity (60). The onset of McArdle disease may be at the teenage years during which decreased sensitivity to insulin has been noted, so that there may well be limited transport and oxidation of extracellular glucose and nonesterified fatty acids resulting in reduced exercise tolerance. Insulin sensitivity decreases with age which may play a part in the late onset of some cases (61).

Considering the inefficient utilization of glycogen in McArdle disease and long chain fatty acids in CPT2 deficiency, a working hypothesis may be the application of repeated short duration bouts followed by appropriate rest in both cases. This approach may allow to gain the benefits of exercise through phosphocreatine consumption as the main energy substrate to fuel contraction in McArdle disease and through glycogen consumption in CPT2 deficiency in presence of a strict compliance to a dietetic regimen in which reduction of fat is adequately compensated by carbohydrates intake.

Preliminary results on the feasibility of this approach in ameliorating the muscle function in McArdle disease have been recently put forward by Santalla and collaborators (54).

Conclusions and perspectives

Without the deep knowledge of the physiological adaptations to exercise training, declined in terms of quality, intensity, frequency and duration, it is not possible to ascertain whether it is, or not, beneficial in neuromuscular diseases. This knowledge should be translated to pathophysiology, with the aim to find out the optimal matching between potential training adaptations and clinical evolution of the diseases. Without attempting this approach, feasibility of physical interventions will be far to be established.

Conflict of interest

The Authors declare to have no conflict of interest.

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Exercise in neuromuscular disorders: a promising intervention

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Although performing exercise studies in patients with neuromuscular disorders (NMD) is difficult, the number of randomized controlled trials is steadily increasing. There is growing evidence for a positive effect of aerobic exercise in several NMD, on the other hand, the evidence for the effect of strength training is still scarce. Many NMD patients are captured in a vicious circle of physical inactivity, and it is important to let patients adhere to an active lifestyle, in order to prevent further chronic cardiovascular and muscle deconditioning and increased cardiovascular health risks. Exercise has to be prescribed as if it is medicine, in order to increase the adherence of patients and to optimize the efficacy of the intervention. Exercise in NMD is safe, although for some metabolic myopathies there is a contraindication for strenuous exercise. In NMD known to affect cardiac muscle, it is usually safe to exercise, but the consultation of a cardiologist is advised. Based on recent research, an increase in physical activity of moderate intensity and of sufficient duration, i.e. a physically active lifestyle, could be at least as effective and relevant as physical training. Underlying mechanisms of effect of exercise could be the influence of epigenetic mechanisms and the anti-inflammatory effect of exercise, but further studies are needed to confirm these hypotheses.

Key words: neuromuscular disorders, exercise, physical activity

Introduction

Scientific research regarding exercise in neuromuscular disorders

There are several limitations to consider when reviewing training studies in neuromuscular disorders (NMD). First of all, there are very few randomized controlled trials, each small in sample size. Second, studies are not immediately comparable because the training protocols often differ regarding the intensity and duration of the training, targeted muscle groups, type of strength or aerobic training, i.e. isometric or isokinetic, high or low intensity, and type of controls. The majority of exercise training studies have evaluated non-supervised home programs of relatively short duration, using submaximal, low-intensity training levels. The short duration of most studies does not allow differentiation between neural training effects versus muscle fiber hypertrophy and a real increase of aerobic capacity, which generally occurs after six weeks. Third, the compliance of patients, especially during non-supervised home protocols, is a possible confounding factor in all training studies. Fourth, because of the scarcity of patients of each NMD, studies have often grouped together several disorders. Persons with different types of NMD may however respond very differently to exercise (1). Fifth, some studies used the contralateral non-exercised muscle as a control in muscle strengthening interventions (2-4). The problem with this study design is that there may be confounding cross-over effect in the non-exercised muscles. Moreover, one can hardly expect meaningful effects of a single-limb training program on a patient's activities, participation and well-being (1).

Altogether, scientific research regarding the effect of training in NMD is still scarce, but steadily growing. In 2013, a Cochrane review was published on aerobic training and strength training in muscle diseases (5). Only five randomized clinical trials (RCTs) met the inclusion criteria. The other studies were not randomized or used a healthy control group. The authors of the Cochrane review concluded that strength training in facioscapulohumeral muscular dystrophy (FSHD) and myotonic dystrophy did not show any positive, but also no negative effect. A combination of strength training and aerobic training is not harmful and shows a positive effect on aerobic capacity in patients with mitochondrial myopathy.

In 2004, a Cochrane review on training in patients with peripheral neuropathy appeared (6). Only one study was included in this review (7). This study in 34 patients

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with Charcot-Marie-Tooth (CMT) consisted of 24 weeks of isokinetic strength training of hip extension and knee extension and showed an improvement on the isokinetic knee extension force. Also, the required time for the 6-meter walk test decreased significantly. The authors of the Cochrane review conclude that there is little evidence for training in peripheral neuropathies, but that there is some evidence for strength training in CMT.

In 2013, a Cochrane review was published on training for Amyotrophic Lateral Sclerosis (ALS) and motor neuron disorders (8). In this Cochrane review, two trials were included that grouped the results of "endurance exercise" (unspecified) of limbs and thoracic muscles in 25 ALS patients (9) and strength training of arms and legs in 27 ALS patients (10). A significant improvement on the Amyotrophic Lateral Sclerosis Functional Rating Scale was observed after 3 months. There was no improvement in quality of life (measured with the SF-36), fatigue (measured with the Fatigue Severity Scale) or isokinetic and isometric muscular strength. No adverse reactions were reported. The general conclusion is that the numbers of patients in these studies are too small to be able to extrapolate the results to the general population.

After the appearance of these Cochrane reviews, more (large) RCTs have been published on exercise in NMD. The "No Use is Disuse" study describes a positive effect of cycling training with dynamic support on the functioning of boys with Duchenne, measured with the Motor Function Measure (MFM) (11). After 24 weeks, the MFM score had remained stable in the training group while it had dropped in the control group. No adverse effects of the training were found. The mechanism by which training could oppose the physical deterioration in children with a NMD is still unclear. Muscle fibers in NMD patients are abnormally vulnerable to contraction-induced injury due to the absence, or lack, of mechanical reinforcement of the sarcolemmal membrane (12). Eccentric exercises should therefore be avoided (13).

Three recently published RCTs in FSHD show a positive effect of cycling training on respectively aerobic capacity, walking speed, muscular strength, fatigue and of High Intensity Interval training on aerobic capacity (14-16). Fitness and strength training have a positive effect of on aerobic capacity and quality of life in polymyositis and dermatomyositis (17).

The Dutch FACTS-2-NMD study included three RCTs on the effect of cognitive behavioral therapy (CBT) and aerobic exercise in respectively ALS (18), post-polio syndrome (19) and FSHD (20, 21). An increase in the degree of physical activity was part of the CBT intervention. The FACTS-2-FSHD study studied the effect of 16 weeks of cycling training or CBT (including an activity module) in 57 patients with FSHD and severe chronic fatigue (22). After both cycling training and CBT patients were less fatigued and physically more active. After CBT, there was an increase in quality of life, the patients found themselves more active and the sleep quality improved. Approximately 80% of the participants in both intervention groups remained active even after the study. MRI measurements of the thigh showed a deceleration of the increase in fatty infiltration, after both cycling exercises and CBT, compared to the control group.

In contrary to the effect of cycling training and CBT, after 16 weeks of CBT or physical training in patients with Post-polio syndrome, no effect was seen on any outcome measure (19). The reason for the absence of effect is not yet known. No differences were found in fatigue-related cognitions between patients with Post-polio syndrome and patients with FSHD (23).

Recently, the results of the FACTS-2-ALS study were published. In this trial, 16 weeks of cycling training and usual care was not superior to usual care alone in preserving health related quality of life in ambulatory ALS patients. However, the study was unfortunately underpowered, because only 10 patients completed the protocol. The authors concluded that cycling training and usual care may preserve disease-specific health related quality of life in slow progressors.

Data from the "OPTIMISTIC" study, in which severely fatigued adult patients with myotonic dystrophy type 1 were included showed that, by month 10, cognitive behavioral therapy increased patients' capacity for activity and participation, compared with standard care alone. Additionally, several secondary outcome measures of fatigue (Checklist Individual Strength, subscale fatigue and the fatigue and daytime sleepiness scale), exercise capacity (6-min walk test), and objective physical activity as measured with accelerometry were significantly improved with cognitive behavioral therapy compared with standard care alone (24). However, improvements in outcome measures for quality of life and disease burden were not significantly different between groups at 10 months. It should be noted that the trial was not powered for any of the secondary outcome measures except the 6-min walk test.

Strength training

The studies that have been conducted on strength training have been small, usually with mixed intervention groups and often without control groups (5, 25). The results of these studies must therefore be interpreted with caution. The aim of strength training is to maintain existing strength or reduce the progression of muscle weakness, and not necessarily to strengthen the affected muscles (26). Any increase in muscle strength is probably the

result of effects on muscles that are relatively unaffected by the neuromuscular disease, but which may be deconditioned as a result of inactivity. Low intensity strength training (10-15 repetitions) may be beneficial for persons with sufficient muscle strength to move against gravity (27). There is no evidence that heavy strength training has additional beneficial effects beyond those of moderate exercise, and such training should therefore be avoided as it may lead to overloading of muscles (27). Heavy eccentric strength training is not recommended either for the same reason (28). The latter is also thought to be a frequent cause of serious muscle injury in those without NMD. Studies of limb girdle muscular dystrophy, FSHD, myotonic dystrophy type 1 and mitochondrial myopathies have shown that moderate strength training is safe and can have an impact on muscle strength and endurance, but results vary (27-29). Although studies generally point towards beneficial effects of moderate strength training, there is not yet sufficient evidence to make general recommendations for patients with NMD (5, 25). Major individual differences are seen in the intensity of training that can be tolerated, both between patients with different muscle diseases and among those with the same genetic disease variant.

