Published in final edited form as:

Am J Phys Med Rehabil. 2018 October ; 97(10): 734–740. doi:10.1097/PHM.0000000000000957.

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

Abhinandan Batra, PT, MA, PhD¹, Ann Harrington, PT, DPT, PhD², Donovan J Lott, PT, PhD, CSCS¹, Rebecca Willcocks, PhD¹, Claudia Senesac, PT, PhD¹, William McGehee, PT, PhD¹, Dandan Xu, MS³, Sunita Mathur, BScPT, MSc, PhD⁴, Michael J Daniels, PhD³, William D Rooney, PhD⁵, Sean C Forbes, PhD¹, William Triplett, BS¹, Jasjit K Deol, PT¹, Ishu Arpan, PT, PhD⁷, Roxanne Bendixen, PhD⁸, Richard Finkel, MD⁹, Erika Finanger, MD¹⁰, Gihan Tennekoon, MBBS, MRCS, LCRP¹¹, Barry Byrne, MD, PhD¹², Barry Russman, MD¹⁰, Lee H Sweeney, PhD¹³, Glenn Walter, PhD, and Krista Vandenborne, PT, PhD.¹

¹Department of Physical Therapy, University of Florida, Gainesville, Florida, USA

²Department of Physical Therapy, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

³Department of Statistic University of Florida, Gainesville, Florida, USA

⁴Department of Physical Therapy, University of Toronto, Toronto, Ontario, Canada

⁵Advanced Imaging Research Center, Oregon Health and Science University, Portland, Oregon, USA

⁶Department of Neurology, Oregon Health and Science University, Portland, Oregon, USA

⁷Department of Occupational Therapy, School of Health and Rehabilitation Sciences, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

⁸Department of Pediatrics, Nemours Children's Hospital, Orlando, Florida, USA

⁹Department of Pediatrics, Oregon Health and Science University, Portland, Oregon, USA

¹⁰Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

¹¹Department of Pediatrics, University of Florida, Gainesville, Florida, USA

¹²Department of Pharmacology and Therapeutics, University of Florida, Gainesville, Florida, USA

¹³Department of Physiology and Functional Genomics, University of Florida, Gainesville, Florida, USA

Corresponding Author: Krista Vandenborne, PT, PhD, University of Florida, Dept. of Physical Therapy, Box 100154, UFHSC, Gainesville, FL 32610, kvandenb@phhp.ufl.edu, (352) 273-6085.

Competing Interest: None

Financial Benefit to authors: None

Previous presentation: None

Abstract

Objective—The main objective of this study were to examine the effect of disease on strength in two functionally important lower limb muscles over a period of two-years in children with Duchene Muscular Dystrophy (DMD).

Design—Seventy-Seven DMD children participated in this study. Plantar flexors (PF), knee extensors (KE) strength and performance on timed tests (Six-min walk, 4-stairs, 10m-walk, supine-up) was assessed yearly over two-years. Multivariate normal regression was used to assess changes in strength over time in the DMD group. Spearman correlations were computed to examine relationship between strength and function.

Results—Normalized PF and KE strength, showed a significant decrease ($p<0.05$) over 2 years, with larger declines in KE. At baseline, KE strongly correlated with performance on timed tests. However, PF strength was found to be a stronger predictor of *loss* in ambulatory function. Modest correlations ($r=0.19-0.34$) were found between the decline in strength and functional performance over two-years.

Conclusions—This study describes the loss of lower limb strength in a large cohort of DMD children over two years. The findings support that lower limb strength alone can not account for the decline in performance on functional tests and the role of other contributing factors, such as compensatory strategies, should be considered.

Keywords

Duchenne Muscular Dystrophy; Strength; Function; Quantitative Myometry

Duchenne Muscular Dystrophy (DMD) is characterized by the progressive loss of skeletal muscle strength with children losing the ability to ambulate by 10–15 years of age^{1,2}. Individuals affected by DMD usually pass away in the third decade of life due to cardiopulmonary and/or respiratory complications^{3,4}. Even though DMD is a neuromuscular disorder characterized by a typical pattern of progression, a great degree of variability has been observed between patients in terms of strength and functional ability⁵.

