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Safety, Feasibility, and Efficacy of Strengthening Exercise in Duchenne Muscular Dystrophy

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Abstract

Introduction: This two-part study explored the safety, feasibility, and efficacy of a mild-moderate resistance isometric leg exercise program in ambulatory boys with Duchenne Muscular Dystrophy (DMD).

Methods: First, we used a dose escalation paradigm with varying intensity and frequency of leg isometric exercise to determine the dose response and safety in 10 boys. Second, we examined safety and feasibility of a 12-week in-home, remotely-supervised, mild-moderate intensity strengthening program in 8 boys. Safety measures included T₂ MRI, creatine kinase levels, and pain. Peak strength and function (time to ascend/descend 4 stairs) were also measured.

Results: Dose-escalation revealed no signs of muscle damage. Seven of the 8 boys completed the 12-week in-home program with a compliance of 84.9%, no signs of muscle damage, and improvements in strength (knee extensors $p < 0.01$; knee flexors $p < 0.05$) and function (descending steps $p < 0.05$).

Discussion: An in-home, mild-moderate intensity leg exercise program is safe with potential to positively impact both strength and function in ambulatory boys with DMD.

Keywords

isometric exercise; T₂ MRI; in-home exercise program; functional ability; Duchenne muscular dystrophy

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INTRODUCTION

Only a few therapeutic interventions exist for Duchenne muscular dystrophy (DMD) which have limited impact on disease progression. Because of the enhanced fragility of dystrophic muscle, the thought of strengthening exercises in the DMD population has raised concerns due to potential for increasing muscle damage and injury¹. The majority of this premise may be founded in prior *mdx* mouse studies focused on exercise inducing muscle injury, with results clearly demonstrating that dystrophic muscle is more easily damaged than healthy muscle when subjected to high mechanical forces aimed at promoting muscle injury, as occurs during eccentric muscle actions². These preclinical results have contributed to clinical practice guidelines for those with neuromuscular disease (including DMD), where families are characteristically instructed to avoid strenuous physical activity for fears of inducing further muscle damage. Currently, many health care practitioners seeing patients with DMD caution against their participation in exercise or strength training due to the lack of definitive literature disputing these long-standing concerns of exercise exacerbating muscle damage.

Isometric muscle contractions, where force is generated without a change in length or joint angle, has been suggested as a possible mode of exercise in DMD since it diminishes the potential of exposing the muscle to damaging eccentric contractions³. Another possible benefit of the isometric exercise may relate to findings showing that preconditioning isometric exercise conveys a protective effect to minimize subsequent muscle damage in healthy human muscle⁴. A recent study reported significant improvements in muscle function with isometric contractions in *mdx* mice³, however, this mode of exercise has not been investigated in boys with DMD.

Interestingly, early exploratory clinical studies showed that resistance exercise without an isometric focus did not cause physical deterioration in DMD⁵. Both Vignos⁶ and de Lateur et al.⁷ reported improvements from strength training without any evidence of overload weakness. While these early studies exhibit methodological weaknesses (i.e. very few subjects, heterogenous samples, etc.), they provide some limited support to the idea that strengthening exercise in humans with DMD may not be harmful and may in fact be beneficial. A clinical study in DMD demonstrated that assisted cycling training can be safely implemented and delays the loss of motor function⁸. However, this type of low load, dynamic exercise had no significant effect on the boys' muscle strength. The literature currently contains insufficient evidence to support or refute the use of strengthening exercises in boys with DMD. A need exists to carefully and systematically examine the safety of using strength training in DMD.

Our objectives were: 1) Determine the dose response and safety of mild- to moderate-intensity isometric exercise in children with DMD and 2) Implement a pilot, remotely supervised home exercise intervention consisting of isometric strength training of the thigh musculature to examine its feasibility and safety.

METHODS

Participants:

Ambulatory boys with DMD were recruited to participate through online postings of Parent Project Muscular Dystrophy and the Muscular Dystrophy Association. Inclusion criteria were being 7-10.5 yrs of age, current use of corticosteroid therapy, and having the ability to walk 100m independently and ascend four steps. Exclusion criteria were any contraindication to an MR examination; presence of a secondary condition that would impact muscle function, metabolism, or motor control; and any behavioral problems that would create an inability to cooperate with exercise testing. For every participant in the study a parent gave written consent, and each subject provided written assent. All aspects of this research project were approved by the Institutional Review Board of the University of Florida.