Vicious circle of inactivity

When a training program is created, it is necessary to take into account various factors, among which are the diagnosis, the progressiveness of the condition, the condition of the heart and lungs, complaints of fatigue and pain, age, past and current activity level, kinesiophobia, the availability of exercise tools and lack of facilities. Sometimes it is necessary first of all to overcome kinesiophobia. Kinesiophobia is often based on years of belief that training is harmful to muscles. Many patients with NMD are captured in a vicious circle of inactivity (see Figure 1). Due to fatigue, patients often alter their lifestyles and reduce their activities. Low physical activity levels may lead to even greater weakness and atrophy of skeletal muscles, which causes a vicious circle of disuse and weakness. Physical inactivity in turn can lead to chronic cardiovascular and muscle deconditioning and increased cardiovascular health risks (30). For example, the average maximal oxygen uptake is abnormally low in patients with NMD (31). Body-composition measurements in NMD patients by various methods indicate reduced fat-free mass and increased adiposity in these patients relative to able-bodied control subjects of comparable ages and body weights (32, 33). The excess body fat of NMD patients additionally impairs mobility and further increases the risk of cardiovascular disease.

It is important to break this circle with training and encouraging an active lifestyle, especially in patients with no cardiac or pulmonary co-morbidity, such as in patients with FSHD.

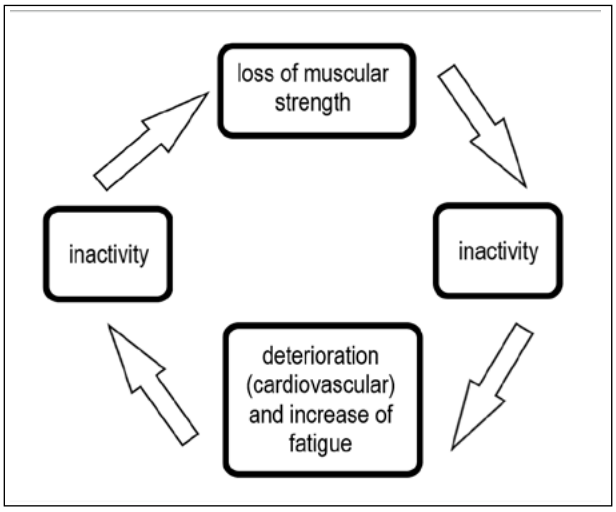

Figure 1. The vicious circle of inactivity. It is important to break this circle with training and encouraging an active lifestyle, especially in patients with no cardiac or pulmonary co-morbidity, such as in patients with FSHD.

Exercise in neuromuscular disorders is safe

In the past, clinicians were reluctant to prescribe exercise to patients with NMD. They often referred to possible muscle damage due to overuse. However, this hypothesis has never been proven with thorough research. Because of the weakness of the muscle membrane there is concern about the potentially damaging effects of eccentric and high-intensity muscle contractions during strength training. In animal models of NMD, there is evidence that eccentric contractions, known to stress muscle fibers, cause greater cell injury to these dystrophic muscle fibers. Although transferring results from animal studies to humans must be done with caution, eccentric training studies in NMD patients are so far being avoided. For some metabolic myopathies there is a contraindication for strenuous exercise. In lipid myopathy, rhabdomyolysis and myoglobulin may occur during training or strenuous exercise due to a defect in intramitochondrial transport and the use of fatty acids or glycogen. Cardiac involvement is common in some NMD. These include many muscular dystrophies (Duchenne, Becker and Emery-Dreyfuss muscular dystrophies, myotonic dystrophy types 1 and 2, limb-girdle muscular dystrophy types 1B, 2C-F, 2G and 2I) and certain congenital myopathies (34). Cardiac involvement may manifest as cardiomyopathy or

cardiac arrhythmias. Training is always contraindicated in left ventricular/aortic outflow obstruction, threatening arrhythmias and cordial congestion. However, recent studies now also show a positive effect of training on the chance of survival and quality of life in patients with heart failure. In cases of known or suspected cardiac involvement, therefore, it is important for the patient to be monitored by a cardiologist irrespective of whether or not they have symptoms. In NMD known to affect cardiac muscle, it is usually safe to exercise, but advice on physical activity must be given after consultation with a cardiologist and preferably following a cardiac examination (34).

Exercise is medicine

What proved to be impossible in drug trials up to now did succeed in research using behavioral and exercise interventions. In FSHD and myotonic dystrophy, aerobic exercise training as well as CBT did not only reduce the degree of disease burden, but also established a beneficial effect at the muscular level probably as a result of increased physical activity. The question arises whether the "number needed to treat" and the (minor) side effect profile based on the FACTS-2-FSHD trial can be achieved with medication in future studies (35). Nevertheless, the scientific acceptance of exercise as medicine in NMD is still difficult. There is still uncertainty (and even scepsis) with regard to the underlying mechanisms. The acceptance of functionally targeted interventions can possibly be accelerated by providing more evidence for underlying mechanisms through basic research. However, the biggest challenge is to get the scientific and clinical world moving forward. This requires a societal change. A change in lifestyle requires a greater effort from patients and practitioners than taking or prescribing a drug. And even medication adherence is limited (36). In CBT, therapy sessions are usually structured by a collaboratively agreed-on agenda. Homework sessions encourage active participation. And during aerobic exercise training, patients exercise at home in addition to supervised training. Research has shown that a patient-centered approach improves treatment adherence in chronic patients and also improves job satisfaction in health professionals (37).

Guidelines for prescribing exercise in neuromuscular disorders

Currently, evidence-based exercise prescriptions do not exist for patients with NMD. Both patients and clinicians experience difficulties in preparing training programs (38). The recommendations for an effective aerobic exercise program by the American College of Sports Medicine are difficult to adhere to by many patients with NMD: 20 to 60 minutes aerobic exercise, 3 to 5 days per week at an intensity of 40 to 85% of the heart-rate reserve (39).

Furthermore, regular exercise tests cannot always be applied. Due to reduced muscular strength, it is often not possible to achieve the theoretical maximum heart rate and a maximal exercise test is less suitable to determine the training intensity. Recently an article has been published that describes that the anaerobic threshold in patients with post-polio syndrome could be determined by a submaximal exercise test in nearly 80% of the participants. If the anaerobic threshold cannot be determined, the authors advise to work with a Borg scale (40).

Both patients and practitioners experience difficulties in drawing up training schedules. Voorn et al evaluated the current application of aerobic exercise in adult neuromuscular rehabilitation in a cross-sectional survey (41). All respondents (n = 52) prescribed aerobic exercise and in a wide variety of NMD, mostly applying sessions of more than 20 min, two days per week, over a period of 9-16 weeks, using different exercise modes and methods to target intensity. The majority (81%) agreed that aerobic exercise should be incorporated into neuromuscular rehabilitation. However, all respondents perceived barriers to the application of aerobic exercise in one or more domains, and 77% of the respondents indicated needing support to improve application of this type of training, mostly with respect to screening procedures (54%) and dosing of exercise programs (48%).

The results of the FACTS-2-FSHD and OPTIMISTIC study and the experiences of the physiotherapists showed that the Borg scale, the talk test (which means that one can carry on a light conversation while exercising), and the rule that activities of daily life should not be negatively influenced by the exercise program are useful indicators for a proper exercise intensity (42). Previous research from Canada has shown that, in clinical practice, the exercise intensity is frequently determined based on simple tests such as the response of participants to the training, the Borg scale and/or the talk test (43).

In any case, to maintain the highest possible compliance, it is recommended to prescribe exercise as medicine with a clear description of exercise duration, frequency, intensity, location and supervision, and to search for a physical activity that the patient prefers. The barriers that patients still experience when exercising such as costs, shame for their limitations, and lack of facilities should be taken into account (44). It is for a reason that the FSHD lifestyle guide refers to "one has to move, if possible. "It is important to realize that a patient does not always have to exercise. The results of the FACTS-2-FSHD study emphasize the relevance of a physically active lifestyle.

Ideally, an intervention for the improvement of chronic fatigue would no longer be needed. When adherence to a physically active lifestyle is already recommended shortly after the diagnosis, and physical activity and exercises are maintained, a patient may not be caught in a downward spiral as a result of physical inactivity.

Physical activity *versus* physical training

During CBT, a reliable increase in physical activity is an important part of the treatment. Aerobic exercise training focuses primarily on physical exercise, for example on an ergometer. At first sight, physical activity and physical exercise seem to be similar, but on second thought they are substantially different. Physical activity is defined as "any effort of skeletal muscles resulting in higher energy consumption than in resting conditions (45)". Physical (aerobic) exercise is a form of physical activity and is defined as "planned, structured and repetitive exercises with an increasing magnitude and intensity in order to maintain or improve physical fitness or aerobic capacity (45)".

The recommendations on physical activity for the healthy population have been prescribed in the Dutch Standard for Healthy Exercise (Nederlandse Norm Gezond Bewegen; NNGB). This standard aims at a physically active lifestyle and comprises a total of 30 minutes of exercise of moderate intensity (at a slightly higher heart and respiration rate than usual) of at least 4.0 MET a day, in blocks of at least 10 minutes at least five days a week.

The MET value or the metabolic equivalent is a unit of measurement within physiology expressing the amount of energy for a certain physical effort compared with the amount of energy required at rest. One MET (metabolic equivalent) corresponds to the resting metabolic rate, the amount of energy consumed during inactivity. One MET is equivalent to 3.5 ml of oxygen per kg of body weight per minute. The NNGB leads to a total duration of 150 minutes of physical activity per week of 4.0 MET, which implies a total increase of 450 MET per week compared to a physically inactive lifestyle. Physical activity within the NNGB includes not only sports activities but also daily-life activities such as household activities, cycling or walking the dog.

