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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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