At present, there is no cure for DMD⁶. Various therapeutic strategies including exon skipping⁷ and gene therapy⁸ are being pursued and moving through the different phases of development. These interventions are intended to ameliorate the disease pathology to improve muscle quality and increase functional ability as well as overall quality of life (QOL). Currently, glucocorticosteroids, noninvasive ventilatory support, cardioprotective and physical therapy management are considered the standard of care and have demonstrated a positive effect on strength, functional ability, pulmonary/cardiac functions, and a delay in the development of physical disabilities^{6,9}.

Since the primary goal of current treatments is to maintain (if not improve) muscle strength and functional ability, changes in these functional measures have been used as endpoints to understand the natural disease progression and evaluate therapeutic efficacy of various treatments^{1,5,10}. A variety of strength and functional tests has been used in both natural history studies^{1,5,10,11} and clinical trials^{7,12}. Quantitative myometry is one of the more

sensitive and reliable methods for examining force production of specific muscle groups and has been used in cross-sectional and longitudinal studies^{1,5,10,13}. To our knowledge, no study has compared the loss of force production in proximal and distal lower extremity muscle groups using quantitative myometry in children with DMD and examined its relationship to decline in functional ability.

The primary objective of this study was to examine the decline in muscle strength in proximal and distal leg muscle groups in a large cohort of children with DMD. We specifically examined the proximal knee extensors (KE) and distal plantar flexors (PF), given their important role in stair climbing and walking over the course of two years. Further, to elucidate the role of lower extremity muscle strength in the decline of functional ability, we also investigated the relationships between decline in lower limb strength and performance on ambulatory functional tests. Finally, we explored the ability of KE and PF strength to predict the loss of the ability to perform specific timed performance tests.

Methods

This study was conducted as part of a multi-center natural history study, referred to as Imaging DMD. Data on Seventy-Seven children with DMD who had participated in the Imaging DMD study over two-years and 46 control healthy individuals were analyzed for this study. Patients included had a confirmed diagnosis of DMD based on genetic report, with an onset of clinical symptoms observed prior to the age of 5 years. All subjects were on a continuous corticosteroid regimen (Deflazacort n=55; Prednisone n=22), able to walk 100 meters and climb four stairs. Patients were excluded if they reported any other medical condition that could affect their muscle function or overall functional performance. Subjects were tested for muscle strength and functional ability at three time points (baseline, one-year, and two-years). The study was approved by the Institutional Review Boards at each of the three participating, *ImagingDMD* sites (University of Florida, The Children's Hospital of Philadelphia, and Oregon Health Science University). At the start of the study written informed consent was obtained from a parent or legal guardian, and written assent was obtained from each subject.

At each time point, the subjects' age, height, and body weight were recorded. In addition, KE and PF isometric peak torque was measured using the isometric mode of a computerized isokinetic dynamometer (Biodex, System 3.0, Biodex Corp, Shirley, NY). Functional ability was assessed using four timed performance tests: the 10m walk/run^{1,5}, supine to stand^{14,15}, climb 4 stairs^{1,5} and six-minute walk¹⁶. For the first three timed tests, up to three trials were performed, and the fastest time to complete the task was recorded. If a subject was unable to complete the task within 45 seconds or without assistance, the subject was considered to have lost the ability to perform that test.

Isometric Muscle Strength testing

Subjects were seated in the Biodex dynamometer chair. KE strength testing was performed with the right knee and hip positioned at 90 degrees of flexion^{1,15}. For PF strength testing, a custom made platform was used, with the knee placed at approximately 20–30 degrees of flexion, while the ankle was placed in a neutral position (0 degrees of plantar flexion)^{1,15}.

For both KE and PF testing, the subject was asked to push against a static pad and maintain a maximal isometric force for approximately 5 seconds, followed by a rest period of one minute before the next trial. Subjects performed a minimum of five trials; in the event that the last trial's torque output exceeded all of the previous trials, the subject was asked to perform additional trials until there was a decrement or plateau in force production. The highest absolute peak torque (PT) value in ft-lb was calculated for both knee extensors (KE_{PT}) and plantar flexors (PF_{PT}). Since there is a great amount of variability in body size with age, both KE and PF peak torques were normalized to body surface area (BSA)^{1,17,18} using the formula below. Normalized torque (PTBSA) for both knee extensors (KE_{PTBSA}) and plantar flexors (PF_{PTBSA}) was also used for analysis.

$$(BSA(m^2) = \sqrt{(\text{height(cm)} \times \text{weight(kg)})/3600})^{17}$$

Functional testing

To examine the functional ability of subjects with DMD, the participants were asked to perform four timed performance tasks in the following order: 10m walk/run, six-minute walk, climbing 4 stairs, and supine to stand. Subjects performed each timed functional task, except for the six-minute walk test, three times, and the fastest time was used for analysis. Subjects were given an adequate break between the tasks to minimize the effect of fatigue¹⁹.

