The Effects of Testosterone and Transcutaneous Muscle Stimulation on Strength and Muscle Mass in Myotonic Dystrophy

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ABSTRACT

In myotonic dystrophy type 1 (DM1) quadriceps weakness often results in severe functional limitations and genu recurvatum. To improve quadriceps strength the effects of isometric tetanic contractions using transcutaneous muscle stimulation (TMS) and testosterone enanthate (TE) were assessed. Ten DM1 subjects underwent unilateral TMS 6 hours per day for 14 days. The stimulated leg was randomly assigned and sham stimulation was done on the opposite leg by transcutaneous nerve stimulation. Muscle mass was estimated by cross-sectional area computed tomography and strength was measured by Cybex ergometry. Following the initial TMS period, 8 of 10 subjects were given a 12-week course of TE (3 mg/kg/wk) followed by 14 days of TMS. Neither TMS nor TE improved strength. Following 12 weeks of TE, there was an average increase in muscle mass of at least 8.7 +/- 1.6 cm^2. These findings are consistent with the TE—increased muscle mass in DM1 as measured by creatinine clearance and total body potassium. The dissociation of mass and strength following TE and the failure of exercise to improve strength may have significance in characterizing the muscle defect in DM1.

Keywords: myotonic dystrophy; testosterone; transcutaneous muscle stimulation; muscle mass

Introduction

Muscle atrophy in myotonic dystrophy (DM1) is characterized by depressed muscle protein synthesis in the absence of accelerated degradation (1). Since exercise and testosterone can enhance muscle protein synthesis, we examined their effects on quadriceps muscle mass in DM1 (2,3). This was achieved using testosterone enanthate (TE) and, as a form of stimulated exercise, transcutaneous muscle stimulation (TMS), both alone and in concert (4–6). Our objective was to focus on the thigh muscles since quadricep muscle weakness and atrophy often result in severe functional limitation in patients with DM1.

For DM1, past studies have had mixed results, with benefits primarily in the arena of symptomatic treatment for myotonia rather than weakness. Mexiletine is well-tolerated by DM1 patients and improves myotonia but does not improve muscle strength or 6-minute walk distance (7–11). In a smaller study of 12 patients, imipramine showed improvements in grip and percussion myotonia (12). Creatine monohydrate tested in DM1 patients did not show significant benefits in muscle strength, though myalgias improved in a minority of myotonic dystrophy type 2 patients studied (13–15). A small study of five patients with DM1 reported subjective and objective (vigorimeter grip strength, electromyogram myotonic discharges) improvements with selenium and vitamin E supplementation, though a larger double-blind placebo-controlled trial did not show benefit (16–18). Thus, there is a clear gap in therapeutics, though several interventions are in the pipeline.

TMS has been studied in DM1 patients in various forms with suggestion that strength and functional status can improve, though other studies suggest no benefit to strength and functional outcome (19–24). One study tested functional electrical stimulation cycle training in four DM1 patients and showed improved muscle strength and endurance (25).

Hormone therapy, including growth hormone, dehydroepiandrosterone sulfate, testosterone, and insulin-like growth factor 1, that can improve muscle protein anabolism have been of high interest, though results have not been promising in regards to improvement of muscle strength and functional status (26–33). Testosterone has been shown to improve muscle mass but not strength in DM1 (34). Hormone therapy has not been tested in conjunction with TMS in this patient population.

Given the possible synergistic effects of TMS and TE, we tested the impact of these modalities on improving muscle mass and strength.

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Methods

The study was conducted at the Ohio State University (OSU) and was approved by the OSU institutional review board.

Patient Selection

Ten male DM1 patients volunteered and gave informed consent to participate in this protocol. The mean age of patients was 31 years (range 25 to 35 years). All patients had myotonia of hand grip and percussion myotonia of the thenar muscles, that was confirmed by needle electromyography. In addition, all patients had a family history for DM1 and exhibited extremity weakness. Genetic testing was not performed. In particular, all patients had knee extensor (quadriceps) muscle weakness: no better than Muscle Research Council (MRC) grade 4.

