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Safety, feasibility, and efficacy of strengthening exercise in Duchenne muscular dystrophy

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Abstract

Background: 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-wk in-home, remotely supervised, mild–moderate intensity strengthening program in eight boys. Safety measures included T_2 MRI, creatine kinase levels, and pain. Peak strength and function (time to ascend/descend four stairs) were also measured.

Results: Dose-escalation revealed no signs of muscle damage. Seven of the eight boys completed the 12-wk in-home program with a compliance of 84.9%, no signs of muscle damage, and improvements in strength (knee extensors $P < .01$; knee flexors $P < .05$) and function (descending steps $P < .05$).

Conclusions: 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
Duchenne muscular dystrophy, functional ability, in-home exercise program, isometric exercise, T_2 MRI

1 | INTRODUCTION

Only a few therapeutic interventions exist for Duchenne muscular dystrophy (DMD), all of which have limited impact on disease progression. Because of the enhanced fragility of dystrophic muscle, the recommendation for strengthening exercises in the DMD population has raised concerns due to potential for increasing muscle damage and injury.[1] The majority of this premise may be founded in prior *mdx* mouse studies that clearly demonstrated 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 actions.[2] These preclinical results have resulted in frequent recommendations to patients with DMD to avoid strenuous physical activity.

Isometric muscle contractions, where force is generated without a change in length or joint angle, has been suggested as a possible

Abbreviations: CK, creatine kinase; DMD, Duchenne muscular dystrophy; KE, knee extensor muscle group; KF, knee flexor muscle group; MRI, magnetic resonance imaging; MVC, maximal volitional contraction; ROI, region of interest; T_2, proton transverse relaxation time.

mode of exercise in DMD, since it diminishes the potential of exposing the muscle to damaging eccentric contractions.[3] Another possible benefit of the isometric exercise may relate to findings showing that preconditioning isometric exercise conveys a protective effect to minimize subsequent exercise-induced muscle damage in healthy human muscle.[4] A recent study reported significant improvements in muscle function with isometric contractions in *mdx* mice[3]; 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 DMD.[5] Both Vignos[6] and de Lateur et al.[7] reported improvements from strength training without any evidence of overload weakness. These early studies 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 study demonstrated that assisted cycling training in DMD can be safely implemented and delays the loss of motor function, but had no significant effect on muscle strength.[8] The literature currently contains insufficient evidence to support or refute the use of strengthening exercises in boys with DMD.

Our objectives were to: (a) determine the dose response and safety of mild- to moderate-intensity isometric exercise in boys with DMD and (b) implement a pilot, remotely supervised home exercise intervention consisting of isometric strength training of the thigh musculature to examine its feasibility and safety.

2 | METHODS

2.1 | 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 y of age, current use of corticosteroid therapy, and having the ability to walk 100 m independently and ascend four steps. Exclusion criteria were any contraindication to a magnetic resonance imaging (MRI) 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.

2.2 | Research design

2.2.1 | 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 (Supporting Information Figure S1, which is available online) focused on a dose escalation paradigm with varying intensity and frequency of exercise: (a) one bout at 30% of maximal volitional contraction (MVC); (b) one bout at 50% MVC; and (c) three bouts at 50% MVC. On day 1 of these three experiments, baseline assessments were performed, consisting of three safety measures [MRI 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 3, one exercise session was performed with safety measures repeated 48 h later. For experiment 3, exercise sessions were repeated on days 8 and 10 with safety measures repeated on day 12.

2.2.2 | 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 (Supporting Information Figure S2). 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-wk training program, baseline assessments of safety, strength, and function; three exercise sessions; and a follow-up safety assessment were conducted at the University of Florida over a period of 5 days. These 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 would be used in their homes. If the follow-up safety measures did not indicate any signs of muscle damage, exercise equipment was shipped to the participant's home. The exercise training prescription parameters were to exercise (~1.5 h/session) both legs 3 days/wk at an intensity of 50% of the baseline MVC, and every exercise session was monitored remotely by the research team. Midway through the training, participants returned to the University of Florida for reassessment. The exercise intensity was then increased by 10% for the remaining 6 wk of the exercise program, and patients returned for a final assessment at the end of 12 wk.

2.3 | 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): (a) MRI proton transverse relaxation time (T_2) of the KE and KF musculature, (b) serum CK levels, and (c) 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.