Research Design:

Study 1: In order to determine the dose response and safety of isometric leg strengthening exercise in boys with DMD, a first study was performed consisting of three experiments (Supplemental Fig 1) focused on a dose escalation paradigm with varying intensity and frequency of exercise: 1) an acute bout of isometric exercise at 30% of maximal volitional contraction (MVC) in four boys with DMD; 2) an acute bout of isometric exercise at 50% MVC in another group of four boys with DMD; and 3) three bouts of isometric exercise at either 30% or 50% MVC in two boys with DMD, depending on which intensity was found to be safe in at least three of four boys tested in the previous two experiments. On day one of Experiments 1 and 2, baseline assessments were performed, consisting of three safety measures [magnetic resonance imaging of leg muscles, serum creatine kinase (CK), and pain rating] and determination of peak strength (MVC) of both the knee extensors (KE) and knee flexors (KF) of the right leg. On day three, one exercise session was performed, with safety measures repeated 48 hours later. Because all four participants in experiment 1 showed no evidence of muscle damage, the second experiment assessing 50% MVC (Supplemental Fig 1b) was performed in another group of DMD boys. Experiment 3 (Supplemental Fig 1c) used an intensity of 50% MVC that was found to be safe in the two previous experiments.

Study 2: The second study examined the safety and feasibility of an in-home, mild to moderate-intensity strengthening exercise program in ambulatory boys with DMD (Supplemental Fig 2). This study was performed following the determination of safety of one to three bouts of isometric exercise performed at 50% MVC (results from Study 1). Prior to the 12-week training program, baseline assessments were conducted at the University of Florida over a period of five days. On day one, safety measures, determination of peak strength for the bilateral KE and KF muscles, and measurement of functional ability (time to ascend and descend four steps) were performed. Following these assessments, an exercise session was performed later that day using both legs at the intensity deemed safe from Study 1 (50% MVC). A second exercise session was performed on day three, with safety measures re-assessed at day five. Following this assessment, a third exercise session was performed on day five. If safety measures were confirmed following these three exercise sessions, the study team would subsequently ship the exercise equipment to the participant's

home for the duration of the training program. The exercise training prescription parameters were to exercise (~1.5 hours/session) both legs three days per week at an intensity of 50% of the baseline MVC. Midway through the training (at 6 weeks), participants returned to the University of Florida for reassessment of safety, strength, and functional ability. The exercise intensity was then increased by 10% for the remaining 6 weeks of the exercise program. Patients returned to the University of Florida for a final assessment at the end of 12 weeks.

Safety Measures:

Three outcome measures were performed to assess the safety of the isometric exercise and to monitor the potential of any muscle damage from the exercise bout(s): 1) magnetic resonance (MR) proton transverse relaxation time (T_2) of the KE and KF musculature, 2) serum CK levels, and 3) subjective rating of any pain. Muscle damage was determined to have occurred if the primary measure of T_2 MR imaging and at least one of the other two safety measures were noted to be positive for indicating damage.

T_2 MRI: T_2 weighted MRI has been extensively used as a construct of muscle damage and inflammation/edema, when performed 24-48 hours following exercise⁹⁻¹⁶. It detects acute muscle damage *in vivo* and has been correlated with histological markers to become a non-invasive, sensitive marker of muscle injury¹⁷⁻²¹. In this study, MRI was performed with a Philips 3.0T whole body scanner (Philips Achieva Quasar Dual 3T, Philips, Best, the Netherlands) with subjects positioned supine in the magnet. Multi-slice (6 axial slices) multi-echo (16 echoes with equal spacing from 20-320 ms) T_2 -weighted MR imaging was performed on the bilateral upper legs (thigh)²². T_2 maps of the thigh muscles were created as previously done²³. Using custom written software, regions of interest (ROI) were manually drawn on the T_2 maps for eight KE and KF muscles (rectus femoris, vastus lateralis, vastus intermedius, vastus medialis, semitendinosus, semimembranosus, long head of the biceps femoris, and short head of the biceps femoris). All axial slices which had a clear representation and identifiable cross-sectional area were chosen for analysis. Mean T_2 values for each of the eight KE and KF muscles were then calculated within each of the eight ROIs. An elevation of the mean T_2 by 20% or greater (based on unpublished data) in any individual muscle was used as the threshold to indicate muscle damage had occurred.