For physical exercise, the Dutch government has issued a standard for physical fitness. This standard is aimed primarily at maintaining aerobic capacity through physical exercise and requires intense physical activity of at least 6.0 MET for at least 20 minutes and at least three times a week. Although the intensity is higher than in the NNGB, the total length and the increase in MET per week is less, namely 300 MET. Thus, one can still have a physically inactive or sedentary lifestyle, in spite of meeting the standard for physical fitness. In other words, the NNGB leads to a higher level of physical activity than the Dutch standard for physical fitness.

The Dutch standard for physical fitness and the NNGB are defined only for healthy adults and for healthy elderly. The minimum standard for patients with a chronic disease, including FSHD, has not yet been defined. The NNGB not only leads to a higher level of physical activity; this standard is probably also more feasible for patients with FSHD, because daily-life activities are included. In other progressive neurological diseases, such as Parkinson's disease, there is already growing evidence for a positive effect of decreasing the sedentary time (46). The question now arises whether physical exercise of minimum intensity and an increase in aerobic capacity are really necessary for the treatment of fatigue in patients with NMD. Would an increase in physical activity of moderate intensity and of sufficient duration, i.e. a physically active lifestyle, not be much more relevant?

Underlying mechanisms of effect of exercise and physical activity

Both CBT and aerobic exercise slow down the progression of fatty replacement of muscle tissue in FSHD. This raises the question: "How is it possible that an increase in physical activity causes a beneficial effect at the muscular level?" Epigenetics and the inflammation theory can possibly offer an explanation.

FSHD is a genetic disorder. More than 95% of cases of FSHD are associated with the absence of certain pieces of DNA at the end of chromosome 4 (genetic location: 4q35), the so-called D4Z4 deletion. This results in expression of the harmful DUX4 gene and production of a toxic protein (DUX4) that causes dystrophy (fatty replacement) of the skeletal muscles (47). The conversion of DNA into functional products for the cell, such as proteins, is dependent on both the DNA code itself (genetics) as well as on factors that may affect the activity of genes (gene expression), so-called epigenetic factors (48, 49). Epigenetic phenomena determine the "open" or "closed" state of parts of the genome and, thus, control the "on" or "off" position of genes. This can take place by means of changes in methylation, RNA molecules (intermediates between DNA and protein), or by the so-called histone proteins that are involved in the packing (and hence access) of the DNA in the chromosomes. FSHD is, therefore, an epigenetic disease (49). In FSHD patients, the degree of methylation of the DNA influenced by epigenetic factors plays an important role. Sometimes a small molecule group is added to the DNA, a so-called methyl group, which carries additional information. FSHD patients with a D4Z4 deletion (FSHD-1) show a decreased methylation of the D4Z4 region on the chromosomes 4q and 10q.

However, the degree of methylation is not already determined at birth. It varies between persons and may change under the influence of environmental factors during one's lifetime.

Epigenetic factors ensure that the genetic defect in different people, even within families, can be expressed differently (50). In recent research, the difference in severity of the disease within families with FSHD is, among other phenomena, attributed to epigenetic factors (51).

An increase in physical activity and/or physical exercise can cause changes in the DNA methylation of healthy persons (52). It is possible that a physically active lifestyle is an epigenetic factor for FSHD and can slow down the progression of fatty replacement of muscle tissue by changes in DNA methylation. It is not a coincidence that the perpetuating factors of fatigue, i.e. physical inactivity, sleep disorders and pain, are known epigenetic factors (53). The degree of methylation can be different for every individual cell under the influence of epigenetic factors. This could be an explanation for the differences in effect on the fatty replacement between different muscles of patients with FSHD after CBT and aerobic exercise, as measured by quantitative magnetic resonance imaging (MRI) (54). To conclude, the first hypothesis is that AET as well as CBT influence the fatty replacement of muscle tissue by modifying epigenetic mechanisms.

A second explanation can perhaps be found in the beneficial effect of physical activity on inflammation. Inflammatory reactions seem to play a role in the increase in fatty replacement of muscle tissue in patients with FSHD and also in the development of chronic experienced fatigue in various neurological disorders (55). In approximately 5% of the muscles of patients with FSHD, edema has been observed using MRI(54, 56). There is evidence that an increase in edema is preceded by inflammation and is followed by fatty replacement of the muscle tissues (57, 58). The inhibition of inflammatory reactions could, therefore, theoretically slow down the progression of the disease. In healthy people, the anti-inflammatory effect of physical activity has already been proven extensively (59). Not only immune cells produce molecules that play a role in inflammatory responses (cytokines). Skeletal contracting muscles also release significant amounts of interleukin IL-6. IL-6 is a pro-inflammatory cytokine, in this situation also called a myokine. IL-6 causes inflammation when it is excreted as a cytokine by immune cells, but fights inflammation when it is released as a myokine by muscle cells. This is most likely because other cytokines are not produced anymore and another, "healthier" environment has been created (60, 61). In healthy adults, the production of IL-6 during exercise is for at least 50% related to the intensity and duration of the exercise (62, 63) To conclude, the second hypothesis is that aerobic exercise and CBT influence the fatty replacement of muscle tissue by positively influencing inflammatory reactions. This again argues in favor of a physically active lifestyle beyond physical exercise of limited duration.

To summarize, the evidence regarding the effect of aerobic exercise and a physically active lifestyle in NMD is increasing. However, there is still a strong need for a more tailored approach, in order to increase the magnitude of effect.

Conflict of interest

The Author declare to have no conflict of interest.

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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 it's 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

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dystrophy", "facioscapulohumeral 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 training", "aerobic exercise", "endurance training", "endurance 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 provided a well-described exercise intervention. We included 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 focusing on training of respiratory muscles were also excluded. 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 LGMD2L. Patients with LGMD2L completed a 10-week moderate aerobic training program (8). The six patients completing the training experienced improvements in fitness, functional capacity, and lower limb strength. No adverse events were reported. Moderate endurance training also improved aerobic capacity in 9 patients with LGMD2I (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-induced 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

Sczesny-Kaiser et al. (11) performed a treadmill exercise study using hybrid assistive limb (HAL®) in three LGMD patients; LGMD2A, LGMD2I, 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 sample size, the results are interesting, and the technology allows 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-supported training allows patients to work at a certain percentage 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 exercise 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 galvanic 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 muscle. The exercise therapy group consisted of bilateral progressive resistance exercise of the deltoid and quadriceps muscles. The electrical stimulation therapy group gained muscle strength and physical function improved. The exercise 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 improvements 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_{2max}	VO_{2max}, lower limb strength, 6MWT, 5 x STS, 6SST.
Cycling N = 9 (9)	12 weeks	50 sessions in total 30 min/session	65% of VO_{2max}	VO_{2max}, workload, self-reported physical endurance, lower limb muscle strength, and walking distance.
Strength: LOIT N = 6 HIT N = 3 Control group N = 6 (10)	 6 months 3 months	 3 days/week Twice at home and once at lab 3 days/week at lab	Low intensity Knee extension, Elbow flexion 40% of 1RM, increase with 5% every other week 3 sets x 12-15 reps 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	Bicep strength and endurance, wrist flexion, extension, and endurance
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

▼

Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Anti-gravity: N = 3 (12)	10 weeks of control period 10 weeks of training	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	70-80% of HRmax 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 Strength N = 13 (14)	8 weeks	3 days/week	Shoulder abduction Knee extension 25% 1RM, 2 sets x10 reps 30% 1RM, 3 sets x 10 reps 35% 1RM, 3 sets x 10 reps 50% 1RM, 3 sets x 10 reps Monophasic wave type. Surface electrodes. Pulse frequency 50Hz, voltage output 0-500 V, pulse duration 200 μσ, duty cycle 5:10, 10 minutes of stimulation	Strength, VAS, climb 8 steps, 10MWT, dressing with t-shirt, endurance (number of reps per minute), and modified Lawton ADL.

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-

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 N = 11 Control group N = 7 (15)	12 weeks 12 months F/U	50 sessions in total 30 min/ session	65% of VO_{2max}	VO_{2max}, workload, hip abduction, and ankle plantar flexion and dorsiflexion
Treadmill N = 1 (16)	4 weeks	3 days/week 20 min/ session	65-80% HRmax	Lower limb strength, TUG, 10MWT, and 6MWT
Strength: LOIT N = 2 HIT N = 1 Control group N = 6 (10)	 6 months 3 months	 LOIT 3 days/week Twice at home and once at lab HIT 3 days/week at lab	Low intensity: Knee extension, Elbow flexion 40% of 1RM, increase with 5% every other week 3 sets x 12-15 reps 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	Bicep strength and endurance, wrist flexion, extension, and endurance
Anti-gravity: N = 5 (12)	10 weeks of control period 10 weeks of training intervention	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 = 5 (13)	10 weeks control period 10 weeks of training intervention	3 days/week 40 min/ session	70-80% of HRmax 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

sity 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

Table 3. A representation of exercise interventions done in FSHD. Number in parenthesis represents the article reference.

Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Cycling N = 8 Control group N = 7 (17)	12 weeks	5 days/week 35 min/session	65% VO_{2max}	VO2max, workload, and ADL
Cycling + post exercise protein-carbohydrate supplement N = 18 Cycling + placebo supplement N = 13 Control group N = 10 (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

▼

Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Cycling N = 20 Cognitive-behavioral therapy N = 13 Usual care N = 24 (19)	16 weeks	3 days/week (2 days at home and 1 day supervised) 38 min/session, including a 5 min warm up 30 min exercise 3 min cool down Cognitive-behavioral therapy comprised of 6 modules: Dysfunctional cognitions regarding fatigue, activity, pain, or other symptoms; fatigue catastrophizing (a cognitive process that involves negative outcome expectations from fatigue); dysregulation of sleep or activity; poor social support; and negative social interactions. Both aerobic exercise therapy and cognitive behavioral therapy were found to be superior to usual care in reducing fatigue	50-65% HRmax 12-14 RPE (Borg Scale)	Fatigue
Cycling N = 8 Control group N = 8 (20)	24 weeks	3 days/week 35 min/session	2 sessions at 60% max aerobic power 1 session interval training 40% and 80% max aerobic power	VO_{2max}, 6MWT, and fatigue severity scale
Strength N = 34 Control N = 31 (21)	52 weeks	3 days/week	10 RM, 2 sets x 5-10 reps Dynamic and isometric strength: Elbow flexion and ankle dorsal flexion	1RM, and dynamic elbow flexor strength
HIT: Cycling N = 6 UC N = 7 Control group N = 7 (22)	8 weeks supervised 8 weeks with 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. 3 days/week	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	VO_{2max} and workload
NMES N = 9 (23)	5 months	5 days/week 20 min/session	Rise time 1.5s; steady tetanic stimulation time: 6s; fall time 1.5s	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 (24)	12 weeks	5 days/week 35 min/session	65% of VO_{2max}	Self-reported improvements in ADL, VO_{2max}, and workload
Strength N = 27 Control group N =14 (25)	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
Strength N = 6 (26)	12 weeks	3 days/week	Knee extension 60-80% of 1RM, 3 x 10 reps	1RM
Strength N = 33 (27)	24 weeks	3 days/week 30 min/session	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

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Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Strength N = 33 (28)	24 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
Functional electrical stimulation induced cycling N = 4 Strength and cycling N = 4 (29)	3 weeks 6 weeks	Functional electrical stimulation: 30 minutes 5 days/week Strength: 5 days/week 30 min/session Cycling: 5days/week 30 min/session	Functional electrical stimulation: Frequency of 30 Hz (pulse width, 200 µseconds) Strength training: Knee extension, knee flexion, ankle dorsiflexion, ankle plantarflexion 2 sets x 10 reps at 60% of 1RM (week 1-3) 2 sets x 5 reps at 80% of 1RM (week 4-6) Cycling: 60% of HRmax	MRC, 6MWT and 10MWT
Hand-training Cross-over study N = 9 Group A N = 4 Group B (30)	12 weeks of training 12 weeks of wash out 12 weeks of control	Minimum of 27 sessions 60 min/session	Week 1-4: 1 set x 10 reps Week 5-8: 2 sets x 10 reps Week 9-12: 3 sets x 10 reps Isolated finger movement: 1 set x 3 reps, 2 sets x 3 reps, 3 sets x 3 reps Wrist extension/flexion Finger extension/flexion Isolated finger extension/flexion Thumb extension/flexion Finger adduction/abduction Stretching wrist in flexion/flexion	Handgrip, pinch, and wrist strength

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-

Table 5. A representation of exercise interventions done in McArdle disease. Number in parenthesis represents the article reference.

Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Cycling N = 8 (32)	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 (33)	12 weeks	4 days/week 60-90 min/session	65-70% of HRmax	Aerobic capacity and work load
Acute: Cycling (strictly monitored) N = 46 Control group N = 46 Chronic: Walking or cycling N = 9 (34)	Acute: 1 day Chronic: 8 months	1 day 5 days/week 60 min/session	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 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	Aerobic capacity, peak power output, and ventilatory threshold
Strength N = 1 (35)	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, walkinglunges, push-ups on the wall). Benchpress with free weights, multipower squat, shoulder press, armcurls 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

provement in functional capacity and strength (39). 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	Frequesncy	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, VO2max, 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 45 min/session on treadmill 10-15 min/session upper body ergometer	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 (40)	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 (41)	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 Control group N = 12 (42)	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 Control group N = 4 (43)	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 Control group N = 13 (44)	12 weeks	50 sessions in total 30 min/session	65-75% HRmax	Oxidative capacity, VO_{2max}, and workload
Cycling N = 10 Control group N = 10 (45)	12 weeks	3 days/week 30 min/session	70-80% HRmax	Mitochondrial function and functional ability
Cycling N = 4 (46)	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

Exercise mode/N	Duration	Frequency	Intensity	Improved outcome
Cycling and strength N = 10 Control group N = 10 (47)	12 weeks	3 days/week 60 min/session	70% of peak work load Shoulder press, chest press, bicep curl 50% of 1RM 1 set x 10-15 reps (first two weeks) From week 3: 2 or 3 sets x 10-15 reps (according to tolerance)	Oxygen uptake, work output, endurance, shuttle walking test, muscle strength, NHP, and clinical symptoms
SAVT N = 7 (49)	12 weeks	3 days/week	5-20 Hz (steady increase within 2 weeks) Week 1: 5 Hz 1 min on, 1 min off, 1 min on Week 2: 10 Hz 2 min on, 1 min off, 1 min on Week 3: 15 Hz 2 min on, 1 min off, 1 min on Week 4: 20 Hz 2 min on, 1 min off, 1 min on Week 5–12: 20 Hz 2 min on, 1 min off, 2 min on	Some increase in muscle force

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

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 (50)	12 weeks	Week 1-2: 2 days/week Week 3-4: 3 days/week Week 5-12: 5 days/week 30 min/session	65-70% VO_{2max}	Workload and citrate synthase
Cycling N = 8 (51)	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_{2max}, workload, and 6MWT
Head lift (Shaker exercise) N = 6 (52)	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 Stretching N = 26 (53)	12 weeks	Week 1+2: 2 days/week Week 3 - 12: 3 days/week Weeks 4-6: 3 days/week Week 7-12: 3 days/week	Trunk sit back, STS, standing squat with theraband row, standing lunge with theraband, forward reach, double limb heel raise, and wall pushup Week 1+2: 1 set x max reps at 50-70%% of 1RM Week 3 - 12: 1 set x max reps at 50-70%% of 1RM 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	No functional changes

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 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 N = 5 (54)	12 weeks	3 days/week 30 min/session	60% HRmax	Cycling distances and durations
Cycling N = 6 Control group N = 9 (55)	12 weeks	2-4 days/week (gradual increase) 30 min/session	65-70% of VO2max 60-75% max HR	Aerobic capacity
Home based strength training N = 9 (56)	12 weeks	3 days per week 45-60 min/session	2 sets x 15 reps All participants exercised the Shoulder flexion, shoulder extension, elbow flexion, and elbow extension. Additionally, ambulatory participants exercised lower extremity muscles including the hip flexion, hip extension, and knee extension	Some improvement in upper limb strength
Home based cycling and strengthening N = 9 Control group N = 7 (57)	1 month lead in period 6 months - intervention 12 month - all exercised	Cycling 5 days/week 30 min/session Strengthening: 3 days/week	Exercise regimen was structured based on participant performance on the exercise tolerance test and strength assessments	Exercise ability increased slowly and VO_{2max}

Conflict of interest

The Authors declare to have no conflict of interest.

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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

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Exercise therapy in muscle diseases: open issues and future perspectives

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In muscle diseases different molecular mechanisms are responsible, by distinct cellular pathways, of muscle fibers contraction insufficiency and exercise intolerance. Depending on that, exercise therapy is a promising avenue to efficaciously counteract the loss of muscle fiber function or also the secondary effects due to the sedentary lifestyle as a consequence of the motor impairment. It has been debated whether or not muscle exercise is beneficial or harmful for patients with myopathic disorders, especially in some conditions as eccentric or maximal exercise. Several reports now suggest that supervised aerobic exercise training is safe and may be considered effective in improving oxidative capacity and muscle function in patients with various muscle disorders, including muscular dystrophies and metabolic myopathies, providing that it can be personalized and sized over the single patient capability. In doing that, advancement in outcomes measure recording and exercise delivery monitoring with comfortable investigation methods to assess muscle function and structure can be useful to detect the beneficial effects of a supervised motor training. Based on these considerations, but also especially considering the emerging new therapies in the field of neuromuscular disorders, exercise training can be included as part of the rehabilitation program for patients with a muscle disease, assumed it should be strictly supervised for its effects and to prevent involuntary muscle damage.

Key words: muscle diseases, muscle fatigue, muscle exercise therapy

Introduction

The concept that exercise is a useful tool in the therapeutic management of muscle disease is a longstanding matter that however in the last years has reached a relevant level of interest (1), somehow contradicting a previous axioms within this field of this neurological disorders by which contractile activity had traditionally been considered detrimental in conditions largely characterized by progressive worsening due to the characteristic pathogenic processes underlying them (2). While this has appeared a sort of paradoxical assumption in the way that what is performed for which a biological system is built up for by the biological evolutionary process, at the same time can have negative consequences over the system, this conversely clearly demonstrated by a bulk of scientific data and explained on the basis of the physiopathologic process itself (3-4). However, improved knowledge over the molecular events associated to the pathological processes characterizing the different muscle diseases, as well as a better knowledge on how muscle exercise can accordingly and effectively be modulated in these conditions, along with the availability of new treatments that have now started to envisage differently prognostic profiles , has conducted to an increase interest in that area (3,5).

Protocols and different strategies for exercise therapy

While in healthy individuals physical exercise training is considered a suitable intervention to improve muscle strength, endurance and cardiopulmonary function, its effects in counteracting sarcopenia, on the other hand an age-related loss of musculature, is still debated in muscle diseases. At the same time inducing positive effects in the prevention of possible associated clinical features of muscle involvement, such as bone osteoporosis and overweight (1) and also improving cognition and mood in a every day life quality of life dimension, it is not yet clear at which extent exercise therapy is able, in these conditions, to efficaciously stimulate reparative and regenerative mechanisms in skeletal muscle from one hand, without inducing mechanic muscle damage on the other hand. Regular physical exercise are planned with different structured regimens of muscle activity. In particular, strength training is defined as a training performed primarily to improve muscle strength and endurance and it is typically carried out performing repeated muscle contrac-

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tions against resistance. Indeed, aerobic exercise training, or cardiorespiratory fitness training, is a training that consists of an activity or combination of activities that involves large muscle groups and that can be maintained over long period, rhythmical and aerobic, i.e. performed at submaximal, under lactate production threshold, contractile activities, conditions realized in sports such as walking, running, cycling, or swimming.