Evaluation of Muscle Mass

Computed tomography (CT) planimetry was used to measure the cross-sectional area of the thigh muscles. The level scanned was standardized to be one third the distance from the gluteal furrow to the level of minimum circumference just above the knee. The level was marked and maintained throughout the study. Measurements were made at the viewing console using a joystick device to guide a cursor around the area of interest. The contours of the quadriceps and the femur were outlined. Quadriceps muscle size was the area inside a curve separating the subcutaneous tissue from the muscle, minus the area of the femur.

Evaluation of Strength

Electromechanical isokinetic ergometry (Cybex dynamometer, Tumex Inc., Bay Shore, New York) was used to measure knee extensor strength at velocities of 60 degrees per second and 180 degrees per second. The strength was the mean of nine measurements taken during three individual settings over a two-day period.

Study Design

Phase 1. During the first phase, 10 male DM1 volunteers were admitted to the Clinical Research Center (CRC) and underwent unilateral TMS of the quadriceps muscle group. A Medtronic Respond II 3128 Neuromuscular Stimulator was utilized. A surface electrode was placed over the mid belly of the muscle. Prior to stimulation, the subject had each leg splinted to maintain the knees in 10 degrees of flexion. The stimulation was increased to produce a maximal, non-painful muscle contraction for 5 seconds every minute. Two three-hour stimulation periods were performed each day for 14 days. At the end of each treatment period, the knee splints and electrode were removed and the subjects were allowed to resume normal activity. The stimulated leg was splinted and had been randomly assigned. The control leg received sham stimulation at identical stimulation points over the anterior thigh during the same period with transcutaneous nerve stimulation (TENS). TENS produced no muscle contraction.

Phase 2. During the second phase, eight subjects (2 dropped out due to pain) had weekly intramuscular (IM) injections performed, in one leg (quadriceps muscles that were previously subjected to TMS), of TE, 3 mg/kg/week, for 12 weeks as outpatients.

Phase 3. During the final phase, eight subjects received TE and returned for a second CRC admission. Just as in phase 1, the same randomly assigned leg received 14 days of TMS while the control leg had sham stimulation with TENS.

Statistical methods

All analyses were performed in R (version 4.5.0) (35). All plots were generated using ggplot2 (36). Linear mixed effects models were fit using lmerTest (37).

A linear mixed effects model was fit to the change from baseline for each of the three phases. Subject-specific and subject-phase-specific random effects were included to capture the within-subject correlation amongst measurements for each leg. Covariates included in the mixed effects model included treatment group (non-stimulated side served as reference), phase (post-stimulation served as reference), and the interaction of treatment group and phase. T-test was used to compare changes in strength across the different phases.