Creatine Kinase levels: Blood samples were collected for determination of CK levels. An elevation in CK of 7,000 U/L from baseline was considered the threshold for muscle damage. This was based on pilot data we collected in a longitudinal, natural progression study involving 10 boys with DMD (unpublished data) where 7,000 U/L was equal to two standard deviations. This amount of change in CK for an indicator of muscle damage is far more stringent than has been suggested by others when using CK levels to assess muscle damage post-intervention in DMD²⁴.

Pain: Pain was assessed using a Wong-Baker FACES Pain Rating Scale with faces and corresponding numbers ranging from 0 (No Hurt) to 10 (Hurts Worst)²⁵. Subjects were asked to select one of the faces with its corresponding numerical rating and pain description. An increase in pain 4 was considered the threshold for muscle damage.

Muscle strength:

For strength assessment, isometric MVC was determined using a Biodex dynamometer as done previously (Biodex Medical Systems, Inc, Shirley, NY)^{22,26–28}. The hip was set at 90 degrees of flexion while the KF and KE were both tested at 60 degrees and 30 degrees of knee flexion. Subjects were strongly encouraged to kick (KE) or pull (KF) as hard as possible for approximately five seconds with one minute of rest between trials for a minimum of five trials at both knee positions. The highest torque value was used as the MVC for each of the four tests.

Functional Ability:

The time to ascend and descend four stairs was measured to assess functional ability²⁹. Up to three trials were performed, and the fastest time was recorded for both ascent and descent.

Exercise Sessions:

For Study 1, all of the exercise sessions were done with the right leg using a Biodex dynamometer. For Study 2, all of the exercise sessions were done for the bilateral lower extremities using a custom-built exercise set-up consisting of a modified leg curl machine (Valor Fitness, Seminole, FL), load cell and transducer cable (Interface Inc, Scottsdale, AZ), and a laptop (Supplemental Fig 3a). Exercise was done with the same positioning as the strength assessments. For both Study 1 and 2, participants performed four sets of six repetitions of isometric knee extension and knee flexion at both 30 and 60 degrees of knee flexion with a one-minute rest between each set³⁰. For all sessions done at the University of Florida, participants received both visual feedback from the computer monitor/laptop as well as verbal encouragement to hold the contraction for each repetition for three to five seconds. For the exercise sessions done at home for Study 2, real-time video conferencing via Skype (Skype Communications S.A.R.L., Luxembourg) was used to monitor each training session and provide verbal and visual feedback to the participants. Each laptop was also equipped with software that provided visual guidance for the subjects to achieve the target intensity. This target was a pair of horizontal lines within the software application that the research team individually placed on the laptop screen for each exercise session set at approximately $\pm 10\%$ of the desired intensity for each exercise (Supplemental Fig 3b). After the reassessment visit at 6 weeks, the exercise intensity was increased by 10% of the 6 weeks MVC and used for the exercise sessions from week six until week 12.

Statistical Analyses:

Descriptive statistics were used for all variables. Wilcoxon-signed rank tests (SPSS version 25) were used for assessing any changes over the course of the exercise intervention in Study 2. Significance was set at $\alpha < 0.05$.

RESULTS

Ten boys with DMD enrolled in Study 1, and eight of these same 10 boys later enrolled in Study 2 (average \pm SD time between enrollment in Study 1 and Study 2 was 1.0 ± 0.5 yrs). Table 1 provides the demographic information for all the participants at time of enrollment.

