Different genetic mutations underlying distinct pathogenic mechanisms have been identified as cause of muscle fibers degeneration and strength loss in limb girdle muscular dystrophies (LGMD). As a consequence, exercise tolerance is affected in patients with LGMD, either as a direct consequence of the loss of muscle fibers or secondary to the sedentary lifestyle due to the motor impairment. It has been debated for many years whether or not muscle exercise is beneficial or harmful for patients with myopathic disorders. In fact, muscular exercise would be considered in helping to hinder the loss of muscle tissue and strength. On the other hand, muscle structural defects in LGMD can result in instability of the sarcolemma, making it more likely to induce muscle damage as a consequence of intense muscle contraction, such as that performed during eccentric training. Several reports have suggested that supervised aerobic exercise training is safe and may be considered effective in improving oxidative capacity and muscle function in patients with LGMD, such as LGMD2I, LGMD2L, LGMD2A. More or less comfortable investigation methods applied to assess muscle function and structure can be useful to detect the beneficial effects of supervised training in LGMD. However, it is important to note that the available trials assessing muscle exercise in patients with LGMD have often involved a small number of patients, with a wide clinical heterogeneity and a different experimental design. Based on these considerations, resistance training can be considered part of the rehabilitation program for patients with a limb-girdle type of muscular dystrophy, but it should be strictly supervised to assess its effects and prevent possible development of muscle damage.

Key words: limb girdle muscle dystrophies, muscle fatigue, muscle exercise

Introduction

In limb girdle muscular dystrophies (LGMD), different genetic mutations, through distinct pathogenic mechanisms, determine a failure of muscle fibers in maintaining their physical structure during contraction, leading to sarcolemma breakdown, progressive muscle fibers degeneration and strength loss. Depending on that, exercise tolerance is affected in patients with LGMD, either as a direct consequence of loss of muscle fibers, but also secondary to the sedentary lifestyle due to the motor impairment. However, the cellular mechanisms that triggers skeletal muscle dysfunction and, ultimately, leads to muscle necrosis is still unclear, and available therapies are consequently inadequate.

Pathophysiology of fatigue and exercise intolerance in muscular dystrophies

Muscular dystrophies are genetic muscle diseases characterized by a progressive loss of motor unit constituents, due to different degeneration mechanisms, and by a wide range of phenotypes. Like dystrophinopathies (Duchenne and Becker muscular dystrophy, DMD, BMD), the majority of LGMD, that result from mutations in genes encoding specific structural protein, are prototypes of failure of the muscle fiber to maintain its physical structure during contraction, leading to sarcolemma breakdown, myofiber degeneration and necrosis. As a consequence, more than 60% of dystrophic patients experiences severe fatigue as a common and precocious symptom of disease manifestation. Muscle fatigue
occurs when the intended physical activity can no longer be continued or is perceived as excessive effort and discomfort, 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. At molecular level, although the loss of skeletal muscle mass accompanying the dystrophic process may be considered as a pathogenic factor in reduced muscle force generation in LGMD, several other and often interconnected mechanisms, as excitation-contraction coupling or energy breakdown, are involved in the genesis of muscle fatigue. However, the exact mechanism of the progressive muscle fibers necrosis in muscular dystrophies is still unknown, as well as the role of energy production in the cascade of events ending with muscle fiber degeneration. Related to that, evidence that the tricarboxylic acid cycle and some reactions in glycolysis are dependent on the integrity of cytoskeletal organization may suggest a role for defective energy metabolism in muscle fiber degeneration. In the clinical setting, a careful analysis of the muscle function is important to characterize the “phenomic” of muscle force impairment and fatigue in muscular dystrophies and to design outcome measures and optimal strategies to treat patients with decreased fatigue resistance (1).

