Recommendations to Define Exercise Prescription for Duchenne Muscular Dystrophy

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GRANGE, R.W., and J.A. CALL. Recommendations to define exercise prescription for duchenne muscular dystrophy. *Exerc. Sport Sci. Rev.*, Vol. 35, No. 1, pp. 12–17, 2007. *Duchenne muscular dystrophy yields pervasive and progressive muscle weakness. This weakness may be attenuated by regular, low-intensity exercise. However, there is a critical lack of data to support appropriate exercise prescription. Because inappropriate activity may exacerbate the dystrophic process, a systematic analysis of muscle function to determine potential exercise load thresholds to avoid injury in dystrophic mice and dogs, and then in humans, is recommended.*
Key Words: muscle injury, *mdx* mice, *mdx*:utrophin$^{-/-}$ mice, exercise prescription

INTRODUCTION

Muscular dystrophy describes a group of approximately 40 inherited heterogeneous disorders characterized by progressive muscle weakness and muscle wasting (6). Duchenne muscular dystrophy (DMD) is the most severe and fatal, affecting 1/3500 boys (7). DMD is characterized by progressive loss of contractile function caused by the absence of the membrane-associated protein, dystrophin, and the associated proteins of the dystrophin glycoprotein complex (6). However, at present, the specific pathophysiological mechanisms that lead to onset of the disease have not yet been clearly defined.

DMD is an X chromosome–linked recessive disorder only affecting the male population, although some female carriers are mildly affected. DMD has a childhood onset and often occurs in children within the same family. Coincident with progressive muscle weakness is a gradual increase in the size of many affected muscles known as pseudohypertrophy. The later stages of the disease are characterized by abundant fibrosis and adipose tissue within the muscle (7). Therapeutics that are currently being used and developed for DMD include drug and gene interventions. Although some drugs are already being used to treat DMD patients (*e.g.*, prednisone), gene therapy has been limited to animal models. Because DMD is characterized by weak muscles, and overload resistance training is known to improve muscle strength, this should be a suitable therapy. For example, exercise has been used effectively to attenuate the loss of muscle strength and endurance with aging, but is there sufficient data in the literature to justify a sound exercise prescription to blunt or reverse the effects of DMD? Unfortunately, none. Limited use of exercise has been reported for patients with muscular dystrophy for approximately 50 yr, and is considered to be beneficial by some if performed at low intensity (2), but definitive human studies on the use of exercise as a treatment have not been conducted (Fig. 1). Determining the parameters of exercise prescription is not a simple case of assessing various training paradigms to improve muscle strength in those with DMD because exercise itself could exacerbate muscle damage. Thus, the limits to improve muscle function and minimize muscle damage must be carefully established. The purpose of this article is to propose that the exercise prescription necessary to improve strength and muscle endurance needs to be determined for individuals with DMD. It is suggested that a systematic analysis in dystrophic mice to establish musclefunctional capabilities and adaptations may be the safest approach to define the fundamentals of this exercise prescription.

DMD AND PHYSICAL ACTIVITY

Exercise, if properly prescribed and performed, is known to improve physiological capacities of muscle such as strength

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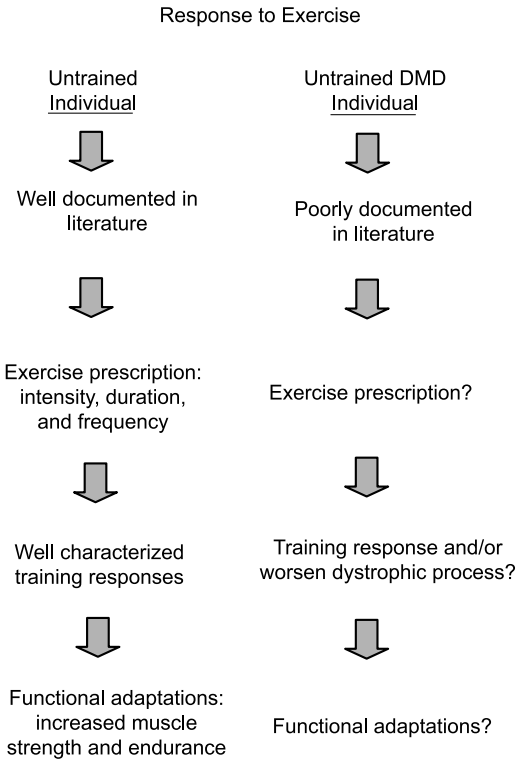