Study 1:

Four boys with DMD completed the first experiment at 30% MVC with no indications of muscle damage. Therefore, four more boys with DMD participated in the second experiment at 50% MVC, with no signs of muscle damage. Two additional participants with DMD completed the third experiment of exercising for three sessions at an intensity of 50% MVC. No evidence of muscle damage was observed. The mean T_2 percentage change after exercise at 30% and 50% MVC was 1.1 [standard deviation (SD) 2.4] across all participants, and no meaningful increase in pain was reported by any of the boys. Figure 1 demonstrates the minimal impact acute isometric exercise at 50% MVC had on CK values.

Study 2:

Based on the results from Study 1, the exercise training program was performed for the first six weeks at 50% MVC for Study 2. Seven of the eight boys with DMD enrolled in Study 2 completed the 12-week in-home, moderate intensity strengthening exercise program. The subject who withdrew from the study did so due to the burden of participation coupled with anxiety he was experiencing. For the boys who completed the study, compliance to perform the prescribed exercise sessions was high [84.9 (SD 9.0)%]. The primary safety outcome measure (MRI T_2) did not indicate signs of muscle damage for any of the participants (Fig 2a). Only one participant had an increase in CK >7,000 U/L (8,397 U/L), but he reported no pain (0/10) and only had minor increases in T_2 at 12 weeks (1.8 ms for KE and 0.4 ms for KF). Notably, strength and functional ability both improved after the exercise training program (Fig 2b), with all 7 participants who completed the program demonstrating strength gains.

DISCUSSION

Our results from Study 1 provide promising data that one to three bouts of mild- to moderate-intensity isometric exercise do not cause acute muscle damage in boys with DMD. Furthermore, results from Study 2 suggest a moderate-intensity isometric strengthening exercise program is not only safe but also promotes improvements in strength and function in ambulatory boys with DMD. To date, resistance exercise training is the only therapeutic strategy, other than corticosteroids, to increase muscle strength in boys with DMD. Our current study supports previous exploratory reports of improved muscle strength after a resistive exercise program^{6,7} and provides quantitative evidence of increased peak torque and improved function (time to descend 4 stairs). This pilot work supporting isometric strengthening exercise in children with DMD will assist in laying a foundation upon which much-needed future guidelines can be established for exercise prescription in patients with DMD.

Safety of acute isometric strengthening exercise for DMD:

Isometric strength training has never been assessed in DMD prior to our study despite its potential to induce strength gains without the risk of eccentric-associated muscle damage. Study 1 focused on developing isometric exercise at two different intensities, using a dose escalation paradigm similar to what is often used in Phase 1 pharmaceutical trials to determine a therapeutic dose for a new drug³¹. Our safety measures did not indicate any

muscle damage as a result of either 30% or 50% MVC isometric exercise. This finding contrasts with previous reports that serum CK increases in boys with DMD after acute bouts of exercise³², thereby reflecting their greater susceptibility to muscle injury with exercise¹. Variability in CK levels over time is known to be large in boys with DMD, with Jackson et al. reporting the coefficient of variation for CK to be approximately 35%³³. We selected an increase in CK by 7,000 U/L, which is quite conservative relative to what others have used as a threshold for indicating exercise-induced muscle damage²⁴. However, given variability in day-to-day levels of CK in DMD, other safety outcome measures reflecting potential muscle damage (i.e. T₂ MRI) are advocated. Given its high day-to-day reproducibility³⁴ and its sensitivity to detect change in inflammation/damage in muscle of boys with DMD²², T₂ MRI was our primary safety measure and revealed no increase after acute exercise.

Safety and feasibility of isometric strength training as an intervention for DMD:

The moderate intensity 12-week exercise program was safely performed in-home three times per week at 50-60% MVC, with every exercise session monitored remotely by the research team. Various strategies were implemented to promote the excellent compliance obtained. The first three exercise sessions were done on site with the investigative team to build a rapport with the participants and their families using the same equipment that was shipped to their homes. For the subsequent weeks while exercising at home, the boys received visual feedback on their performance by watching the screen of the laptop. The laptop displayed in real time the amount of torque they were producing for each exercise repetition with lines individually placed on the screen for them to have a goal of achieving the desired intensity of MVC. We also used video conferencing, with a member of the research team instructing and encouraging the participants for the duration of every exercise session. Others have successfully used close supervision involving therapists, teachers, and parents to promote feasibility and compliance in exercise studies with DMD^{8,35}. These methods, including parent engagement, mode of exercise, and ability to do the program in the participants' home environment may have contributed to the successful feasibility and compliance in this study. These are important considerations for future exercise studies as feasibility and compliance can be quite challenging in this patient population³⁶.