Results

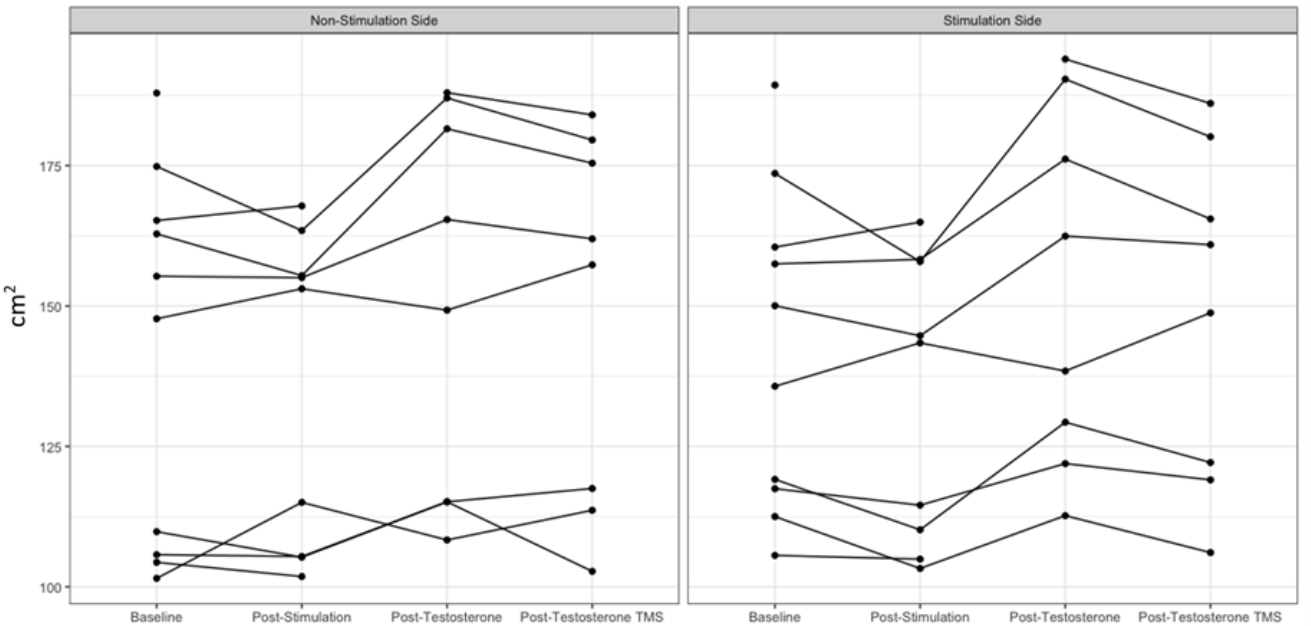
The data suggest that relative to baseline (table 1), there is increased muscle mass post-testosterone ($p = 0.008$) and post-testosterone with TMS ($p = 0.04$). However, relative to the non-stimulation side receiving TENS, there was no significant difference during any of the three phases in the stimulation side, relative to baseline. TMS did not produce any significant increase in muscle mass. Figure 1 shows the changes in muscle size across the study.

Relative to the previous phase (table 2), there was an increase in muscle mass post-testosterone ($p = 0.04$). However, relative to the non-stimulation side, there was no significant difference during any of the three phases, relative to the previous phase (Table 3). The combination of TE and TMS did not result in larger muscle mass compared to the TENS leg.

Table 1: Changes in muscle size relative to baseline

	Estimate (cm^2)	Std. Dev.	p-value	95% CI
Post Stimulation	-0.78	2.27	0.73	(-5.10, 3.49)
Post Testosterone	8.92	3.18	0.008	(2.79, 14.91)
Post Testosterone TMS	6.72	3.18	0.04	(0.58, 12.71)
Difference in Stimulated Side at Post Stimulation	-2.76	3.07	0.37	(-8.54, 3.02)
Difference in Stimulated Side at Post Testosterone	3.49	4.47	0.44	(-4.93, 11.92)
Difference in Stimulated Side at Post Testosterone TMS	1.12	4.47	0.80	(-7.31, 9.55)

Figure 1: Muscle size across the different phases of the study separated by non-stimulated and stimulated leg



Ten participants started the study and eight completed the study. The figure shows changes to muscle area (cm^2) across the study.

Table 2: Changes in muscle size relative to each phase

	Estimate (cm^2)	Std. Dev.	p-value	95% CI
Post Stimulation	-0.56	2.94	0.85	(-6.11, 5.00)
Post Testosterone	9.21	2.62	0.04	(1.12, 17.31)
Post Testosterone TMS	-1.65	4.29	0.70	(-9.74, 6.44)
Difference in Stimulated Side at Post Stimulation	-2.76	4.29	0.30	(-7.77, 2.24)
Difference in Stimulated Side at Post Testosterone	7.07	3.82	0.08	(-0.23, 14.36)
Difference in Stimulated Side at Post Testosterone TMS	0.39	3.82	0.92	(-6.91, 7.69)

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Table 3: Changes in muscle size across phases between non-stimulated and stimulated leg

	Non-Stimulation Side	Stimulation Side
Median Baseline (IQR)	151.52 (57.91)	142.88 (41.87)
Median Post-Stimulation (IQR)	153.07 (50.03)	143.43 (47.76)
Median Post-Testosterone (IQR)	157.33 (67.80)	150.44 (52.26)
Median Post-Testosterone TMS (IQR)	159.65 (59.94)	154.85 (47.81)
Change from Baseline		
Post-Stimulation	-0.31 (7.15)	-2.93 (9.77)
Post-Testosterone	8.13 (6.25)	7.40 (9.46)
Post-Testosterone TMS	7.18 (7.42)	4.77 (8.36)
Change Relative to Previous Phase		
Post-Stimulation	-0.31 (7.15)	-2.93 (9.77)
Post-Testosterone	9.81 (14.57)	13.58 (11.47)
Post-Testosterone TMS	-3.93 (5.93)	-6.88 (5.93)