In Muscular dystrophies (MD) some more than 60% of all dystrophic patients suffer from severe fatigue as common and precocious symptoms of disease manifestation (2). Muscle fatigue would occur when the intended physical activity can no longer be continued or is perceived as involving excessive effort and discomfort, this depending on the interaction between the required force, the maximum force that the myofiber produces, as well as its endurance, also defined as fatigue resistance. Muscle fatigue is characterized by a progressive loss of motor unit constituents, although due to different degeneration mechanisms, depending on the genotype. Also for metabolic myopathies muscle fatigue represents a critical clinical features, quite often differently related to type of exercise performance depending upon the causative metabolic defect (3), as is the case of the so call "second wind" phenomenon in myophosphorylase deficiency myopathy

However, in last decade, a growing number of studies has shown that exercise can be safe and beneficial for several muscle diseases, but, to date, it is still unknown what kind of exercise, for instance aerobic versus strength training (4), would be recommendable, and for which duration, frequency and intensities it should be performed. Starting from what is the current knowledge, the field still appears quite undetermined in its border, but at the same time more and more promising studies are addressing the issue whether or not motor training can play a therapeutic effect for muscle disease (5).

Aerobic training

Aerobic moderate-intensity exercise at home on a cycle ergometer for 30 minutes, 3 times weekly, for 10 weeks is able to improve oxidative capacity and muscle function in ambulant patients with LGMD2L (6), a recessively inherited dystrophy caused by mutations in ANO-5 gene encoding for the putative calcium-sensitive chloride channel anoctamin 5 that plays a role in membrane repair,. The training was performed at a heart rate interval corresponding to 70% of their maximal oxygen uptake (VO_{2max}), reporting a significant improvement in VO_{2max} and the time to perform 5-repetitions-sit-to-stand test requiring patients to rise and sit from a chair as rapidly as possible.

Also in Pompe's disease, a metabolic myopathy due to a genetic defect in acid maltase gene with peculiar tracts featuring also an autophagic progressive disorder, submaximal and aerobic functional exercise, such as swimming and cycling without excessive resistance, with active assist as needed, and functional activities, performed with respect for the limitations of cardiopulmonary and muscular endurance, are considered beneficial and may maximize the benefits of ERT as it has become available (7). Therefore submaximal, graded, regularly scheduled exercise is considered beneficial in optimizing strength and avoiding additional disuse muscle atrophy (8).

Endurance training

Also low-intensity aerobic endurance training is considered to have positive effects on MD patents. Sveen and coworkers (9) in nine patients with limb-girdle muscular dystrophy type 2I (LGMD2I), caused by mutation of fukutin-related protein, a cytosolic protein that glycosylates alpha-dystroglycan, one of the two, together with integrin alpha-7beta-1D, main laminin receptors in skeletal muscle, playing a major role for the integrity of the sarcolemma, showed positive response to a training program consisting of a total of fifty 30-minute training sessions on cycle ergometer for 12 weeks at a heart rate of 65% of VO_{2max}. As a marker of exercise-induced muscle damage, plasma CK was measured before and after the 12-week training period, 24 to 48 hours after the final training session. Plasma lactate and heart rate were used to validate the degree of exhaustion during cycle tests before and after training. Training improved VO_{2max} and maximal workload, by 21 and 27%, now comparable to the normal physiologic response to training in healthy subjects, in LGMD2I patients. Plasma CK levels tended to increase after training in patients, but also increased in nine matched healthy controls. Self-reported questionnaires showed that a majority of subjects with LGMD2I felt an improvement in physical endurance, leg muscle strength, and walking distance. No worsening of their condition or adverse events were reported.

Resistance training

Pilot studies on the effect of low-intensity and high-intensity strength resistance training in patients with LGMD2I, LGMD2A and Becker muscular dystrophy (BMD), mildly- moderately affected (10). In low-intensity study the resistance-training program lasted for 6 months on quadriceps (knee extension) and biceps brachii (elbow flexion) muscle groups, the weight lifted during knee extension and elbow flexion starting at 40% and then increased by 5% every other week, with a significant increase in both muscle maximal strength and endurance (number of repetitions possible at 60% of maximal strength). As a marker of exercise-induced muscle dam-

age, plasma CK was measured monthly during the training period. In high-intensity study, the training program lasted for 3 months with 3 sessions per week on several muscle groups over the course of 12 weeks, with at least 1 day of rest between each training session. Patients were tested for maximum strength monthly and endurance, as many repetitions as possible at 60% of their repeat maximum, which was found at the initial strength test. Two patients with LGMD2A dropped out of the study due to training-induced CK elevations and myalgias. After 12 weeks of training, the strength of the patients improved in wrist flexion and extension, without however changes in patient's self-reported daily status and quality of life, results indicating that resistance training could be safe and effective in increasing muscle strength and endurance in muscular dystrophies with proximal weakness as LGMD.

Also in McArdle (11) and lipidic myopathies (12) supervised, low-load resistance or strength training with number of exercise repetitions comparable to strength training in healthy persons was well tolerated and did not produce any muscle damage. Although this encouraging, care should still be deserved when considering such training, and it has to be supervised.

How exercise can intercept the molecular pathology

As like dystrophinopathies (Duchenne and Becker muscular dystrophy, DMD, BMD), the majority of limb girdle muscular dystrophies (LGMD), resulting from mutations in specific structural protein encoding gene, are prototypes of failure of the muscle fiber to maintain its physical structure during contraction, leading to sarcolemma breakdown, myofiber degeneration and necrosis.

At cellular level several conditions have to be taken into account to understand how the generation of force and resistance to fatigue are impaired in in muscle diseases. Loss of skeletal muscle mass, mostly accompanying the dystrophic process in muscular dystrophies (MD), is without doubt considered the main pathogenic factor in reducing muscle force generation in such conditions, however other detrimental and often interconnected events in skeletal muscle function can be relevant in determining strength production decay, among their sarcolemmal damage, nucleus-cytoplasm interplay, proteasome machinery involvement. In doing that, different molecular mechanism intervene as fundamental pathogenic events, as is the case for dystrophin-sarcoglycan complex instability in dystrophinopathies MD and sarcoglycanopathies limb girdle muscular dystrophies (LGMD), dysregulation of Ca2+ homeostasis in the skeletal muscle in calpain 3 LGMD2A, structural connection with interstitial endomysial tissue such as in congenital muscular dystrophies, sarcolemmal excitability and mRNA instability in myotonic dystrophies, this also featuring possible strategies of therapeutic approaches.

Other conditions figure out for additional molecular pathophysiological pathways, as is the case of excitation-contraction coupling alterations congenital myopathies due to in Ryanodine Receptor 1-Related Myopathies or protein catabolism in inclusion body myopathies. In all these conditions muscle exercise and training differently interact, both at physiological and pathological level, with the underlying cellular and molecular defect in determining all the possible consequences in terms of structural and functional skeletal muscle modifications and adaptations to exercise, the knowledge of which become important in the understanding of indications and limitation of the exercise in view of its possible usefulness in muscle diseases. On the other hand, all these mechanisms seem to converge in some common cellular and molecular pathways, both in terms of cell damage and cell rescue as two faces of the same medal which manifest themselves depending upon several and not clearly understood modulating factors related to exercise.

Another interesting and fundamental scenario which has to be considered in relation to exercise therapy is that one related to the energy breakdown impairment as typically figuring out metabolic myopathies. In these conditions the pathologic mechanism responsible for the disease differently but directly affects the source of the energetic fuel delivery, as is the case of the diseases of the carbohydrate or lipid metabolism, or of the mitochondrial diseases.

Also at this level a translational approach to understand which molecular events underlie these conditions is relevant both to understand the effects of exercise in skeletal muscle as well as its potential beneficial effect when performed in a supervise profile, making it possible to apply at clinical level what basically considered suitable to be applied for exercise physiology.

Exercise-related cell and molecular common final pathways

Irrespective from the cause of the disease, muscle metabolic changes that accompany exercise can be useful in understanding the role energy utilization plays in contractile insufficiency and pathogenic mechanisms. Studies with 31Phosphorus (31P) magnetic resonance spectroscopy (MRS) have observed significant differences in several metabolite ratios also in dystrophic patients indicating a lower energy state (13). A reduced cytosolic acidification during exercise suggests a defective glycolytic activity in skeletal muscle of patients with Becker muscular dystrophy (BMD). However, the exercise-relat-

ed muscle metabolism in mildly affected BMD patients during an incremental workload can show downregulation of resting pH and intramuscular membrane breakdown, as well as increased reliance upon anaerobic metabolism during sustained submaximal contraction and the maintenance of oxidative function during recovery (14). Similarly, LGMD2A and 2B patients showed, as from 31P MRS data acquired from exercising calf muscles during an incremental workload consisting of isometric intermittent plantar flexions of the dominant leg through an MR-compatible ergometer. starting from 20% of the mean maximal voluntary contraction (MVC) and progressively increased by 10% MVC every 30 seconds until exhaustion, significantly at rest higher cytosolic pH, phosphodiesters (PDE), this as marker of membrane rupture, and adenosine diphosphate (ADP), while a reduction of phosphocreatine (PCr) compared with controls. At the end of exercise, PCr recovery rate in LGMD2A was significantly reduced compared to LGMD2B and healthy controls, suggesting in those an alteration of oxidative metabolism.

In addition to decreased intracellular pH as a results of anaerobic glycogenolysis after muscle performance anaerobically, effects of ionic changes can be responsible for muscle fatigue, as failure of calcium release appears to be a major contributor to fatigue due to sarcoplasmic reticulum (SR) Ca2+ stores decline during fatigue. It has been demonstrated that the increased inorganic phosphate (Pi) affect fatigue by an effect on SR Ca2+ handling, then reducing cross-bridge force and the Ca2+ sensitivity of the myofilaments, this in turn leading to precocious drop in force (15).