Efficacy of strength training in DMD:

Our results are notable in demonstrating improvements in muscle strength and function after 12 weeks of training. Being able to maintain and/or improve leg strength and walking ability may be the most important rehabilitation goals for ambulatory children with DMD³⁵. While recent exercise studies have highlighted the potential for cycle ergometry to improve functional abilities in DMD, they did not have any impact on muscle strength^{8,35}.

Interestingly, early exploratory studies assessing the value of exercise in DMD showed that strengthening exercise had a positive effect on strength with no evidence for overload weakness nor physical deterioration⁵⁻⁷. These studies used various range-of-motion, active-assisted or active-resistive strengthening exercises (not isometric). They concluded that strength exercise was not deleterious to patients with DMD and advocated for starting exercise early in the course of disease when there is a maximum amount of functional muscle. Despite these positive reports, advancement in the application of strength exercise

to boys with DMD did not occur. These early studies did not provide details on what safety measures or outcomes were used to monitor muscle damage and thereby conclude that exercise had no ill-effects. Therefore, to build upon these studies, we utilized a systematic approach to assess the potential of exercise-induced muscle damage. Taken together, the results support the notion that appropriately dosed strengthening exercise has the potential to be beneficial and safe in DMD.

Isometric exercise was the mode used throughout the two studies. While the exact mechanisms as to how isometric exercise impacts muscle in a protective fashion are unknown, various explanations have been put forth³⁷ including an apparent oxidant-mediated response to contractile activity³⁸, an increase in heat shock proteins³⁹, and neural adaptations³⁸ such as improvement in neuromuscular junction function or excitation-contraction coupling³. Exploring the mechanisms of how isometric contractions protect muscle will be key for future exercise prescription guidelines in the DMD patient population.

Study Limitations:

There are limitations to this work. First, there was no randomization nor a control group involved in this pilot study. Therefore, the results can not be generalized to ambulatory boys with DMD. A randomized controlled clinical trial is needed in order to confirm how this type of exercise program affects boys with DMD. However, it should be noted that all seven of the participants who completed Study 2 demonstrated an improvement in strength over the course of 12 weeks in spite of having a progressively debilitating disease. Another potential limitation to the exercise program in this study was the length of time to complete an exercise session. Each session was approximately 90 minutes in duration. While excellent compliance was noted, the sustainability of an exercise program for young boys should be more streamlined and efficient to better accommodate the patients' attention spans as this kind of exercise may not be deemed "fun" from the children's perspective. We recommend further investigation into means to shorten the amount of time for an exercise session to be no more than 30-45 minutes for these children. Last, there was no focus on exploring the mechanism(s) of the positive changes seen from exercise nor were measures included to assess functional changes beyond the timed stair test. Future work should include additional measures to assess the potential mechanisms for improvements from exercise and changes in functional mobility.

Conclusion:

The results of this work suggest an in-home, mild- to moderate-intensity isometric exercise program done 3x/week is safe and potentially has a positive effect on strength and function in ambulatory boys with DMD. No evidence of muscle damage was found after single bouts of isometric exercise nor after the 12-week isometric exercise training program. Boys who completed the exercise program had significantly greater leg strength and improved ability to descend stairs. Future research should include randomized controlled clinical trials with a larger sample to confirm the findings of this study and to optimize exercise parameters, especially in the context of a therapeutic study. In addition, other exercise paradigms (such as aerobic and/or combined aerobic and resistance) should be investigated with varying

modes and parameters of exercise to determine optimal exercise prescription for boys with DMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

BMI	Body mass index
CK	Creatine kinase
DMD	Duchenne muscular dystrophy
KE	Knee extensor muscle group
KF	Knee flexor muscle group
MR	Magnetic resonance
MVC	Maximal volitional contraction
ROI	Region of interest
SD	Standard deviation
T₂	Proton transverse relaxation time