2.3.1 | T_2 MRI

T_2 weighted MRI has been extensively used as a construct of muscle damage and inflammation/edema, when performed 24–48 h following exercise.[9-16] It detects acute muscle damage in vivo and has been correlated with histological markers to become a non-invasive, sensitive marker of muscle injury.[17-21] In this study, MRI was performed with a Philips 3.0T whole body scanner (Philips Achieva Quasar Dual 3 T, Philips, Best, the Netherlands) with subjects positioned supine in the magnet. Multi-slice (six axial slices) multi-echo (16 echoes with equal spacing from 20 to 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 done.[22] Using custom written software, regions of interest (ROIs) 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 that 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.

2.3.2 | CK levels

Blood samples were collected for determination of CK levels. An elevation in CK of 7000 U/L above 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 7000 U/L was equal to 2 SDs. 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 DMD.[23]

2.3.3 | 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).[24] 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.

2.4 | Muscle strength

For strength assessment, isometric MVC was determined using a Biodex dynamometer as done previously (Biodex Medical Systems, Inc, Shirley, NY).[25-28] The hip was set at 90° of flexion while the KF and KE were both tested at 60° and 30° of knee flexion. Subjects were strongly encouraged to kick (KE) or pull (KF) as hard as possible for approximately 5 s with 1 min 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.

2.5 | Functional ability

The time to ascend and descend four stairs was measured to assess functional ability.[29] Up to three trials were performed, and the fastest time was recorded for both ascent and descent.

2.6 | 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 (Supporting Information Figure S3a). Exercise was done with the same positioning as the strength assessments. For both studies 1 and 2, participants performed four sets of six repetitions of isometric knee extension and knee flexion at both 30° and 60° of knee flexion with a 1-min rest between each set.[30] 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 3 to 5 s. For the exercise sessions done at home for study 2, real-time video conferencing via Skype (Skype Communications SARL, 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 ±10% of the desired intensity for each exercise (Supporting Information Figure S3b). 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. After the reassessment visit at 6 wk, the exercise intensity was increased by 10% of the 6 wk MVC and used for the exercise sessions from week 6 until week 12.

2.7 | Statistical analyses

Descriptive statistics were used for all variables. Wilcoxon-signed rank tests (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) were used for assessing any changes over the course of the exercise intervention in study 2. Significance was set at alpha <0.05.

3 | RESULTS

Ten boys with DMD enrolled in study 1, and eight of these same 10 boys later enrolled in study 2 (average ± SD time between

TABLE 1 Demographics

	Study 1 (n = 10)	Study 2 (n = 8)
Age (y)	8.3 (±0.8)	9.3 (±0.8)
Height (cm)	122 (±6)	125 (±7)
Weight (kg)	27.5 (±7.3)	30.0 (±9.2)
BMI (kg/m²)	18.6 (±5.0)	19.0 (±4.6)
KE strength (N*m)	18.4 (±12.6)	16.9 (±12.1)

Note: All values given in mean (±SD).
KE strength is maximal volitional contraction assessed at 60° of knee flexion at initial visit.
Abbreviations: BMI, body mass index.

enrollment in studies 1 and 2 was 1.0 ± 0.5 y). Table 1 provides the demographic information for all the participants at time of enrollment.

3.0.1 | 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.