Statistical analysis

To examine the longitudinal progression in both absolute and normalized peak torque for both KE and PF, a multivariate regression analysis was used with time as the covariate (using SAS proc mixed, (2015) SAS Institute Inc., Cary, NC, USA). This approach assumes the missing data is ignorable (missing at random). In order to further examine the effect of age on disease progression, subjects were divided into four age groups: 5–6.9 years, 7–8.9 years, 9–10.9 years, and 11+ years. Subjects who were no longer able to perform timed performance tasks were assigned values higher than the most rapidly progressing ambulatory child and the lowest value was assigned for the six-minute walk test. We subsequently used rank based approaches that are invariant to the actual value used. For timed performance measures not available due to missing time points, we imputed them using a multivariate normal imputation approach (using the R package norm R Core Team (2012). R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). Since, subjects who were no longer able to perform functional tasks were assigned values, Spearman correlation coefficients (rank based) were used to determine the relationship between strength and functional abilities at baseline. This method was also used to determine the relationship over time, but for this analysis we did not include those that lost the ability to complete the “timed performance tests as just filling in the ‘extreme’ value as we did for baseline does not work in a longitudinal setting”. Area under the receiver operating characteristic (ROC) curve was used to determine the ability of strength in PF and KE to predict loss of ability in performing timed functional tasks. The level of significance for all the analysis was set at alpha = 0.05. Data are presented as Mean ± SE, unless otherwise stated.

Results

Subjects demographics

The demographics of subjects with DMD (n=77) who completed the 2 year study and age-matched controls (n=46), studied at a single time point, are provided in Table 1. The Lower Extremity Brooks score in patients with DMD ranged from 1 to 3.

Cross-sectional comparison of lower limb strength in DMD and age matched healthy controls

Both KE and PF peak torque were significantly lower in DMD patients compared to controls ($p<0.0001$). At baseline, a five fold difference was found in KE_{PT} (DMD= 11.8 ± 0.8 ftlb, control= 58.4 ± 4.8 ftlb) and a two-fold difference in PF_{PT} (DMD = 25.9 ± 1.0 ftlb, control = 59.6 ± 3.6 ftlb). A similar pattern was found when normalizing peak torque to body surface area, with both KE_{PTBSA} and PF_{PTBSA} showing significantly lower ($p<0.0001$) values in DMD ($KE_{PTBSA} = 12.3\pm0.9$ ftlb/cm²; $PF_{PTBSA} = 26.2\pm0.8$ ftlb/cm²) in comparison to controls ($KE_{PTBSA} = 49.5\pm2.5$ ftlb/cm²; $PF_{PTBSA} = 51.6\pm2.1$ ftlb/cm²).

Stratification of the control healthy and DMD subjects by age, showed a progressive increase in both absolute and normalized torque with age in control healthy subjects. In contrast, DMD subjects showed a trend towards increase in PF_{PT} , but not KE_{PT} , and both muscle groups when normalized to BSA showed a decline in force production with age (Table 2). This resulted in a widening of the gap between controls and DMD with age, with a 10-fold difference in KE_{PTBSA} in the oldest age group (11–14years).

Longitudinal changes in lower limb strength

In subjects with DMD, KE_{PT} , but not PF_{PT} , showed a significant but small decline over the period of two-years. However when strength was normalized to BSA (KE_{PTBSA} and PF_{PTBSA}), both muscle groups showed a significant decline over two-years at $P<0.001$ and $P<0.01$, respectively (Table 3).

When we examined the change in strength over two-years in the different age groups, a significant decline in absolute peak torque (KE_{PT} and PF_{PT}) was found in the 7–8.9 year age group, but not in the other age groups (Fig 1). When strength was normalized to BSA a significant decline in both KE_{PTBSA} and PF_{PTBSA} was found in the 7–8.9 years and 9–10.9 year old age group (Fig 1).