Figure 1. The figure shows that exercise prescription for strength and endurance training are well documented for untrained individuals in nondisease states. Unfortunately, for the patient with DMD, the data necessary to define exercise prescription for any of these functional properties are not presently known as are the responses to exercise by the dystrophic muscle. This can be corrected by conducting appropriate studies in dystrophic mice.

and endurance, with the adaptations dependent on the specific physiological system being stressed. Exercise, as a physiological stressor, stimulates various signaling pathways to increase expression of genes and their protein products that represent the adaptation to the stress (14) and, ultimately, yields the changes in physiologic function. Although the complete details of these pathways are not yet clear, the pathways evoked are dependent on the type of stressor. For example, the pathways that respond to endurance training, although not mutually exclusive, do differ from those of the hypertrophic response to overload resistance training (14). The physiological outcomes of resistance training include increased muscle mass and metabolic changes to provide for increased strength and less fatigue during physical activity. From a quality-of-life perspective, these are very desirable outcomes for individuals with DMD.

What are the major limitations to exercise in patients with DMD? In general terms, there are at least five major considerations. First, our understanding of the role that exercise might play in treatment of DMD is undefined because of insufficient well-controlled human studies and because exercise studies in *mdx* mice have been few and limited to descriptive measures of endurance exercise performance (2,11). This limitation could be caused by the ethical issues of placing individuals with DMD in a nontreatment group or worsening the dystrophic process with the physical activity prescribed. Second, exercise could exacerbate degeneration/regeneration and potentially lead to increased connective tissue deposition and exhaustion of satellite cell proliferative capacity. Third, improvement in muscle function may be limited because of the fragility of the dystrophic muscle membrane. Fourth, it is not presently known if animal or human dystrophic muscles respond to an exercise stressor in the same way as nondystrophic muscles. Fifth, given the first four limitations, in humans, how can we best assay the outcomes of the exercise prescription to prevent injury that might result from the physical activity?

The onset of DMD and its progression are associated with the onset of bipedal locomotion in children (2–3 yr of age), particularly when locomotion includes eccentric contractions such as walking down stairs (7). A hallmark of the dystrophic process is increased serum muscle creatine kinase, which suggests that the membranes of the muscles are fragile and leaky. Thus, muscle membrane weakness is considered a likely contributor to the onset and progression of DMD from signaling and/or mechanical perspectives (10). However, although weak muscle membranes are characteristic of older dystrophic mice, this does not seem to be true for younger dystrophic mice (Fig. 2) (9). This suggests, for dystrophic mice at least, that the exercise studies should be initiated at an early age. Although potential beneficial effects of exercise on skeletal muscle membrane are not specifically known, one could reasonably assume that a healthy muscle fiber membrane would adapt to the stresses placed on it, and it is known that signaling processes through the membrane become more efficient (*e.g.*, glucose uptake). Whether dystrophic muscle membranes respond similarly or if their mechanical and signal integrity is further compromised with regular exercise is not presently known. This indicates that a systematic approach to determine threshold stresses at which the muscle membranes are damaged and how this may