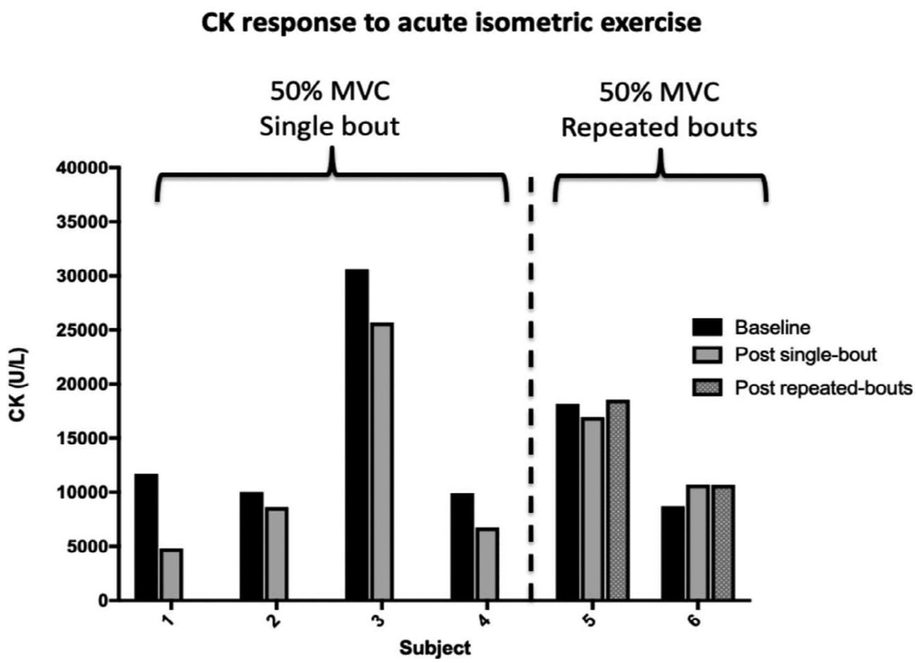

FIGURE 1 The six participants from study 1 who performed single or repeated bouts of acute moderate-intensity strengthening exercise did not demonstrate any clinically meaningful increases in CK levels. Values are shown before (baseline) and after a single bout (subjects 1–4 from experiment 2) or after 3 bouts (subjects 5 and 6 from experiment 3) of exercise

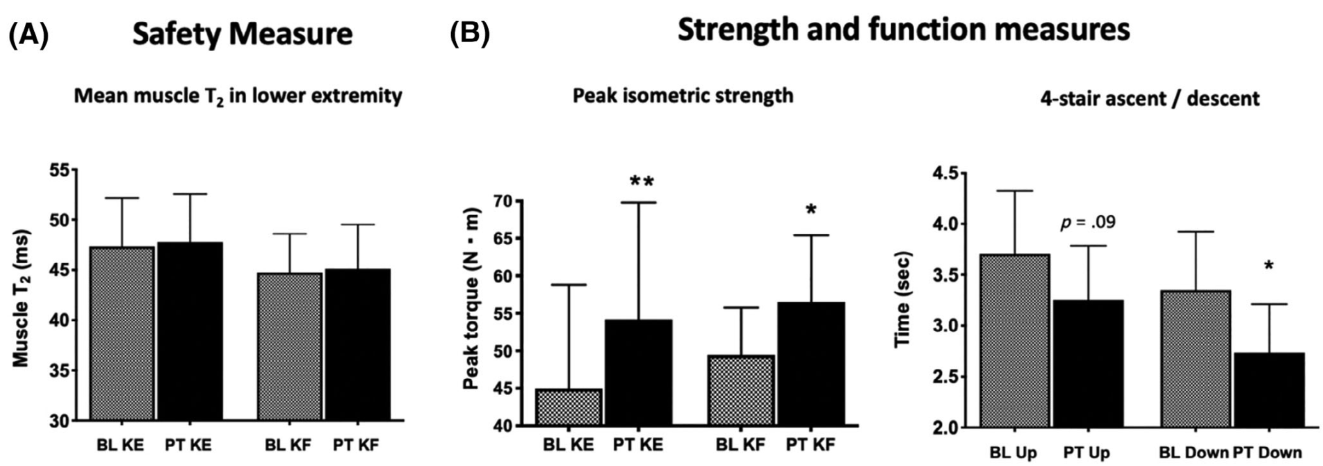

FIGURE 2 Baseline (BL) measures compared to post-training (PT) of the KE and KF after 12 wk of moderate-intensity isometric exercise: (A) No increase in the primary safety measure of MRI T_2 (a construct of muscle damage) was noted (non-significant increase in mean T_2 from baseline to 12 wk: KE = 2.3% [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 wk of leg strengthening. Differences noted between BL and PT (**P* < .05, ***P* < .01)

The mean T_2 percentage change after exercise at 30% and 50% MVC was 1.1 (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.

3.0.2 | Study 2

Based on the results from study 1, the exercise training program was performed for the first 6 wk at 50% MVC for study 2. Seven of the eight boys with DMD enrolled in study 2 completed the 12-wk 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 with 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 (Figure 2a). Only one participant had an increase in CK >7000 U/L (8,397 U/L), but he reported no pain (0/10) and only had minor increases in T_2 at 12 wk (1.8 ms for KE and 0.4 ms for KF). Notably, strength and functional ability both improved after the exercise training program (Figure 2b), with all seven participants who completed the program demonstrating strength gains.

4 | 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 four stairs).