A better knowledge of the muscle metabolic changes during exercise may be useful in understanding the role energy utilization plays in contractile insufficiency and pathogenic mechanisms. For these purposes, 31P magnetic resonance spectroscopy (MRS) may be used to study skeletal muscle metabolism in vivo. The technique has become an important tool in the study of the pathophysiology of muscle diseases. 31P-MRS is used for providing information about the biochemical composi- tion and metabolism of tissue without invasive sampling, and it has the unique ability to measure intracellular pH. Given that MRS is well tolerated and examinations are easily repeated, it may also be applied in longitudinal studies of disease progression or outcomes. Interestingly, studies performed by muscle 31P-MRS have shown significant differences in several metabolite ratios in dystrophic patients indicating a lower energy state (2). In particular, the reduced cytosolic acidification during exercise suggests a defective glycolytic activity in skeletal muscle of patients with Becker muscular dystrophy. A recent work performed by our group studied the exercise-related muscle metabolism in mildly affected BMD patients assessed by muscle 31P-MRS during an incremental workload in 10 mildly affected LGMD2A (6 males, 4 females, mean age 31.4 ± 9.5) patients and 3 LGMD2B patients, and 20 healthy controls (unpublished data). The incremental workload exercise test consisted of isometric intermittent plantar flexions of the dominant leg through an MR-compatible ergometer. Test normalization was obtained with reference to individual isometric maximal voluntary contraction (MVC), a valuable force indicator in contracting muscles. The in-magnet exercise protocol was made up of an incremental workload starting from 20% of the mean MVC (re-measured at rest 1 hour before the examination) and progressively increased by 10% MVC every 30 seconds until the subject’s exhaustion (3). 31P MRS data were acquired from calf muscles. At rest, LGMD-2A and -2B subjects had a significantly higher cytosolic pH (p < 0.03), an increase in phosphodiesters (PDE), as markers of membrane rupture, and adenosine diphosphate (ADP) (p < 0.02), while they showed a reduction of phosphocreatine (PCr) (p < 0.01) compared with controls. No significant differences were found in mean values of metabolic variables during exercise between LGMD subjects and controls, while, at the end of exercise, PCr recovery rate in LGMD-2A and -2B subjects had a significantly higher cytoplasmic pH (p < 0.03), an increase in phosphodiesters (PDE), as markers of membrane rupture, and adenosine diphosphate (ADP) (p < 0.02), while they showed a reduction of phosphocreatine (PCr) (p < 0.01) compared with controls. No significant differences were found in mean values of metabolic variables during exercise between LGMD subjects and controls, while, at the end of exercise, PCr recovery rate in LGMD2A was significantly reduced (p < 0.02) in comparison with LGMD2B subjects and healthy controls, suggesting an alteration of oxidative metabolism.

However, when considering metabolic pathway related to fatigue in muscular dystrophies, reports have shown that lactic acid does not have always a deleterious influence on muscle contraction and it does not cause muscle fatigue. In fact, although the reduced intracellular pH may alter muscle performance, given that the glycogen storage is more rapidly depleted when consumed anaerobically, producing lactic acid, it is also likely that its deleterious effects have been overestimated (5).

Alternatively, it has been proposed that the effects of ionic changes, i.e. the changes in the homeostasis of Ca2+ and reactive oxygen species (ROS) in the myoplasm, cause muscle fatigue.

Failure in calcium release is one of the major contributor to fatigue. Sarcoplasmic reticulum (SR) Ca2+
stores decline during fatigue. It has been demonstrated that the increased inorganic phosphate (Pi) affect fatigue development by acting on SR Ca2+ handling, by reducing cross-bridge force and the Ca2+ sensitivity of the myofilaments, with secondary early drop in force (1). According to the “Ca2+ precipitation theory”, if Pi goes into the SR during fatigue, this can result in Ca-Pi precipitation and decrease of the Ca2+ available for release.

There is also a growing literature that indicates the “oxidative stress” as major source of signal pathway in the generation of muscle fatigue (6, 7). The superoxide anion (O2−) is one of the major reactive oxygen species (ROS). In addition, O2− reacts with nitrogen oxide (NO), with the production of peroxynitrite (ONOO−), a reactive nitrogen species (RNS). Muscle contraction requires a large amount of ATP. The majority of ATP is produced by mitochondrial oxidative phosphorylation (OXPHOS); during exercise, mitochondria utilize an amount of O2 which is up to 100-fold higher than the one used during resting. The high rate of O2 consumption in skeletal muscles determines also an electron dispersion from the electron transfer chain during OXPHOS, with secondary generation of O2− (8). ROS/RNS production in muscles causes oxidative stress that is dangerous for cellular DNA, proteins and lipids. ROS have been identified as endogenous mediators of muscle fatigue, highlighting the importance to develop antioxidants as therapeutic interventions for fatigue treatment (8).