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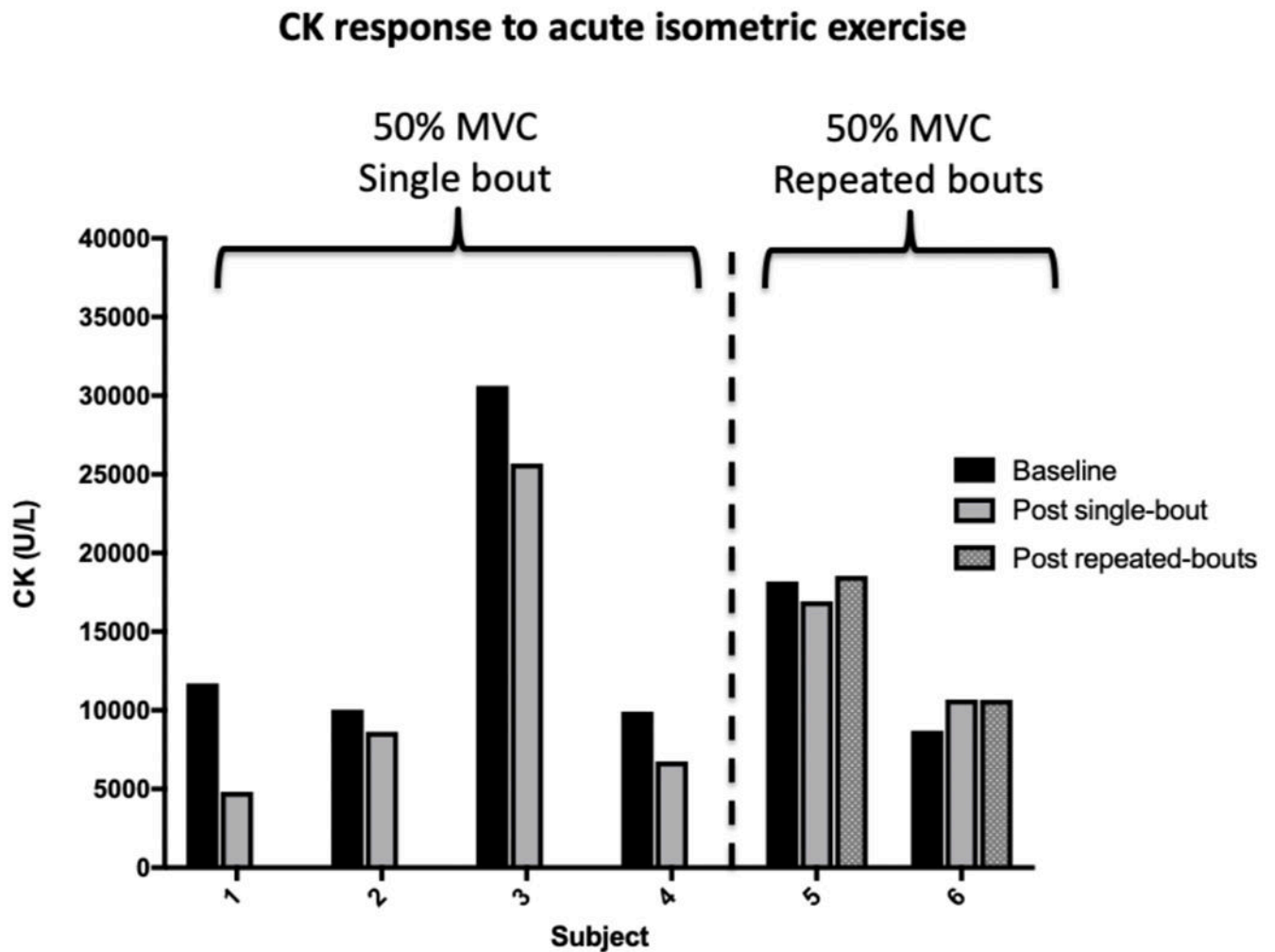


Figure 1.