4.1 | Safety of acute isometric strengthening exercise for DMD

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 drug.[31] 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 exercise,[32] thereby reflecting their greater susceptibility to muscle injury with exercise.[1] 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 7000 U/L, which is quite conservative relative to what others have used as a threshold for indicating exercise-induced muscle damage.[23] However, given variability in day-to-day levels of CK in DMD, other safety outcome measures reflecting potential muscle damage (ie, T_2 MRI) are advocated. Given its high day-to-day reproducibility[34] and its sensitivity to detect change in inflammation/damage in muscle of boys with DMD,[25] T_2 MRI was our primary safety measure and revealed no increase after acute exercise.

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

The moderate intensity 12-wwkeek exercise program was safely performed in-home 3x/wk at 50%–60% MVC. As outlined in the Methods section, various strategies were implemented to promote the excellent compliance obtained. 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 population.[36]

4.3 | Efficacy of strength training in DMD

Being able to maintain and/or improve leg strength and walking ability may be the most important rehabilitation goals for ambulatory children with DMD.[35] 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 deterioration, and advocated for starting exercise early in the course of disease when there is a maximum amount of functional muscle.[5-7] 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. The current study, in conjunction with previous studies, supports the notion that appropriately dosed strengthening exercise has the potential to improve strength and ability to descend stairs while being safe for boys with 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 forth,[37] including an apparent oxidant-mediated response to contractile activity,[38] an increase in heat shock proteins,[39] and neural adaptations[38] such as improvement in neuromuscular junction function or excitation-contraction coupling.[3] Exploring the mechanisms of how isometric contractions protect muscle will be key for future exercise prescription guidelines in the DMD patient population.

4.4 | 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 cannot 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 wk despite 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 min 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 min 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.

4.5 | Conclusions

The results of this work suggest an in-home, mild- to moderate-intensity isometric exercise program done 3x/wk is safe and potentially has a positive effect on strength and function in ambulatory boys with DMD. 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.

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.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Spaulding HR, Selsby JT. Is exercise the right medicine for dystrophic muscle? *Med Sci Sports Exerc*. 2018;50(9):1723-1732. https://doi.org/10.1249/MSS.0000000000001639. Review. PMID: 29649068.
2. Markert CD, Case LE, Carter GT, Furlong PA, Grange RW. Exercise and Duchenne muscular dystrophy: where we have been and where we need to go. *Muscle Nerve*. 2012;45(5):746-751. https://doi.org/10.1002/mus.23244 22499105.
3. Lindsay A, Larson AA, Verma M, Ervasti JM, Lowe DA. Isometeric resistance training increases strength and alters histopathology of dystrophin-deficient mouse skeletal muscle. *J Appl Physiol (1985)*. 2019;126(2):363-375. https://doi.org/10.1152/japplphysiol.00948.2018. Epub 2018 Dec 20. PMID: 30571283.
4. Chen HL, Nosaka K, Pearce AJ, Chen TC. Two maximal isometric contractions attenuate the magnitude of eccentric exercise-induced muscle damage. *Appl Physiol Nutr Metab*. 2012;37(4):680-689. https://doi.org/10.1139/h2012-035. Epub 2012 May 11. PMID: 22574731.
5. Scott OM, Hyde SA, Goddard C, Jones R, Dubowitz V. Effect of exercise in Duchenne muscular dystrophy. *Physiotherapy*. 1981;67(6):174-176. PMID: 7029578.
6. Vignos PJ Jr, Watkins MP. The effect of exercise in muscular dystrophy. *JAMA*. 1966;197(11):843-848. PMID: 5952771.
7. de Lateur BJ, Giaconi RM. Effect on maximal strength of submaximal exercise in Duchenne muscular dystrophy. *Am J Phys Med*. 1979;58(1):26-36. PMID: 434131.
8. Jansen M, van Alfen N, Geurts AC, de Groot IJ. Assisted bicycle training delays functional deterioration in boys with Duchenne muscular dystrophy: the randomized controlled trial "no use is disuse". *Neurorehabil Neural Repair*. 2013;27(9):816-827. https://doi.org/10.1177/1545968313496326. Epub 2013 Jul 24. PMID: 23884013.
9. LeBlanc AD, Jaweed M, Evans H. Evaluation of muscle injury using magnetic resonance imaging. *Clin J Sport Med*. 1993;3(1):26-30. PMID: 11538201.
10. Sorichter S, Koller A, Haid C, et al. Light concentric exercise and heavy eccentric muscle loading: effects of CK, MRI, and markers of inflammation. *Int J Sports Med*. 1995;16(5):288-292. https://doi.org/10.1055/s-2007-973007. PMID: 7558524.