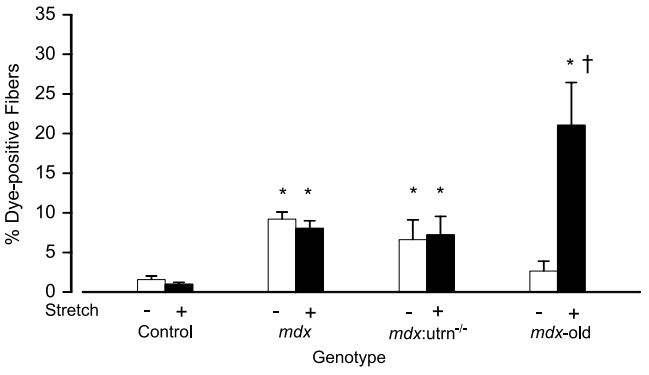

Figure 2. The figure shows that the uptake of the fluorescent dye procion orange as a marker of membrane damage is not different in the stretch (+) vs nonstretch (-) condition for the young control, *mdx*, or *mdx*:utrn$^{-/-}$ mice aged 9–12 d, but is different for *mdx*-old mice aged ~110 d. *Greater than control ($P < 0.05$). †Stretch condition greater than nonstretch condition ($P < 0.05$). EDL muscles were subjected to a stretch injury protocol *in vitro* (9). These data suggest that dystrophic membranes of early maturing dystrophic mice may not be as susceptible to membrane damage as older dystrophic mice. (Reprinted from Grange, R.W., T.G. Gainer, K.M. Marschner, R.J. Talmadge, and J.T. Stull. Fast-twitch skeletal muscles of dystrophic mouse pups are resistant to injury from acute mechanical stress. *Am. J. Physiol. Cell Physiol*. 283: C1090–C1101, 2002 (4). Copyright ® 2002 The American Physiological Society. Used with permission.)

change with age should both be clearly delineated in the dystrophic mouse.

Based on studies on animal muscle fibers *in vitro* and myotubes in culture, alterations in the sarcolemmal membranes and/or calcium channels within the membranes can lead to increased intracellular calcium and subsequent calcium-dependent proteolysis. Disruption of signal pathways such as those dependent on integrins or nitric oxide, and changes in the contractile apparatus also seem to contribute to the dystrophic process (12). All of these disease-associated outcomes complicate the beneficial effects of exercise, as for example, the membrane will be strained and possibly damaged during physical activity, and thereby exacerbate progression of the dystrophy. Thus, the exercise type and quantity and, potentially, the age (state of disease progression) at which the physical activity is undertaken may also be key determinants of dystrophic onset and progression. How best to reconcile the positive from the negative effects of exercise in dystrophic muscle represents a significant challenge.

Improved skeletal muscle strength and endurance are considered key requirements for individuals with DMD, particularly in children (3). Although there are beneficial effects of adopting an active lifestyle that involves low- to moderate-intensity resistance and aerobic exercise for slowly developing myopathies, high-resistance training and eccentric exercise should be avoided, especially in DMD (2). What seems to be most important is the type of muscular dystrophy to be treated (*i.e.*, on a continuum from less to more severe). Because DMD is considered the most severe of the muscular dystrophies, exercise prescription, unless based on sound scientific data, may be contraindicated.

HUMAN AND ANIMAL EXERCISE STUDIES IN DMD

Can exercise principles be applied to treat DMD? At present, there is no clear answer, but many questions. A major goal is to improve quality of life, but what are the risks? How best can responses to exercise be assessed noninvasively? Do human and animal dystrophic muscles respond to the same stressors in the same way as nondystrophic muscle? Given the known benefits of regular exercise to improve strength, these challenging questions must be addressed. Controlled studies to determine exercise prescription in boys with DMD are lacking, but are sorely needed. Yet, a very practical limitation is the number of subjects willing and capable of participating. Obviously, this is not a problem with *mdx* mice, and there have been two general approaches with exercise studies: 1) exercise as a therapeutic modality, typically voluntary wheel running, and 2) exercise to exacerbate the dystrophic condition, typically enforced treadmill running. Nevertheless, from a muscle mechanistic perspective, with a suitable shift in the emphases of animal studies, they are warranted and more appropriate than human studies. Simply put, the prescription of exercise and its beneficial and/or harmful effects in human dystrophic muscle are not known at present.

Human

A major goal is to improve the quality of life of patients with DMD by increasing muscle strength and muscle and cardiovascular endurance. It is likely that low-intensity activities are not detrimental, but the absence of controlled studies severely limits the necessary data for establishing clear principles for exercise prescription (2,3,11). It is also not clear how physical training influences the evolution of the muscular dystrophies (2).

Among the purposes of exercise in patients with DMD, there are those that are directed at clinical evaluation and functional improvement, such as inspiratory training and skeletal muscle strength training (3). Cardiovascular endurance seems less important than strength training, particularly in children (3), but this aspect of training should not be ignored. Furthermore, exercise tests which assess appropriate functional capabilities are desirable (3). What is most deficient, however, are the intensity, frequency, and duration parameters to define appropriate exercise prescription.

In humans with DMD, there have been studies conducted to address mechanisms of the disease (*e.g.*, gene expression analyses) but very few on the adaptation to physical activity. Understanding both the mechanisms of the disease and adaptations to exercise would benefit from additional gene array studies. More important are studies that will look at the expression of the gene protein products and their functions in response to specific exercise paradigms, and ultimately, the changes in physiological function. As noted, these types of studies are difficult to perform in humans because of ethical and practical issues. Thus, appropriately designed studies should first be conducted in dystrophic mouse models.