The six participants from Study 1 who performed single or repeated bouts of acute moderate intensity strengthening exercise did not demonstrate any clinically meaningful increases in creatine kinase (CK) levels. Values are shown before (Baseline) and after a single bout (Subjects 1-4 from Experiment 2) or after 3 bouts (Subjects 5 and 6 from Experiment 3) of exercise. Each bout consisted of four sets of six repetitions of isometric knee extensor and knee flexor exercise at both 30 and 60 degrees of knee flexion at an intensity of 50% maximal volitional contraction (MVC).

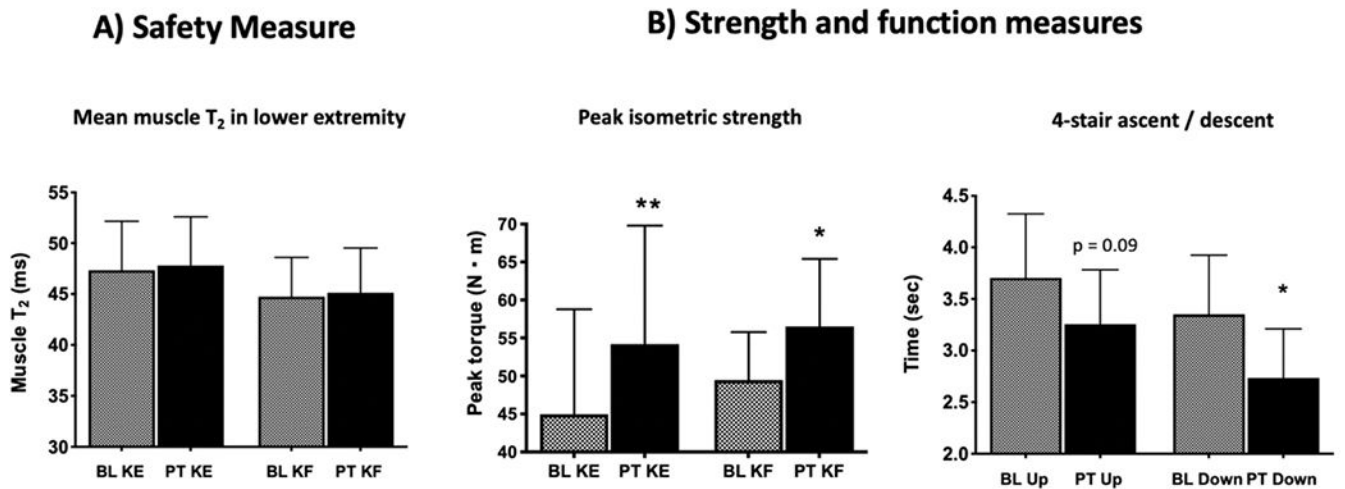


Figure 2.

Baseline (BL) measures compared to post-training (PT) of the knee extensors (KE) and flexors (KF) after 12 weeks of moderate intensity isometric exercise: A) No increase in the primary safety measure of MRI T₂ (a construct of muscle damage) was noted [non-significant increase in mean T₂ from baseline to 12 weeks: KE = 2.3 (SD 3.6)% and KF = 0.4 (SD 4.6)%]; B) Significant improvements occurred for both outcome measures assessing strength (sum of KE or KF at both leg positions tested) and functional ability. Peak torque increased by 20.6% for KE and 14.3% for KF, and the time to ascend (13.5%) and descend (22.7%) four steps improved after 12 weeks of leg strengthening. Differences noted between BL and PT (*p < 0.05, **p < 0.01).

Table 1.

Demographics

	Study 1 (n=10)	Study 2 (n=8)
Age (yrs)	8.3 (\pm 0.8)	9.3 (\pm 0.8)
Height (cm)	122 (\pm 6)	125 (\pm 7)
Weight (kg)	27.5 (\pm 7.3)	30.0 (\pm 9.2)
BMI (kg/m ²)	18.6 (\pm 5.0)	19.0 (\pm 4.6)
KE strength (N*m)	18.4 (\pm 12.6)	16.9 (\pm 12.1)

All values given in mean (\pm SD).

BMI = Body mass index; KE = Knee extensor musculature

KE strength is maximal volitional contraction assessed at 60 degrees of knee flexion at initial visit.

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