11. Foley JM, Jayaraman RC, Prior BM, Pivarnik JM, Meyer RA. MR measurements of muscle damage and adaptation after eccentric exercise. *J Appl Physiol*. 1999;87(6):2311-2318. https://doi.org/10.1152/jappl.1999.87.6.2311. PMID 10601183.
12. Liu M, Bose P, Walter GA, Anderson DK, Thompson FJ, Vandenborne K. Changes in muscle T2 relaxation properties following spinal cord injury and locomotor training. *Eur J Appl Physiol*. 2006;97(3):355-361. https://doi.org/10.1007/s00421-006-0199-4. PMID: 16770473.
13. Larsen RG, Ringgaard S, Overgaard K. Localization and quantification of muscle damage by magnetic resonance imaging following step exercise in young women. *Scan J Med Sci Sports*. 2007;17(1):76-83. https://doi.org/10.1111/j.1600-0838.2006.00525.x. PMID: 17305942.
14. Fulford J, Eston RG, Rowlands AV, Davies RC. Assessment of magnetic resonance techniques to measure muscle damage 24 h after eccentric exercise. *Scand J Med Sci Sports*. 2015;25(1):e28-e39. https://doi.org/10.1111/sms.12234. Epub 2014 Apr 17. PMID: 24738493.
15. Maeo S, Ando Y, Kanehisa H, Kawakami Y. Localization of damage in the human leg muscles induced by downhill running. *Sci Rep*. 2017;7(1):5769. https://doi.org/10.1038/s41598-017-06129-8. PMID: 28720871.
16. Maeo S, Saito A, Otsuka S, Shan X, Kanehisa H, Kawakami Y. Localization of muscle damage within the quadriceps femoris induced by different types of eccentric exercise. *Scand J Med Sci Sports*. 2018;28(1):95-106. https://doi.org/10.1111/sms.12880. Epub 2017 Apr 6. PMID: 28314055.
17. Frimel TN, Walter GA, Gibbs JD, Gaidosh GS, Vandenborne K. Noninvasive monitoring of muscle damage during reloading following limb disuse. *Muscle Nerve*. 2005;32(5):605-612. PMID: 16003743.
18. Stekelenburg A, Oomens CW, Strijkers GJ, Nicolay K, Bader DL. Compression-induced deep tissue injury examined with magnetic resonance imaging and histology. *J Appl Physiol*. 2006;100(6):1946-1954. https://doi.org/10.1152/japplphsiol.00889.2005. PMID: 16484364.
19. Heemskerk AM, Drost MR, van Bochove GS, van Oosterhout MFM, Nicolay K, Strijkers GJ. DTI-based assessment of ischemia-reperfusion in mouse skeletal muscle. *Magn Reson Med*. 2006;56(2):272-281. https://doi.org/10.1002/mrm.20953. PMID: 16826605.
20. Mathur S, Vohra RS, Germain SA, et al. Changes in muscle T2 and tissue damage after downhill running in mdx mice. *Muscle Nerve*. 2011;43(6):878-886. https://doi.org/10.1002/mus.21986. Epub 2011 Apr 12. PMID: 21488051.
21. Ye F, Mathur S, Liu M, et al. Overexpression of insulin-like growth factor-1 attenuates skeletal muscle damage and accelerates muscle regeneration and functional recovery after disuse. *Exp Physiol*. 2013;98(5):1038-1052. https://doi.org/10.1113/expphysiol.2012.070722. Epub 2013 Jan 4. PMID: 23291913.
22. Barnard AM, Willcocks RJ, Finanger EL, et al. Skeletal muscle magnetic resonance biomarkers correlate with function and sentinel events in Duchenne muscular dystrophy. *PLoS One*. 2018;13(3):e0194283. https://doi.org/10.1371/journal.pone.0194283. eCollection 2018. PMID: 29554116.
23. Vry J, Schubert IJ, Semler O, Haug V, Schönau E, Kirschner J. Whole body vibration training in children with Duchenne muscular dystrophy and spinal muscular atrophy. *Eur J Paediatr Neurol*. 2014;18(2):140-149. https://doi.org/10.1016/j.ejpn.2013.09.005. Epub 2013 Oct 11. PMID: 24157400.
24. Wong DL, Baker CM. Pain in children: comparison of assessment scales. *Pediatr Nurs*. 1988;14(1):9-17. PMID: 3344163.
25. Arpan I, Willcocks RJ, Forbes SC, et al. Examinaton of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS. *Neurology*. 2014;83(11):974-980. https://doi.org/10.1212/WNL.0000000000000775. Epub 2014 Aug 6. PMID: 25098537.