Animal

Exercise studies to address DMD have most typically been conducted on *mdx* mice. The *mdx* mouse has a naturally occurring single-point mutation in the dystrophin gene which results in the expression of a truncated nonfunctional dystrophin protein. As a result, the dystrophin glycoprotein complex is absent from the membrane. Thus, this mouse model is genotypically the same as DMD. The muscles of

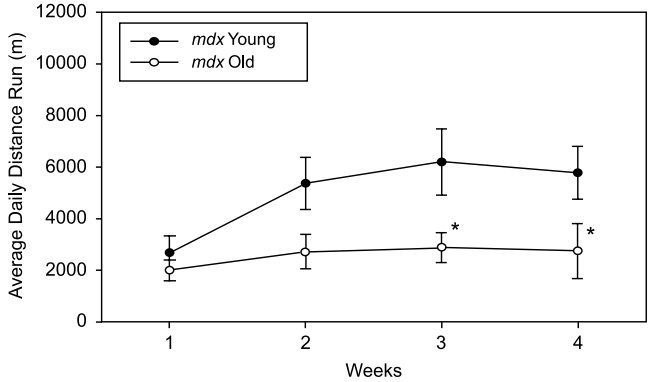

Figure 3. The figure shows that voluntary average daily running wheel distance is increased for young (4-wk-old), but not old (6-month-old), *mdx* mice over a 4-wk training period (4). These data suggest that voluntary endurance exercise when initiated at an early age can yield increased endurance capacity as a functional adaptation in *mdx* mice. [Adapted from Carter, G.T., M.A. Wineinger, S.A. Walsh, S.J. Horasek, R.T. Abresch, and W.M. Fowler Jr. Effect of voluntary wheel-running exercise on muscles of the mdx mouse. *Neuromuscl. Disord.* 5:323–32, 1995. Copyright ® 1995 Elsevier. Used with permission.]

the *mdx* mouse undergo degeneration/regeneration cycles similar to DMD, most acutely between ages 3 and 10 wk. Improved muscle stability after age 10 wk is attributed to upregulation of utrophin, a protein homolog of dystrophin. Another mouse model which more closely mimics the DMD phenotype is the *mdx*:utrophin$^{-/-}$ (*mdx*:utrn$^{-/-}$) mouse which lacks both dystrophin and utrophin. The *mdx*:utrn$^{-/-}$ mice exhibit nearly all symptoms of DMD, including reduced growth, diminished mobility, limb contractures, muscle weakness, spinal deformities (kyphosis), cardiomyopathy, myofibrosis, and premature death. In addition, skeletal muscle mass and stress-generating capacity are significantly reduced compared with control. However, few, if any, exercise studies have been conducted on these mice. Of the animal models, the golden retriever muscular dystrophy (GRMD) model most closely mimics DMD, but because of the limited availability of these animals and the expense of maintaining a colony, their use in exercise studies would be limited. However, once suitable exercise prescription has been defined in dystrophic mice, a directed exercise study with the GRMD dogs would be a good bridge to human studies.

There is an interesting divergence in the use of exercise with dystrophic mouse models, one approach to attenuate the dystrophic process (*e.g.*, voluntary running), and the other to exacerbate it (*e.g.*, enforced treadmill running). Remarkably, few studies have focused on inspiratory training or limb muscle strength training, which were identified as primary goals for patients with DMD (3). However, these types of training studies may be more difficult paradigms for mouse models.

Among the mouse studies directed at functional assessment and attenuation of the progression of muscular dystrophy, these most often used voluntary wheel running