The nitric oxide (NO) pathway has also been implicated in the genesis of muscle fatigue in muscular dystrophies. NO synthesized from L-arginine catalyzed by NO synthase is a widespread biological mediator with many functions, including cell signaling and protection from reactive oxygen intermediate superoxide. Loss of normal NO production in dystrophic muscle is expected to have a broad, disruptive effect on muscle function (9). Neuronal nitric oxide synthase (nNOS) is a key muscle enzyme in the production of NO, that is involved in the regulation of vasorelaxation and muscle blood supply. NOS is associated with dystrophin-associated protein complex at the sarcolemmal level, where it provides stability to the myofiber membrane during contraction. In the absence of dystrophin, as observed in dystrophinopathies, the concentration of NOS at the cell membrane and in the cytoplasm decreases, and the concentration of NOS mRNA is also reduced (10). It has been hypothesized, both in mdx mice and boys with Duchenne muscular dystrophy (11-13), that the displacement and the secondary loss of nNOS and abnormalities in the levels of its expression in muscle significantly contribute to fatigue by inducing muscle ischemia during contraction. Interestingly, nNOS-null mice display a specific deficit in adapting to exercise and develop profound fatigue upon repeated muscle contraction (14). nNOS levels were also reduced in other genetic forms of muscle disease, including those resulting from defects in extracellular matrix proteins laminin α2 and collagen VI. Mutations in dysferlin are also shown to be characterized by reduced levels of nNOS. Loss of the sarcoglycan–sarcospan complex in muscle, as observed in sarcoglycanopathies, causes a reduction in the levels of nNOS expression at the membrane, even in the presence of normal dystrophin expression (15).

**Effects of exercise training in muscular dystrophies**

In healthy individuals physical exercise training is considered one of best intervention to improve muscle strength, endurance and cardiorespiratory function. Regular exercise can also prevent diseases such as diabetes mellitus, arteriosclerosis, some forms of cancer, bone fractures, overweight, and it may improve cognition and mood. Moreover, it can avoid the age-related loss of muscle, called sarcopenia. Physical fitness training is a planned and structured regimen of regular physical exercise. In particular, strength training is defined as a training performed primarily to improve muscle strength and endurance and it is typically carried out making repeated muscle contractions against resistance. Indeed, aerobic exercise training, or cardiorespiratory fitness training, is a training that consists of an activity or combination of activities that uses large muscle groups, that can be continuously maintained, and that is rhythmical and aerobic, for example walking, running, cycling, or swimming (Fig. 1).

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**PHYSICAL FITNESS TRAINING**

*a planned and structured regimen of regular physical exercise*

- **Strengthening** is defined as a training performed to improve muscle strength and endurance. It is typically carried out making repeated muscle contractions against resistance.

- **Aerobic exercise training** consists of an activity or combination of activities that uses large muscle groups, that can be maintained continuously, and that is rhythmical and aerobic.

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Fig. 1.
Studies of exercise training in patients with different neuromuscular diseases seem to suggest a positive effect without susceptibility to muscle injury (16–18). In fact, strength training, which is performed to improve muscle strength and muscle endurance, or aerobic exercise programs, which involve training at moderate levels of intensity for extended periods of time (for example, distance cycling) might maximize muscle and cardiorespiratory function and prevent additional disuse atrophy (19). Previous studies demonstrated a beneficial effect of low- to moderate-intensity resistance and aerobic training in slowly progressive myopathies (20). An improvement in aerobic capacity may prevent type 2 diabetes, cardiovascular disease, and other lifestyle diseases. Patients with neuromuscular disorders are known to have a higher risk of developing disorders associated with obesity and a sedentary lifestyle, such as metabolic syndrome, when compared with the general population. Therefore, the positive effect of a training program on aerobic capacity in these patients is of substantial importance for their long-term health and quality of life (21, 22). However, clinicians are still afraid about muscle overuse during exercise in people with muscle disease and have a cautious approach to training. Limitations in patient number, design, and, most importantly, lack of supervision have often precluded any firm conclusion from previous studies (23). Importantly, as the pathophysiology of muscular dystrophies and myopathies differs, their reaction to training intervention might be different.