Table 4: Impact of TMS, TE, and TMS with TE on strength in the non-stimulated and stimulated sides

Phase	Angular velocity	TMS vs TENS	Mean (N/m)	Standard error
Phase 1 (TMS vs TENS)	60 degrees/sec	TMS	4.3	2.69
		TENS	5	3.79
	180 degrees/second	TMS	4.4	1.61
		TENS	3.5	1.71
Phase 2 (TE only)	60 degrees/sec	TMS	2.88	1.11
		TENS	1.75	1.95
	180 degrees/second	TMS	0.88	1.7
		TENS	0.88	1.26
Phase 3 (TE + TMS)	60 degrees/sec	TMS	5.13	1.3
		TENS	3.38	3.82
	180 degrees/second	TMS	2.63	1.93
		TENS	1.38	1.51

In phase 1, there was no significant difference in Cybex strength measurement at 60 degrees or 180 degrees per second between TMS and TENS (p= 0.5). In phase 2, TE treatment for three months showed no effect on muscle strength compared to baseline (p= 0.15). In phase 3, there was no increase in strength between TMS or TENS in combination with TE treatment (p= 0.15) (table 4).

Discussion

The results reported here are a direct demonstration of increased thigh muscle mass following three months of TE administration in DM1. This supports previous indirect evidence by Griggs et al. that TE can increase muscle mass as estimated by creatinine excretion and total body potassium as well as the evidence that TE increased muscle protein synthesis in DM1 (38). Testosterone, an anabolic steroid, has also been shown to increase muscle mass in trained athletes (39). Its mechanism of action in those athletes includes the induction of protein synthesis in skeletal muscle and an anticatabolic effect that counteracts the catabolic influence of endogenously stimulated glucocorticoids. Despite the increased muscle mass and congruence with other studies, we were unable to demonstrate that TE produced an increase in strength in association with increased muscle mass.

In distinction to the effects of TE in DM1, TMS failed to show the increase in thigh muscle size seen after nine days in paraplegic patients with upper-motor neuron lesions (40). Our randomized controlled trials showed no effect on strength after 14 days of TMS. Because of the duration of TMS and the limitations of ergonometric, a small effect on strength could have been missed.

Novel approaches to improving strength in DM1 are needed given the lack of disease-modifying pharmacologic

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therapies. Nonpharmacologic approaches including TMS and strength training, or the combination of the two, have been tested not only in DM1, but also in a variety of other neuromuscular disorders (41–45). Neither strength training nor aerobic exercise appear to alter clinical outcomes measures in DM1, though there is conflicting data (46,47).

Other therapeutics are in development to achieve a disease modifying effect, such as antisense oligonucleotide targeted to the 3' untranslated region of the DMPK gene, which has shown promise in mouse models by improving strength (48). Adeno-associated virus type 6-mediated administration of miR30 RNAi hairpins to target the pathogenic *HSLAR* transgene in mice showed molecular and physiologic benefits (49). Various medications approved for other indications continue to be tested for use in DM1, including metformin and chloroquine. A small phase II study of metformin suggested a beneficial effect on mobility and gait abilities in myotonic patients (50). Chloroquine led to functional improvement in drosophila and mouse models of DM1 (51). In terms of improving symptoms, novel approaches are also being explored, such as with robotics and transcranial magnetic stimulation (52,53). With advances in robotics, exoskeleton assisted rehabilitation training was trialed in one patient with DM1 that showed improvement in strength and functional status (53).

Though this study did not show a benefit for strength of TE and TMS in isolation or in combination, research and drug development are actively being pursued. Several studies, including this, have shown that increasing muscle mass alone is not sufficient for improvement in strength, which may be related to defective function of diseased myofibers. TMS alone without an exercise program is not sufficient to lead to strength improvements. Future studies should not simply work to increase muscle mass but also increase strength.