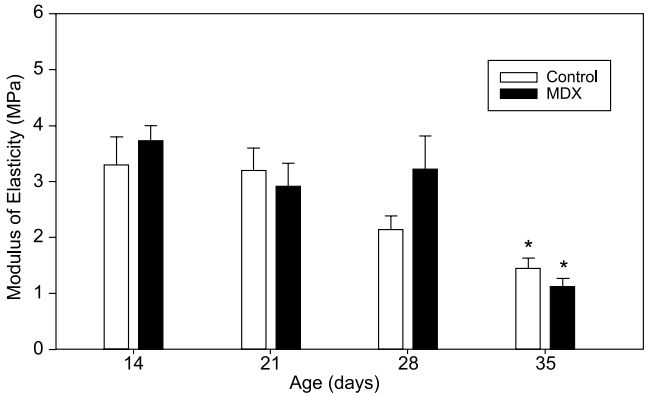

Figure 4. The figure shows that passive parallel stiffness (*i.e.,* modulus of elasticity) is not different between control and *mdx* EDL muscles during early maturation. *Parallel stiffness at age 35 d is less than that of other ages (n = 7, $P < 0.05$). These data suggest that the absence of dystrophin from the muscle membrane (part of parallel stiffness) does not influence stiffness if the imposed muscle stress is submaximal (*e.g., mdx*, ~70% of maximal isometric tetanic stress at age 28 d) (15). Does this hold true at greater stresses when the muscles are contracting? If so, this response could partially explain the ability of 4-wk-old young *mdx* mice to endurance train. Stress is muscle force divided by cross-sectional area. (Reprinted from Wolff A.V., A.K. Niday, K.A. Voelker, J.A. Call, N.E. Evans, K.P. Granata, and R.W. Grange. Passive mechanical properties of maturing EDL are not affected by lack of dystrophin. *Muscle Nerve* 34(3):304–312, 2006. Copyright ® 2006 John Wiley & Sons, Inc. Used with permission.)

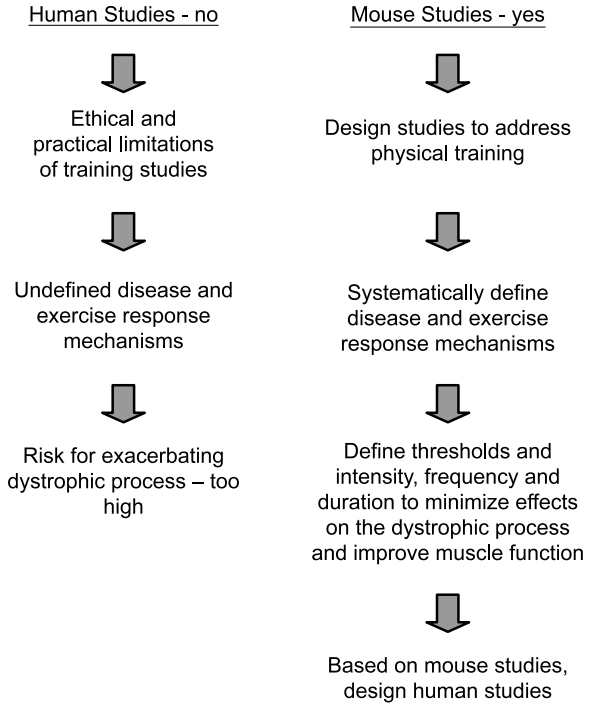

Figure 5. The absence of current scientific literature to support strength and endurance training in patients with DMD and the risks of conducting human studies in individuals with DMD suggest that studies should be first conducted in dystrophic mice.

exercise (4,5). Voluntary running seems to have positive effects, particularly if started at an early age. For example, young (4-wk-old) *mdx* mice increased voluntary running distance over a 4-wk training period (Fig. 3) (4), and extensive wheel running for 10–13 months was not found to be deleterious, even for diaphragm function, when initiated at age 3 wk in *mdx* mice (5). Positive outcomes from voluntary wheel running include increased fatigue resistance and muscle strength (5). These data suggest that endurance training is not deleterious to the dystrophic process if 1) the activity is voluntary and 2) it is begun at an early age. Recent evidence suggests that despite the absence of dystrophin and the dystrophin-glycoprotein complex, dystrophic membranes are less susceptible to injury during early maturation (9). Furthermore, at ages spanning the onset, initiation, and progression of the dystrophic process, passive mechanical properties, such as stiffness, do not differ between *mdx* and control extensor digitorum longus (EDL) muscles if the stress imposed is submaximal compared with maximum muscle capacity (Fig. 4) (15). As noted above, although weak muscle membranes are characteristic of older dystrophic mice, this may not be true for younger dystrophic mice, suggesting that exercise studies can be initiated at an early age. If mechanical properties between control and dystrophic muscles are also similar during active contractions at these ages, this may partially explain why voluntary running exercise initiated at an early age is beneficial rather than detrimental. These data also suggest that there may be a functional threshold for muscle activity below which dystrophic muscle damage, particularly at the membrane, will be limited, whereas muscle strength is improved. Determining this threshold could greatly guide suitable exercise prescription.