**Muscle damage and exercise in LGMD**

The damage of skeletal muscle during exercise may be caused by metabolic or mechanical mechanism. The metabolic damage is the result of ischemia or hypoxia during prolonged exercise, resulting in changes in ion concentration, accumulation of ROS and deficiency of ATP. Mechanical stimuli can determine muscle damage as direct consequence of overload of muscle fibers or inappropriate balance of exercise variables, with a secondary disruption of the sarcomeric Z lines (24) and plasma membrane with loss of muscle proteins, such as creatine kinase (CK), lactate dehydrogenase, aldolase, myoglobin, troponin.

Muscle contractions may determine mild and no-significant damage of muscle fibers during daily common activities (25). More severe injuries accompanied by myalgias are also possible, especially during predominantly lengthening (eccentric) contractions. There are three different types of contractions. If the force developed by the muscle is greater than the load on the muscle, a shortening (concentric) contraction occurs. When the force developed by the muscle and the load are equivalent, or the load is immovable, a fixed length, or isometric contraction, results. The third type of contraction occurs when the load on the muscle is greater than the force developed by the muscle and the muscle is stretched, producing a lengthening (eccentric) contraction. Depending on the severity of the injury, complete recovery may require from 7 to 30 days. Training with protocols of lengthening (eccentric) contractions produces a hypertrophic and stronger muscle. The “trained” muscle is then able to perform the protocol of repeated lengthening contractions that previously caused injury without sustaining an injury. It may be hypothesized that tear and load due to exercise on a sick muscle could accelerate the disease process in muscular dystrophies, in which sick fibres of different sizes, with disorganised myofibrillar structure, often undergoing regeneration or necrosis, in association with fibrosis and adipose tissue, does not seem for contractile activity. Based on the above considerations, patients with neuromuscular disorders in the past have been advised to refrain from strenuous exercise. But, one of the consequences of this is that patients develop severe deconditioning, with potential acceleration of the primary muscle disease process.

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 (aerobic versus strength training) should be recommended, and at what duration, frequency and intensities it should be performed. Starting from actual knowledge, there is the need to plan future studies aimed at addressing if motor training for muscle disease can play a therapeutic effect (26).

**Endurance training in LGMD2I (Sveen et al., 2007) (27)**

Sveen and coworkers (27) analyzed the effect of low-intensity aerobic training in 9 patients with limb-girdle muscular dystrophy type 2I (LGMD2I), caused by mutation of fukutin-related protein, that is a cytosolic protein that glycosylates alpha-dystroglycan. Aplha-dystroglycan and integrin alpha-7beta-1D are the two main laminin receptors in skeletal muscle, playing a major role for the integrity of the sarcolemma. Exercise could be deleterious in patients with LGMD2I, considering the importance of alpha-dystroglycan in linking the sarcolemma to the extracellular matrix. The AA also evaluated the effect of a training program consisted in fifty 30-minute training sessions on cycle ergometer for 12 weeks, at a heart rate corresponding to 65% of their maximal oxygen uptake (VO₂max). As a marker of exercise-inducing muscle damage, plasma CK was measured before and after a 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 VO₂max and maximal workload in patients with LGMD2I. Plasma
Muscle exercise in limb girdle muscular dystrophies: pitfall and advantages

lactate levels and heart rate at rest and at VO_{2max} did not differ significantly before and after training. Plasma CK levels tended to increase after training in patients, but also increased in nine matched healthy controls. Self-reported questionnaires showed that the 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.

The authors concluded that 12 weeks of low intensity aerobic training was effective and safe in increasing fitness in patients with LGMD2I. Training raised the patient’s VO_{2max} and workload capacity in watts by 21% and 27%, corresponding to the normal physiologic response to training in the healthy subjects. Increased work capacity was paralleled by self-reported improvements in endurance, leg muscle strength, and walking distance (27).