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References

1. Griggs RC, Jozefowicz R, Kingston W, Nair KS, Herr BE, Halliday D. Mechanism of muscle wasting in myotonic dystrophy. Ann Neurol. 1990 May;27(5):505–12.

2. Goldberg AL, Etlinger JD, Goldspink DF, Jablecki C. Mechanism of work-induced hypertrophy of skeletal muscle. Med Sci Sports. 1975;7(3):185–98.

3. Griggs RC, Halliday D, Kingston W, Moxley RT. Effect of testosterone on muscle protein synthesis in myotonic dystrophy. Ann Neurol. 1986 Nov;20(5):590–6.

4. Gould N, Donnermeyer D, Pope M, Ashikaga T. Transcutaneous muscle stimulation as a method to retard disuse atrophy. Clin Orthop. 1982 Apr;(164):215–20.

5. Williams JG, Street M. Sequential faradism in quadriceps rehabilitation. Physiotherapy. 1976 Aug;62(8):252–4.

6. Eriksson E, Häggmark T. Comparison of isometric muscle training and electrical stimulation supplementing isometric muscle training in the recovery after major knee ligament surgery. A preliminary report. Am J Sports Med. 1979 Jun;7(3):169–71.

7. Fossati B, Sansone V, Panzeri MC, Zanolini A, De Ambroggi G, Cappato R, et al. Tolerability and safety of mexiletine in patients with myotonic dystrophy type 1 over time. J Neurol. 2009;256(SUPPL. 2):S128–9.

8. Sansone V, Panzeri M, Zanolini A, Fossati B, Meola G, Testa M, et al. Effects of mexiletine on cardiac parameters, muscle strength and myotonia in myotonic dystrophy type 1. Med Genet. 2009;21(3):435–6.

9. Logigian EL, Martens WB, Dilek N, Barbieri CA, Annis CL, Thornton CA, et al. Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. Neurology. 2010;74(18):1441–8.

10. Heatwole C, Luebbe E, Rosero S, Eichinger K, Martens W, Hilbert J, et al. Mexiletine for myotonic dystrophy type 1 (DM1): Results from a randomized, placebo controlled, clinical efficacy trial. Muscle Nerve. 2018;58(Supplement 1):S3.

11. Heatwole C, Luebbe E, Rosero S, Eichinger K, Martens W, Hilbert J, et al. Mexiletine in Myotonic Dystrophy Type 1: A Randomized, Double-Blind, Placebo-Controlled Trial. Neurology. 2021;96(2):e228–40.

12. Gascon GG, Staton RD, Patterson BD, Konewko PJ, Wilson H, Carlson KM, et al. A pilot controlled study of the use of imipramine to reduce myotonia. Am J Phys Med Rehabil. 1989;68(5):215–20.

13. Schneider-Gold C, Beck M, Wessig C, George A, Reiners K, Toyka KV, et al. Creatine monohydrate in DM2/PROMM: A double-blind placebo-controlled clinical study. Neurology. 2003;60(3):500–2.

14. Tarnopolsky M, Mahoney D, Thompson T, Naylor H, Doherty TJ. Creatine monohydrate supplementation does not increase muscle strength, lean body mass, or muscle phosphocreatine in patients with myotonic dystrophy type 1. Muscle Nerve. 2004;29(1):51–8.

15. Walter MC, Reilich P, Lochmuller H, Kohnen R, Schlotter B, Hautmann H, et al. Creatine monohydrate in myotonic dystrophy: a double-blind, placebo-controlled clinical study. J Neurol. 2002;249(12):1717–22.

16. Orndahl G, Sellden U, Hallin S. Myotonic dystrophy treated with selenium and vitamin E. Acta Med Scand. 1986;219(4):407–14.

17. Orndahl G, Rindby A, Selin E. Selenium therapy of myotonic dystrophy. Acta Med Scand. 1983;213(3):237–9.

18. Orndahl G, Grimby G, Grimby A, Johansson G, Wilhelmsen L. Functional deterioration and selenium-vitamin E treatment in myotonic dystrophy. A placebo-controlled study. J Intern Med. 1994;235(3):205–10.