26. Akima H, Lott D, Senesac C, et al. Relationships of thigh muscle contractile and non-contractile tissie with function, strength, and age in boys in Duchenne muscular dystrophy. *Neuromuscul Disord*. 2012;22(1):16-25. https://doi.org/10.1016/j.nmd.2011.06.750. Epub 2011 Jul 31. PMID: 21807516.
27. Mathur S, Lott DJ, Senesac C, et al. Age-related differences in lower-limb muscle cross-sectional area and torque production in boys with Duchenne muscular dystrophy. *Arch Phys Med Rehabil*. 2010;91(7):1051-1058. https://doi.org/10.1016/j.apmr.2010.03.024. PMID: 20599043.
28. Batra A, Harrington A, Lott DJ, et al. Two-year longitudinal changes in lower limb strength and its relation to loss in function in a large cohort of patients with Duchenne muscular dystrophy. *Am J Phys Med Rehabil*. 2018;97(10):734-740. https://doi.org/10.1097/PHM.0000000000000957. PMID: 29734234.
29. Martini J, Caromano FA, Carvalho EV, et al. Boys with Duchenne muscular dystrophy: 1-year locomotor changes in relation to a control group. *Percept Mot Skills*. 2018;125(1):40-56. https://doi.org/10.1177/0031512517740684. Epub 2017 Nov 24. PMID: 29171337.
30. Jones DA, Rutherford OM. Human muscle strength training: the effects of three different regimens and the nature of the resultant changes. *J Physiol*. 1987;391:1-11. PMID: 3443943.
31. Angevin E, Spitaleri G, Rodon J, et al. A first-in-human phase I study of SAR125844, a selective MET tyrosine kinase inhibitor, in patients with advanced solid tumours with MET amplification. *Eur J Cancer*. 2017;87:131-139. https://doi.org/10.1016/j.ejca.2017.10.016. Epub 2017 Nov 14. PMID: 29145039.
32. Pöche H, Hopfenmüller W, Hoffmann M. Detection and identification of myoglobin in serum by immunoblotting. Effect of exercise on patients with Duchenne muscular dystrophy. *Clin Physiol Biochem*. 1987;5(2):103-111. PMID: 3304774.
33. Jackson MJ, Round JM, Newham DJ, Edwards RH. An examination of some factors influencing creatine kinase in the blood of patients with muscular dystrophy. *Muscle Nerve*. 1987;10(1):15-21. PMID: 3561434.
34. Forbes SC, Walter GA, Rooney WD, et al. Skeletal muscles of ambulant children with Duchenne muscular dystrophy: validation of multicenter study of evaluation with MR imaging and MR spectroscopy. *Radiology*. 2013;269(1):198-207. https://doi.org/10.1148/radiol.13121948. Epub 2013 May 21. PMID: 23696684.
35. Alemdaroğlu I, Karaduman A, Yilmaz ÖT, Topaloğlu H. Different types of upper extremity exercise training in Duchenne muscular dystrophy: effects on functional performance, strength, endurance, and ambulation. *Muscle Nerve*. 2015;51(5):697-705. https://doi.org/10.1002/mus.24451. Epub 2015 Mar 5. PMID: 25196721.
36. Hind D, Parkin J, Whitworth V, et al. Aquatic therapy for boys with Duchenne muscular dystrophy (DMD): an external pilot randomised controlled trial. *Pilot Feasibility Stud*. 2017;3:16. https://doi.org/10.1186/s40814-017-0132-0. eCollection 2017. PMID: 28357131.
37. Kostek MC, Gordon B. Exercise is an adjuvant to contemporary dystrophy treatments. *Exerc Sport Sci Rev*. 2018;46(1):34-41. https://doi.org/10.1249/JES.0000000000000131. Review. PMID: 28857889.
38. McArdle F, Spiers S, Aldemir H, et al. Preconditioning of skeletal muscle against contraction-induced damage: the role of adaptations to oxidants in mice. *J Physiol*. 2004;561(Pt 1):233-244. Epub 2004 Aug 26. PMID: 15331678.
39. McArdle A, Pattwell D, Vasilaki A, Griffiths RD, Jackson MJ. Contractile activity-induced oxidative stress: cellular origin and adaptive responses. *Am J Physiol Cell Physiol*. 2001;280(3):C621-C627. PMID: 11171582.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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