Resistance training in patients with LGMD2I and LGMD2A (Sveen et al., 2013) (28)

Sveen and coworkers presented the results of two pilot studies on the effect of resistance training in patients with LGMD2I, LGMD2A and Becker muscular dystrophy (BMD) (28). In particular, in one study they investigated the effect of low-intensity strength training (LOIT) in 2 patients with LGMD2A, in 4 patients with LGMD2I and 2 patients with BMD; in the other, they assessed the effect of high-intensity strength training (HIT) in 4 patients with LGMD2A, in 2 patients with LGMD2I and 1 patient with BMD. All recruited patients were ambulatory and considered to be mildly-moderately affected.

In LOIT study, the resistance-training program lasted 6 months. Two muscle groups were included in the training program: quadriceps (knee extension) and biceps brachii (elbow flexion). During the first 4 months of training the dominant side was trained, while both sides were trained for the final 2 months of training. The weight lifted during knee extension and elbow flexion started at 40% and was increased by 5% a week. Subjects were tested before and after 4 and 6 months of training for maximal strength and endurance (number of repetitions possible at 60% of maximal strength). They also completed a questionnaire, named Sickness Impact Profile (SIP), for assessment of their daily function and quality of life. As a marker of exercise-induced muscle damage, plasma CK was monthly measured during the training period. At the end of the training period, elbow flexion and knee extension showed a significant increase in muscle strength and endurance; there was no change in the results from the SIP questionnaire regarding daily activities.

In HIT study, the training program lasted for 3 months. Additional muscle groups were included for testing, including wrist flexion and extension and plantar flexion, and both the right and left extremities were trained from the beginning. Subjects followed a strength training program with 3 sessions per week over the course of 12 weeks, with at least one day of rest between each training session. Supervision was provided during each session by a personal instructor. Patients were tested for maximum strength monthly. In order to measure endurance, patients performed as many repetitions as possible at 60% of their repeat maximum, which was found at the initial strength test. Each training session started with a 5-minute warm-up on a stationary cycle ergometer at low intensity, followed by three sets of each exercise performed with a 90-150-second interval between sets. In each set, the patient performed the maximum number of repetitions possible. Two patients with LGMD2A dropped out of the study because of training-induced CK elevations and myalgias. After 12 weeks of training, the strength of the patients improved in wrist flexion and extension, while the improvement in the other muscle groups was not significant. It was not observed a correlation between the initial strength level of the muscles and the percentage increase seen in the muscles. SIP questionnaire did not show changes in patient’s self-reported daily status and quality of life.

In conclusion, the preliminary results of this work indicated that resistance training could be safe and effective in increasing muscle strength and endurance in muscular dystrophies with proximal weakness, such as LGMD. The authors highlighted, however, that, until more knowledge is convened, training should be carefully supervised in order to recognize potential adverse effects, particularly in high-intensity protocols (28).

Aerobic training in patients with LGMD2L (Vising et al., 2014) (29)

LGMD2L is a recessively inherited dystrophy caused by mutations in ANO-5 gene, that encodes for the putative calcium-sensitive chloride channel anoctamin 5, which is thought to play a role in membrane repair. In this study, 6 ambulant patients with LGMD2L were selected in order to evaluate the effect of home-based, pulse-watch monitored, moderate-intensity exercise at home on a cycle ergometer for 30 minutes, 3 times weekly, for 10 weeks. Also in the present work, plasma CK was assessed as a marker of muscle damage. Training was performed at a heart rate interval corresponding to 70% of their VO_{2max}.

Primary outcome measures were VO_{2max} and time in the 5-repetitions-sit-to-stand test (FRSTST), requiring patients to rise and sit from a chair 5 times as rapidly as possible. The authors reported a significant improvement in oxidative capacity and muscle function (evaluated by VO_{2max} and FRSTST time), with stable CK levels and no reports of adverse effects (29).
Conclusions

In LGMD, because muscle weakness is the main problem, muscular exercise can help to counteract the loss of muscle tissue and strength in LGMD. Although it is accepted that exercise has a positive role in many diseases, it is not possible to generalize this finding to muscular dystrophy, including LGMD, and there is the need to conduct a systematic search to point out the effects of muscular exercise in experimental settings. To date, there is no certain evidence about the type (endurance or strength), frequency and intensity of muscle exercise. However, a training with moderate (below 70% of predicted maximal aerobic capacity) aerobic exercise seems to play an useful and safe effect in muscular dystrophies (23, 26).

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