19. Unlu Z. Myotonic dystrophy. Meandros Med Dent J. 2019;20(2):186–90.

20. Cudia P, Weis L, Baba A, Kiper P, Marcante A, Rossi S, et al. Effects of Functional Electrical Stimulation Lower Extremity Training in Myotonic Dystrophy Type I: A Pilot Controlled Study. Am J Phys Med Rehabil. 2016;95(11):809–17.

21. Roussel MP, Morin M, Gagnon C, Duchesne E. What is known about the effects of exercise or training to reduce skeletal muscle impairments of patients with myotonic dystrophy type 1? A scoping review. BMC Musculoskelet Disord. 2019;20(1):101.

22. Roussel MP, Morin M, Girardin M, Fortin AM, Leone M, Mathieu J, et al. Training program-induced skeletal muscle adaptations in two men with myotonic dystrophy type 1. BMC Res Notes. 2019;12(1):526.

23. Yoon SH, Baek JH, Leem J. Improved grip myotonia in a patient with myotonic dystrophy type 1 following electroacupuncture therapy: A CARE-compliant case report. Medicine (Baltimore). 2020;99(37):e21845.

24. Brady LI, MacNeil LG, Tarnopolsky MA. Impact of habitual exercise on the strength of individuals with myotonic dystrophy type 1. Am J Phys Med Rehabil. 2014;93(9):739–8.

25. Cudia P, Weis L, Baba A, Kiper P, Marcante A, Rossi S, et al. Effects of Functional Electrical Stimulation Lower Extremity Training in Myotonic Dystrophy Type I: A Pilot Controlled Study. Am J Phys Med Rehabil. 2016;95(11):809–17.

26. Nakazora H, Kurihara T. The effect of dehydroepiandrosterone sulfate (DHEAS) on myotonia: intracellular studies. Intern Med Tokyo Jpn. 2005;44(12):1247–51.

27. Moxley RT 3rd. Potential for growth factor treatment of muscle disease. Curr Opin Neurol. 1994;7(5):427–34.

28. Heatwole CR, Eichinger KJ, Friedman DI, Hilbert JE, Jackson CE, Logigian EL, et al. Open-label trial of recombinant human insulin-like growth factor 1/recombinant human insulin-like growth factor binding protein 3 in myotonic dystrophy type 1. Arch Neurol. 2011;68(1):37–44.

29. Vlachopapadopoulou E, Zachwieja JJ, Gertner JM, Manzione D, Bier DM, Matthews DE, et al. Metabolic and clinical response to recombinant human insulin-like growth factor I in myotonic dystrophy--a clinical research center study. J Clin Endocrinol Metab. 1995;80(12):3715–23.

30. Penisson-Besnier I, Devillers M, Porcher R, Orlikowski D, Doppler V, Desnuelle C, et al. Dehydroepiandrosterone for myotonic dystrophy type 1. Neurology. 2008;71(6):407–12.

31. Sugino M, Ohsawa N, Ito T, Ishida S, Yamasaki H, Kimura F, et al. A pilot study of dehydroepiandrosterone sulfate in myotonic dystrophy. Neurology. 1998;51(2):586–9.

32. Griggs RC, Kingston W, Herr BE, Forbes G, Moxley RT 3rd. Lack of relationship of hypogonadism to muscle wasting in myotonic dystrophy. Arch Neurol. 1985;42(9):881–5.

33. Al-Harbi TM, Bainbridge LJ, McQueen MJ, Tarnopolsky MA. Hypogonadism is common in men with myopathies. J Clin Neuromuscul Dis. 2008;9(4):397–401.

34. Griggs RC, Pandya S, Florence JM, Brooke MH, Kingston W, Miller JP, et al. Randomized controlled trial of testosterone in myotonic dystrophy. Neurology. 1989;39(2 Pt 1):219–22.