Another pathway considered to mediate the terminal effects of fatigue phenomena is the so called oxidative stress as major source of signal pathway in the generation of muscle fatigue (16). However, the mechanisms by the reactive oxygen species (ROS) contributing to muscle fatigue in a number of myopathic conditions other than mitochondria diseases (17). Although the exact mechanism is obscure, on line of evidence indicate that superoxide anion (O2•–) can react with nitrogen oxide (NO) producing peroxynitrite (ONOO–), a reactive nitrogen species (RNS). Excess ROS/RNS production in muscles causes oxidative stress that damages cellular components such as DNA, proteins, and lipids, which in turn causes further damage to cells and tissues. Because muscle contraction requires a large amount of ATP and the vast majority of ATP is generated by mitochondrial oxidative phosphorylation (OXPHOS), muscle mitochondria consume a 100-fold higher amount of O2 during intense exercise compared with that used during resting (18).

The nitric oxide (NO) pathway has also been considered in generation of muscle fatigue in muscular dystrophies. NO, deriving from NO synthase catalyzed L-arginine, is a widespread biological mediator with several functions, among which cell signalling, protection against reactive oxygen intermediate superoxide, vasodilation and muscle blood supply regulation (19). Neuronal nitric oxide synthase (nNOS), a dystrophin-associated protein at the sarcolemmal level where it provides stability to the myofiber membrane during contraction, is lacking in the absence of dystrophin, this leading to a critical concentration collapse of NOS at the cell membrane and its mRNA in the cytoplasm, thus contributing to fatigue by inducing muscle ischemia during contraction, both in mdx mice and boys with Duchenne muscular dystrophy (20). nNOS levels appear also reduced in another genetic form of muscle diseases, congenital muscular dystrophies resulting from defects in extracellular matrix proteins laminin a2 and collagen VI. Also dysferlinopathies and sarcoglicanopathies, with loss of the sarcoglycan–sarcospan complex in muscle, cause a dramatic reduction in the levels of nNOS expression at the membrane, even in the presence of normal dystrophin and syntrophin expression (21).

How therapeutic exercise can be monitored in its effects

Provided that basic mechanisms of resistance to fatigue and exercise intolerance should be at the best clarified, assessment methods to evaluate the effects of exercise therapy need to be designed for a timely application in the clinical setting (22). Several outcome measures have been suggested for that, some of them quite accessible, all aiming to evaluate how skeletal muscle performance can adapt to a motor training minimizing the detrimental effect of fatigue when requested. In doing that, these exercise tests have to be carefully selected in terms of what they want to put in evidence, with particular reference to their modalities of performance and the parameters and variables they want to measure. Examples for the first category are isometric *vs* isokinetics, isotonic *vs* incremental workload, voluntary *vs* motor nerve electrically stimulated, maximal *vs* submaximal, continuous *vs* intermittent, ischemic or not. Biometric parameters to be measured are dynamometric, electrophysiological and kinematic, blood circulating myofiber metabolic and damage intermediates, more generally related to exercise medicine, such as cardiac, respiratory and endocrine. The different variables can yield pathophysiological insights, can help to identify and quantify the molecular mechanism underlying exercise tolerance, a relevant dimension of the patients' quality of life, but they can also offer some diagnostic clues.

Methods originally conceived toward basic physiological mechanisms, and then applied for the functional evaluation of athletes and sport performance, can have a valuable translational application in myopathies with de-

ranged metabolism, such as myophosphorylase deficiency (McArdle disease) or mitochondrial myopathies.

Recording of electrophysiological and dynamometric parameters remain a traditional approach to assess and monitor muscle performance, also thanks to the new telemetric recording techniques that friendly and comfortable apply to the patient.

The impaired O2 extraction capacity by skeletal muscle can be evaluated by the non-invasive near-infrared spectroscopy at different levels, indicating, depending upon the different metabolic conditions, abnormal cardiovascular response to exercise, pulmonary O2 uptake kinetics or impaired intramuscular matching between O2 delivery and O2 utilization.

Studies with 31Phosphorus (31P) magnetic resonance spectroscopy (MRS) can be suitable for gathering data on skeletal muscle energetics *in vivo*. The technique, although usually confined to specialized muscle fatigue laboratory, has evolved to become an important tool in the study of the pathophysiology of muscle diseases. 31P-MRS is used for providing information about the biochemical composition and metabolism of tissue without invasive sampling, and it has the unique ability to measure intracellular pH. Because this investigation is well tolerated and can be easily repeated at clinical level, it can also be applied in longitudinal studies of disease progression or outcomes.

Also some recent techniques of dynamic muscle resonance imaging appear promising tools that yield important informations on skeletal muscle performance in studies for muscle fatigue (23).

Conclusions

Exercise therapy in muscle diseases appears a promising field in which the convergence of a better knowledge on the molecular basic mechanisms underlying pathology and the advancement in technology by which to detect and monitor the phenomenon effects of muscle contraction leads us to envisage improvement of its application in clinical management of the affected patient. This appears of greater importance if considering the emerging new therapies in the field of neuromuscular disorders for which the synergy with therapeutic role of exercise should be pursued.

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Conflict of interest

The Authors declare to have no conflict of interest.

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Fatigue in myotonic dystrophy type 1: a seven-year prospective study

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Objectives. Cross-sectional studies reported fatigue in 50-90% of patients with myotonic dystrophy type 1 (DM1). The aim of this research was to assess frequency of fatigue in DM1 patients during a seven-year period.

Materials and methods. Study included 64 DM1 patients at baseline (50% males, age 42 ± 12 years), and 38 after seven years. Following scales were used: Muscular Impairment Rating Scale (MIRS), Fatigue Severity Scale (FSS, score equal to or greater than 36 indicates significant fatigue), and Daytime Sleepiness Scale (DSS, score of more than six is considered significant).

Results. At baseline, 54% of DM1 patients had fatigue and 46% had excessive daytime sleepiness (EDS). Ten (32%) patients with fatigue had no EDS. At the baseline, patients with fatigue were older, were more likely to had adult-onset DM1, worse MIRS and DSS compared to the patients without fatigue. After seven years, FSS score increased (34 ± 15 *vs* 48 14, p < 0.01), fatigue was found in 82% of patients, and EDS in 60%. Still eight (26%) patients with fatigue had no EDS. Fatigue progression did not parallel MIRS increase.

Conclusions. Fatigue is a common symptom of DM1 and its progression during time did not correlate with the progression of muscle weakness.

Key words: myotonic dystrophy type 1, fatigue, sleepiness, weakness, follow-up

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominant hereditary disease caused by the expansion of CTG trinucleotide repeats in the 3' non-coding region of *DMPK* (*dystrophia myotonica protein kinase)* gene (1). DM1 is considered to be the most common muscular dystrophy in adults, with a frequency of 1 to 20 per 100 000 inhabitants (2). DM1 is a chronic, slowly progressive, multisystemic disease that affects many organs and systems including muscles, eyes, endocrine system, gastrointestinal tract, peripheral and central nervous system (3).

Fatigue may be defined as a subjective feeling of a lack of physical and/or mental energy that only partially withdraws after rest (4). Although fatigue is an important symptom of all progressive, physically disabling diseases, its frequency is greater in DM1 than in other neuromuscular diseases and can be severe even when muscular symptoms are mild (4). Thus, objective muscular weakness cannot fully describe fatigue in DM1.[5] In previous studies, the frequency of fatigue in patients with DM1 varied between 50 and 91% being one of the most common disease symptoms (4, 6-15). Fatigue often occurs in association with the excessive daytime sleepiness (EDS) (14-18). Although some authors believe that EDS and fatigue are most likely to occur as a result of sleep disorders, it seems that these should be considered as two separate clinical entities in DM1 since not all patients with fatigue have EDS and *vice versa* (8). Patients with DM1 reported fatigue as one of the most important factors that disturb their emotional, social and everyday life (14). It also has an impact on the quality of life and safety of DM1 patients (12, 19).

Only two studies so far have longitudinally analyzed fatigue in DM1. Kalkman and colleagues found increase of the Checklist Individual Strength score for fatigue in 70 DM1 patients during a short period of 18 months (19). In the study by Gliem and colleagues, there was no significant progression neither of FSS nor of DSS score during a five-year follow-up period in a small cohort of

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16 DM1 patients (20). Also, percentage of patients with significant fatigue or EDS did not progress during time (21). These contradictory findings raise an importance of further research.

The aim of our study was to analyze fatigue during a seven-year period in a larger cohort of DM1 patients.

Material and methods

We included 64 patients with DM1 who were hospitalized at the Neurology Clinic, Clinical Centar of Serbia in the period from 2011 to 2013 (baseline testing). The diagnosis of the disease was based on the clinical findings, electrophysiological examination and molecular-genetic analysis. Since research was conducted in adult clinic, there were no patients under the age of 18. Patients with congenital and late adult form of DM1 were excluded. Patients were divided into two groups based on their age at the onset of the disease: 1) patients with childhood/ juvenile form of the disease with age at onset between one and 20 years, and 2) patients with classic / adult form with age at onset between 20 and 40 years. During 2018, follow-up testing was carried out. The period between baseline and follow-up testing was 6.7 ± 1.3 years (range 5-8 years). During this period, eight patients died, ten were lost from follow-up (moved, changed phone number, stopped to visit neurologists), while seven refused to participate in retesting. One patient was excluded due to the presence of another serious illness - laryngeal carcinoma. Thus, 38 (59.4%) of 64 patients were retested. This study was approved by the Ethical Board of the Neurology Clinic, Clinical Center of Serbia and all patients gave informed consent to participate.