Enforced treadmill running has been used to exacerbate the dystrophic process, often to assess a therapy (*e.g.*, myoblast implantation). Treadmill running for 4–8 wk initiated at age 3–4 wk in control and *mdx* mice has been found to increase intracellular calcium (8), suggesting that running can impair calcium homeostasis in dystrophic fibers, and therefore likely contributes to disease progression. However, *mdx* mice can run voluntarily up to 11–13 months of age (5). Assuming that calcium homeostasis is impaired in the mice running voluntarily, this change in calcium does not seem to deter the willingness of the mice to run, although the overall volume of activity is decreased compared with control mice. With continued running, do the dystrophic muscles adapt to the increased calcium level, and/or are there different responses to enforced treadmill running versus voluntary running? Okano *et al.* (13) ran control and *mdx* mice on a treadmill for 10 wk and reported that chronic exercise may increase the active cycles of degeneration-regeneration possibly by enhancing regeneration and repair, but decreases in insulin-like growth factor-1 may accelerate age-dependent muscle wasting as the *mdx* mice age. Compared with voluntary running, the overall effects of treadmill running on dystrophic muscle seem more severe, most likely because the mice are forced to adapt to the imposed speeds and inclines. However, the volume and intensity can be more carefully regulated than with voluntary running. Nevertheless, comparison between studies using the two forms of running activity is difficult because the amounts of activity are likely not similar and the same experimental assessments have not been used. Thus, quantifying the work performed and establishing a standard set of assessments will be very helpful in determining the benefits versus detriments of enforced or voluntary running on the dystrophic process.

CONCLUSION

Based on the current literature, a major limitation to the use of exercise to treat neuromuscular diseases in general, and DMD specifically, is the absence of systematic analysis to determine the functional capabilities of the diseased muscles. Thus, there is a huge need for conducting studies to assess the benefits of exercise on DMD that range from training studies to determining physiologic outcomes to exploring the molecular signals that define the adaptive responses to the exercise stress. Because of the ethical and practical issues of determining exercise prescription for individuals with DMD, it is suggested that studies may be best conducted first in dystrophic animals (*e.g.*, mice) specifically to determine functional thresholds to maximize the benefits of the exercise and minimize the potential for exacerbating the dystrophy (Fig. 5). However, to effectively transfer these exercise principles to individuals with DMD, noninvasive assays such as those that have been developed for mouse skeletal muscle (1), should be developed for humans to assess beneficial muscle adaptations and potential muscle damage *in vivo*. Finally, it is suggested that a systematic approach by muscle and cardiovascular physiologists to define exercise prescription should be undertaken in an attempt to positively affect the dystrophic outcome.

FUTURE PERSPECTIVES

Studies in Mice

1. Align the objectives of animal studies with those that best represent the needs of training humans with DMD (*e.g.*, strength training, muscle endurance training, inspiratory training, etc.).
2. To facilitate comparisons among investigators, multiple but consistent assessments should be used to provide a comprehensive profile of the dystrophic muscle response to exercise. It is suggested that time-course studies over a wide range of ages be used to define dystrophic muscle gene expression profiles, biochemical processes, protein expression (*e.g.*, myosin heavy-chain content), and physiologic function before, during, and after defined exercise paradigms.
3. Specifically for strength training, establish a systematic approach to determine functional capabilities in dystrophic mice, including mechanical properties, such as stiffness, and contractile properties, such as work and power. Similar approaches can be designed for muscle endurance and cardiovascular endurance training. Determine exercise intensity, frequency, and duration to improve muscle function.
4. The functional threshold (*e.g.*, expressed as a percent of maximal isometric tetanic stress) at which dystrophic membranes become injured and can no longer be repaired should be determined. The range of stresses imposed on the muscle in these studies should reflect those experienced *in vivo*.
5. As a bridge to implementation in humans, the exercise prescription optimized on the basis of mouse studies should be tested in the GRMD model.

Studies in Humans

1. Design appropriate studies based on the findings from mouse and dog studies.
2. Develop new imaging methods to assay beneficial muscle remodeling and muscle damage *in vivo* that may result from the prescribed exercise.

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