35. R Core Team. R: A Language and Environment for Statistical Computing. Vienna; 2021.

36. Wickham H. ggplot2: Elegant Graphics for Data Analysis. New York: Spring-Verlag; 2016.

37. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. J Stat Softw [Internet]. 2017 [cited 2022 Jun 4];82(13). Available from: http://www.jstatsoft.org/v82/i13/

38. Griggs RC, Kingston W, Herr BE, Forbes G, Moxley RT. Myotonic dystrophy: effect of testosterone on total body potassium and on creatinine excretion. Neurology. 1985 Jul;35(7):1035–40.

39. Haupt HA, Rovere GD. Anabolic steroids: a review of the literature. Am J Sports Med. 1984 Dec;12(6):469–84.

40. Buckley DC, Kudsk KA, Rose B, Koetting CA, Schlatter M, Miller CA. Transcutaneous muscle stimulation

promotes muscle growth in immobilized patients. JPEN J Parenter Enteral Nutr. 1987 Dec;11(6):547–51.

41. Voet NB, van der Kooi EL, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2019;12(100909747):CD003907.

42. Milner-Brown HS, Miller RG. Muscle strengthening through high-resistance weight training in patients with neuromuscular disorders. Arch Phys Med Rehabil. 1988;69(1):14–9.

43. Gianola S, Pecoraro V, Lambiase S, Gatti R, Banfi G, Moja L. Efficacy of Muscle Exercise in Patients with Muscular Dystrophy: A Systematic Review Showing a Missed Opportunity to Improve Outcomes. PLoS ONE. 2013;8(6):e65414.

44. Missaoui B, Rakotovao E, Bendaya S, Mane M, Pichon B, Faucher M, et al. Posture and gait abilities in patients with myotonic dystrophy (Steinert disease). Evaluation on the short-term of a rehabilitation program. Ann Phys Rehabil Med. 2010;53(6–7):387–98.

45. Gianola S, Castellini G, Pecoraro V, Monticone M, Banfi G, Moja L. Effect of Muscular Exercise on Patients With Muscular Dystrophy: A Systematic Review and Meta-Analysis of the Literature. Front Neurol. 2020;11(101546899):958.

46. Hebert L, Roussel M, Gagnon C, Duchesne E. P.26Strength training in myotonic dystrophy type 1: a promising therapeutic strategy. Neuromuscul Disord. 2019;29(Supplement 1):S49.

47. Voet NB, van der Kooi EL, Riphagen II, Lindeman E, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. Cochrane Database Syst Rev. 2010;(1):CD003907.

48. Jauvin D, Chretien J, Pandey SK, Martineau L, Revillod L, Bassez G, et al. Targeting DMPK with Antisense Oligonucleotide Improves Muscle Strength in Myotonic Dystrophy Type 1 Mice. Mol Ther Nucleic Acids. 2017;7(101581621):465–74.

49. Bisset DR, Zavaljevski M, Stoltzman C, Chamberlain JR. AAV6-mediated systemic administration of MIR30-based RNAI hairpins impacts muscle disease in the hsalr myotonic dystrophy mouse model. Mol Ther. 2013;21(SUPPL. 1):S173–4.

50. Bassez G, Audureau E, Hogrel JY, Arrouasse R, Baghdoyan S, Bhugaloo H, et al. Improved mobility with metformin in patients with myotonic dystrophy type 1: a randomized controlled trial. Brain J Neurol. 2018;141(10):2855–65.

51. Bargiela A, Sabater-Arcis M, Espinosa-Espinosa J, Zulaica M, Lopez de Munain A, Artero R. Increased Muscleblind levels by chloroquine treatment improve myotonic dystrophy type 1 phenotypes in in vitro and in vivo models. Proc Natl Acad Sci U S A. 2019;116(50):25203–13.

52. Greene E, Thonhoff J, John BS, Rosenfield DB, Helekar SA. Multifocal Noninvasive Magnetic Stimulation of the Primary Motor Cortex in Type 1 Myotonic Dystrophy -A Proof of Concept Pilot Study. J Neuromuscul Dis. 2021;8(6):963–72.

53. Portaro S, Naro A, Leo A, Cimino V, Balletta T, Buda A, et al. Overground exoskeletons may boost neuroplasticity in myotonic dystrophy type 1 rehabilitation: A case report. Medicine (Baltimore). 2019;98(46):e17582.