Degree of muscle weakness was determined according to the Muscular Impairment Rating Scale (MIRS), that classifies DM1 patients in five categories (22). Level of fatigue was measured by Krupp's Fatigue Severity Scale (FSS) (23). FSS is the most commonly used questionnaire for examining severity and frequency of fatigue, and its effect on physical activity, work, family, social and everyday activities. It is considered particularly suitable for chronic disabling disorders such as DM1. It consists of nine questions with responses given on 1 to 7 scale. Total score equal to or greater than 36 indicates significant fatigue. Level of excessive daytime sleepiness (EDS) was determined using the Daytime Sleepiness Scale (DSS). DSS scale is specifically developed for assessing EDS (by asking about its frequency and in certain situations) in patients with DM1 (24, 25). DSS does not analyze the impact of EDS on patient's everyday life. It consists of five questions and DSS score of more than six is considered significant.

During seven-year period patients did not receive any specific medication for fatigue or EDS. The majority of them had annual three-week rehabilitation in spa since this is funded by the Health Fund. However, data on this were not systematically collected.

SPSS software version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis of the obtained data. For group comparisons, χ^2 test, Mann-Whitney U test and Student t test were used as appropriate. χ^2 test and Student t test for paired samples were used to compare results at baseline and at follow-up. If we evaluate delta FSS as a continuous variable, then the sample size of 38 subjects achieves 99.9% power to detect significant difference between the first and the second measurement, at 0.05 significance level. Using FSS as a categorical variable, the sample size of 38 subjects achieves 100% power to detect significant differences between FSS status before and after the evaluation, at 0.05 significance level. Change between follow-up and baseline FSS score was correlated with disease duration, MIRS change and DSS change during same period of time using Spearman correlation coefficient. For all statistical tests, significant testing was two-sided, where alpha was set at 0.05 for statistical significance and at 0.01 for high statistical significance.

Results

Sociodemographic and clinical characteristics of patients with DM1 at baseline are shown in Table 1. No significant differences were observed in patients who did not repeat testing compared to the patients who were retested.

The frequency of fatigue and EDS was evaluated in 64 patients at baseline. Fatigue was present in 31 (48.4%) patients with DM1. Among 31 patients with fatigue, 32.3% had only fatigue, while 67.7% had both fatigue and EDS. In 18 (28.1%) patients only fatigue or only EDS occurred. DSS score was higher in the group of patients with fatigue (8.2 ± 3.2 to 5.2 ± 2.8, $p < 0.01$).

The association of sociodemographic/clinical characteristics and fatigue was examined at baseline. No association was observed between fatigue and gender, education, or disease duration. Patients with fatigue were older compared to the patients without fatigue (45.7 ± 8.6 *vs* 38.8 ± 11.3 years, $p < 0.01$).

Among patients with fatigue, 87.1% had adult onset of the disease, while in the group of patients without fatigue 48.5% had adult form ($p < 0.01$). Muscle weakness was more pronounced in patients with fatigue compared to the patients without fatigue (MIRS 3.6 ± 0.7 *vs* 3.0 ± 0.6, respectively, $p < 0.01$).

Comparison of the sociodemographic and clinical characteristics of 38 patients at baseline and follow-up is shown in Table 2. MIRS score significantly progressed during a seven-year follow-up period (3.2 ± 0.6 *vs* 4.0 ± 0.6, $p < 0.01$) (Tab. 2). Average FSS score was sig-

Table 1. Sociodemographic and clinical characteristics of DM1 patients at baseline.

Characteristics	Retested patients	Not retested patients
N	38	26
Gender-male (%)	47.7	50
Age (years, mean ± SD)	42.6 ± 9.5	41.6 ± 12.2
Education (years, mean ± SD)	10.6 ± 2.3	10.6 ± 1.5
Age at onset (years, mean ± SD)	23.2 ± 9.4	22.3 ± 9.7
Disease form (%) childhood/juvenile classic/adult	 31.6 68.4	 34.6 65.4
Disease duration (years, mean ± SD)	19.3 ± 8.2	18.7 ± 9.3
MIRS (%) II III IV V	 10.5 55.3 34.2 0	 15.4 50.0 26.9 7.7
MIRS (mean ± SD)	3.2 ± 0.6	3.3 ± 0.8
FSS (mean ± SD)	33.6 ± 15.2	35.2 ± 14.4
Fatigue (%)	44.7	53.8
DSS (mean ± SD)	6.7 ± 3.7	6.4 ± 2.8
EDS (%)	44.7	46.2

SD: standard deviation; MIRS: Muscular Impairment Rating Scale; FSS: Fatigue Severity Scale; DSS: Daytime Sleepiness Scale; EDS: Excessive Daytime Sleepiness

nificantly increased on follow-up compared to the baseline (47.7 ± 14.1 *vs* 33.6 ± 15.2, $p < 0.01$). Fatigue was present in 44.7% of patients at baseline and 81.6% of patients at follow-up ($p < 0.01$). Out of 21 patients who did not have fatigue at baseline, 66.7% developed fatigue at follow-up. In only three patients, FSS score at follow-up improved compared to the baseline, but still remained in the range of significant fatigue. DSS score at follow-up also showed statistically significant progression compared to the baseline (8.0 ± 3.8 *vs* 6.7 ± 3.7, $p < 0.05$), but the frequency of EDS in patients did not significantly change over the years. The frequency of fatigue and drowsiness was retested in 38 patients after a seven-year follow-up period.

Change in the FSS score between follow-up and baseline visit did not significantly correlate neither with

Table 2. Sociodemographic and clinical characteristics of patients with DM1 at baseline and follow-up.

Characteristics	Baseline	Follow-up
N	38	38
Age (years, mean ± SD) **	42.6 ± 9.5	49.2 ± 9.5
Disease duration (years, mean ± SD)	19.3 ± 8.2	26.1 ± 8.0
MIRS **	10.5 55.3 34.2 0	0 18.4 65.8 15.8
II		
III		
IV		
V		
MIRS (mean ± SD) **	3.2 ± 0.6	4.0 ± 0.6
FSS (mean ± SD) **	33.6 ± 15.2	47.7 ± 14.1
Fatigue (%) **	44.7	81.6
DSS (mean ± SD) *	6.7 ± 3.7	8.0 ± 3.8
EDS (%)	44.7	60.5

SD: standard deviation; MIRS: Muscular Impairment Rating Scale; FSS: Fatigue Severity Scale; DSS: Daytime Sleepiness Scale; EDS: excessive daytime sleepiness; ** $p < 0.01$; * $p < 0.05$

the duration of the disease between two testings nor with the difference in muscle weakness. On the other hand, moderate correlation was observed between the change in FSS score and DSS score during years (ρ = -0.40, $p < 0.05$).

Discussion

Around half of our patients with DM1 had significant fatigue at the baseline, while 82% developed fatigue after seven-year follow-up. This is in line with the results of cross-sectional studies in which fatigue was usually reported in more than two thirds of DM1 patients (4, 6-10, 12, 13). We observed progression of FSS score and frequency of fatigue during seven years. All the patients with fatigue at the baseline still had fatigue after seven years. Furthermore, two third of the patients that did not have fatigue at the baseline, reported significant fatigue at the follow-up. These results show that the frequency of fatigue increases with the natural course of the disease in DM1. Accordingly, increase of the Checklist Individual Strength score for fatigue was found in 70 DM1 patients during a short period of 18 months (20). However, in another study percentage of DM1 patients with significant fatigue or EDS did not progress during five years, but this cohort was pretty small consisting of only 16 patients (21). Further studies are needed to resolve this contradictory findings. It would be of interest to create a disease-specific fatigue scale and to analyze its sensitivity, specificity and responsiveness at multiple time points in order to be used in clinical trials and everyday practice.

Although fatigue and EDS are similar symptoms and are caused by similar factors, many authors state that they are different entities in DM1 (8). It has been previously stated that patients with EDS almost always reported fatigue symptoms, while those with fatigue were much less likely to report EDS (13). Some patients with DM1 report that they are tired but not sleepy, because drowsiness is usually perceived as a lack of initiative, while fatigue and exhaustion are more socially acceptable and are most often seen as a consequence of a hard work (26). In line with these findings, the presence/absence of fatigue and sleepiness overlapped in about two thirds of our patients but not in all of them. Besides this, effect of fatigue and EDS on patient's life is different. In one study on 200 adult DM1 patients, fatigue was observed to be an independent factor that significantly influenced the social life of patients, while this effect was not observed for EDS (7). Similar to this, fatigue, but not EDS, was significant predictor of the worse quality of life in DM1 (12). Although these differences exist, overlap between fatigue and EDS is obvious in majority of DM1 patients. Also, we have observed a parallel progression of these two disorders during time. Accordingly, the study group lead by Merkies has developed a specific scale that simultaneously measures both fatigue and EDS in DM1 (28).

At baseline, our DM1 patients with fatigue were about seven years older than patients without fatigue, which indicates that the aging process itself has a certain effect on fatigue. DM1 is often considered a progeroid disease (29). We observed association between fatigue and muscle weakness measured by MIRS score at the baseline. Accordinlgy, in previous study lower muscle strength contributed to lower levels of physical activity, which, in turn, contributed to fatigue severity in three neuromuscular diseases including DM1 (20). Also, Winblad and Lindberg found correlation between Fatigue Impact Scale score and muscle impairment (30). However, we did not notice a parallel progression of fatigue and weakness during time, which suggests that there are other important factors that contribute to the fatigue progression. Alterations in sarcolemmal excitability behind the myotonic phenomenon may also to be considered (31). Fatigue can occur due to the sleep disorders such as periodic limb movements and sleep apneas (5, 16). Besides this, structural brain changes may influence the presence of fatigue in DM1. Previous study found hypochogenicity of the raphe nucleus to correlate with fatigue in DM1 (32). Furthermore, according to Minnerop et al., fatigue was less pronounced in patients with more changes in the brain white matter, probably due to the lack of disease awareness (9).

Main limitation of the study is a small cohort of DM1 patients and lost of patients during time, as well as a lack of multiple testings during time. Also, several further variables would be helpful in understanding fatigue and EDS in DM1, including other concomitant sleep, cardiac and respiratory disorders, and polysomnography data. We also believe that cognitive-behavioural characteristics of DM1 patients, especially unawareness, may affect their report on fatigue and EDS (33).

Conclusions

Fatigue is a common symptom in DM1. Patients with fatigue were older, usually had adult-onset DM1, more severe muscle weakness and more severe EDS. Frequency and severity of fatigue increases during time in DM1, but worsening of the fatigue is independent of the muscle weakness progression.

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Conflict of interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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NEWS FROM AROUND THE WORLD

AIM

The Italian Association of Myology (AIM) has sponsored, in the period between September 2019 and December 2019, various congress events, which took place throughout the national territory. There were nine sponsored events in all, with topics on several neuromuscular diseases ranging from spinal muscular atrophy to neuromuscular junction disorders, metabolic myopathies, limb-girdle muscular dystrophies. Three events took place in Northern Italy, three in Central Italy and three in Southern Italy.

As a member of the Italian Society of Neurology (SIN), AIM was present at the fiftieth congress of the SIN, held in Bologna from 12 to 15 October 2019 with a dedicated stand. There were numerous sessions within the congress that had as their topics the neuromuscular diseases. Among these the interesting Course 'How Genetics can influence therapy in muscular diseases', moderated by Professors Carlo Minetti and Gabriele Siciliano.

In order to strengthen links with other European myology companies, AIM participated in the "17èmes journées de la Société Française de myologie – Actualités en Myologie' which took place in Marseille from 20 to 22 November 2019, with a joint session on neuromuscular diseases. Some particular topics of the joint meeting concerned Pompe disease, facio-scapulo-humeral muscular dystrophy and myofibrilary myopathies.

Carmelo Rodolico
AIM Secretary

MSM

The 14th Meeting of the Mediterranean Society of Myology (MSM) will probably be held in 2020 in Sicily, organised by prof. Antonio Toscano.

WMS

The 24th annual congress of the World Muscle Society was held in Copenhagen from 1st to 5th October, in the old Tivoli Garden Concert Hall and adjoining buildings. Join WMS for the networking reception to be held on Tuesday 1st October in the theatre, *Det Ny Teater*, located a 5-minute walk from Tivoli gardens. This followed the long tradition of WMS to facilitate networking and catch up on the latest developments in myology around the world during this 4-day meeting.

As usual, the meeting was preceded by a teaching course, held in Copenhagen on September 30th and October 1st 2019.

The Copenhagen Neuromuscular Center at the National Hospital, Rigshospitalet, led by John Vissing, has host and organise this meeting. The main thematic topics addressed in the plenary sessions were:

1. Metabolic disturbances in neuromuscular diseases;
2. Extra-muscular manifestations in neuromuscular diseases;
3. Advances in the treatment of neuromuscular disorders.

FORTHCOMING MEETINGS

2019

October 1-5

24th Congress of World Muscle Society. Copenhagen, Denmark. Information: website: *www. https://worldmusclesociety.org*

October 11-13

Myotonic dystrophies: molecular approaches for clinical purposes Framing a European molecular research network. 248th ENMC Workshop. Information: website: *https://www.enmc.org/*

October 12-15

50th Congress of Italian Society of Neurology, Bologna, Italy. Information: website: *http://www.neuro.it*

October 15-19

2919 ASHG Annual Meeting. Houston, TX, USA. Information: website: *www.ashg.org*

October 16-19

American Association of Neuromuscular & Electrodiagnostic Medicine, Austin, TX, USA Information: website: *https://www.aanem.org*

October 24-27

Asia Pacific Heart Rhythm Society (APHRS). Centara Grand & Bangkok Convention Centre at CentralWorld. Bangkok, Thailand. Information: website: *https://www.aphrs.org*

October 28-30

20th Italian Telethon Convention. Riva del Garda, IT. Information: website: *https://www.telethon.it*

October 29-30

TREAT-NMD SMA Expert Masterclass, London, UK. Information: website: *https://treat-nmd.org*

November 6-8

EURO-NMD 3rd Annual Meeting. Ferrara, IT. Information: website: *https://ern-euro-nmd.eu*

November 8

21st Meeting of The Italian Network on Laminopathies, Bologna, IT. Information: website: *www.igm.cnr.it/laminopatie*

November 13-15

3rd International Conference on Genomic Medicine (GeneMed-2019),Baltimore, USA. Information: website: *http://unitedscientificgroup.com/conferences/genemed*

November 15-16

The Action Duchenne International 2019 conference, Hinckley Island, Birmingham, UK. Information: website: https://www.actionduchenne.org/

November 20-22

17th Days of French Society of Myology. Marseille, France. Information: website: https://www.sfmyologie.org

November 28-30

XLIV National Congress of Pediatric Neurology Naples, IT. Information: website: *www.neurologiapediatrica.it*

November 29

Metabolic Myopathies. Meeting in Memory of Stefano di Donato. Milan, IT. Information: First Class S.r.l. Meetings and Conferences; *elettra.marchegiani@fclassevents.com*

November 29 - December 1

The role of brain dystrophin in muscular dystrophy: Implications for clinical care and translational research. 249th ENMC Workshop.Information: website: *https://www.enmc.org*

December 9-11

6th TREAT-NMD International Conference. Leiden, The Netherlands. Information: website: *www.treat-nmd-conference.org*

December 9-11

Polyglucosan storage myopathies. 251st ENMC Workshop. Information: website: *https://www.enmc.org*

2020

February 5-7

2nd International Scientific & Clinical Congress on Spinal Muscular Atrophy. SMA Europe- Evry, France. Information: website: *https://evry2020.sma-europe.eu*

March 6-8

Developing best practice guidelines for management of mouthpiece ventilation in neuromuscular disorders. 252nd ENMC Workshop. Information: website: *https://www.enmc.org*

March 11-14

8th Dysferlin conference, Jain Foundation. Orlando, Florida, USA. Information: website: *https://www.jain-foundation.org*

March 16-17

International Conference on Orphan Drugs & Rare Diseases. Berlin, G. Information: website: *https://www.meetingsint.com/conferences/orphandrugs-raredisease*

March 20-22

Skeletal muscle laminopathies – natural history and clinical trial readiness. 253rd ENMC Workshop. Information: website: *https://www.enmc.org*

April 25 - May 1

72nd Annual Meeting American Academy of Neurology, Toronto, Ontario, Canada. Information: website: *https://www.aan.com*

June 3-6

XX Congresso Nazionale AIM Giugno 2020. Matera, IT. Information: website: *https://www.miologia.org*

June 6-9

The European Human Genetics Conference. Berlin, Germany. Information: website: *https://www.eshg.org*

July 6-9

New directions in Biology and Disease of Skeletal Muscle Conference, New York, NY, US. Information: website: *https://myology.institute.ufl.edu/conferences/new-directions*

September 25-29

Muscle Study Group Annual Scientific Meeting, Washington, US. Information: website: *https://musclestudygroup.org/events/2020-annual-meeting*

September 30 - October 4

25th Congress of World Muscle Society. Halifax. Toronto, Canada. Information: website: *www.worldmusclesociety.org*

October 27-31

ASHG Annual Meeting. San Diego, CA,USA. Information: website: *www.ashg.org*

2021

June 12-15

The European Human Genetics Conference. Glasgow, United Kingdom. Information. website: *https://www.eshg.org*

September 21-25

26th Congress of World Muscle Society. Prague, Czech Republic. Information: website: *www.worldmusclesociety.org*

October 19-23

ASHG Annual Meeting. Montreal, Canada. Information: website: *www.ashg.org*

VOLUME XXXVIII - LIST OF REFEREES CONSULTED IN 2019

Angelini Corrado

Argov Zohar

Chiara Fiorillo

Grandis Marina

Mongini Tiziana

Mora Marina

Peretto Giovanni

Piluso Giulio

Ricci Giulia

Ruggiero Lucia

Russo Vincenzo

Santorelli Filippo M

Santoro Lucio

Savarese Marco

Gabriele Siciliano

Topaloglu Haluk

Trojsi Francesca

Voet Nicoline

INSTRUCTIONS FOR AUTHORS

Acta Myologica publishes articles related to research in and the practice of primary myopathies, cardiomyopathies and neuromyopathies, including observational studies, clinical trials, epidemiology, health services and outcomes studies, and advances in applied (translational) and basic research.
Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within eight weeks. All rebuttals must be submitted in writing to the editorial office.

On-line submission
Manuscript submission must be effected on line: **www.actamyologica.it** according to the following categories:
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Case Reports, Scientific Letters (maximum 1500 words, 10 references, 3 figures or tables, maximum 4 authors). A summary of 150 words may be included.
Letters to the Editor (maximum 600 words, 5 references). Letters commenting upon papers published in the journal during the previous year or concerning news in the myologic, cardio-myologic or neuro-myologic field, will be welcome. All Authors must sign the letter.
Rapid Reports (maximum 400 words, 5 references, 2 figures or tables). A letter should be included explaining why the author considers the paper justifies rapid processing.
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Tables. Tables should be self-explanatory, double spaced on separate sheets with the table number and title above the table and explanatory notes below. Arabic numbers should be used for tables and correspond with the order in which the table is first mentioned in the text.
References. Reference numbers in the text must be in brackets. References in the list must be numbered as they appear in the text.
Standard journal article: Figarella-Branger D, Bartoli C, Civatte M, et al. Cytokines, chemokines and cell adhesion molecules in idiopathic inflammatory myopathies. Acta Myol 2000;19:207-8.
Books and other monographs: Dubowitz V. Muscle disorders in childhood. London: WB Saunders Company Ltd; 1978.
Please check each item of the following checklist before mailing:

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