Relationship between strength and performance on timed functional tests

At baseline, both absolute and normalized torque in the KE showed a significant correlation with performance on the functional tests, with stronger correlations observed with the shorter timed tests ($r=0.56-0.71$) then the six-minute walk test ($r=0.34-0.38$) (Table 4). Absolute peak torque production in the PF did not show a significant correlation with any of the timed tests, but normalized PF_{PTBSA} demonstrated a modest correlation with all functional tests ($r=0.27-0.38$).

When examining the relationship between two-year changes in strength and performance on timed functional tasks, significant correlations were found with absolute and normalized strength in both muscle groups for specific tasks, but the strength of the correlations were weak, as none of the r values exceeded 0.33 (Table 4).

Strength as predictor of loss of functional ability

Using ROC curves, we estimated an optimal threshold and the associated sensitivity and specificity for each strength variable to predict loss of the ability to perform each of the four functional measures (Table 5). In general normalized strength was a better predictor of loss of function than absolute strength. The best predictor was PF_{PTBSA} with relatively high sensitivity and specificity for all the functional measures, except supine to stand.

Discussion

To our knowledge, this is the first study to compare the longitudinal changes in KE and PF strength over 2-years, using quantitative strength testing measures in a large cohort of subjects with DMD. In boys 5–14 years old, all taking corticosteroids, a significant decline in absolute knee extensor strength, but not plantar flexor strength, was detected. However, when normalizing strength to BSA, to compensate for changes in height and body weight, both muscle groups showed a significant decline in strength production. Cross-sectionally, baseline KE (both absolute and normalized) showed a strong correlation with performance on the ambulatory functional tests. However, the correlation between both longitudinal changes in KE and PF strength and changes in performance on functional tests was modest. Using ROC curves, PF strength was found to be a stronger predictor of *loss* in the ability to complete the different timed performance tasks across two years, except for the ability to get up from supine.

The anti-gravity knee extensors and ankle plantar flexors were selected for investigation as these two muscle groups have been shown to play a significant role in daily functions such as standing, walking, stair climbing and getting up from the floor^{20,21}. Both muscle groups are also well known to display atrophy or muscle wasting in a variety of conditions associated with inactivity. Recent, Magnetic Resonance Imaging studies in DMD have demonstrated significant atrophy, fatty infiltration and muscle pathology in the rectus femoris and vasti muscles, responsible for knee extension²². The soleus and gastrocnemius muscles on the other hand typically display muscle hypertrophy, prior to the replacement of muscle by intramuscular fat²³. Finally, KE muscle strength has been used in a number of clinical trials as a functional endpoint. Fewer clinical trials have included PF, presumably due to the difficulty in reliably measuring this muscle group using MMT and quantitative myometry. For this purpose we utilized an isokinetic dynamometer and a custom designed platform.

Strength normalized to BSA was found to be more sensitive to disease progression than absolute strength. Previous studies in pediatric populations have shown the importance of reporting normalized data, as changes in height and weight with growth and normal development can act as confounding factors²⁴. Subjects with DMD demonstrated a decline in both normalized KE and PF over the course of 2 years, while healthy subjects displayed

an increase in normalized strength with age, widening the gap between both populations. These results support earlier pilot findings from our laboratory (2010)¹. Other factors, beyond disease pathology, such as delayed onset of puberty and stocky stature with corticosteroid use may also contribute to increasing gap with age.

No significant decline in lower limb strength was observed over the course of 2 years in boy with DMD in the youngest age group (5–6.9 years). This might be due to the fact that gains in muscle strength with normal growth and development in this age group out way the effect of disease pathology on muscle. In general a decline in muscle strength was seen around 7 years of age. These findings are consistent with results reported by Learario et al (2012)¹⁰ who examined the knee extensors and found deterioration in strength starting at a mean age of 7.5 years. In contrast, Mc Donald et al (1995)⁵ reported a decline in subjects ages 4–6 year old. This difference may be attributed to an improvement in care. All the subjects enrolled in our study were taking corticosteroids, which has been shown to improve force production and functional ability in ambulatory subjects with DMD^{12,25}. While McDonald et al (1995)⁷ did not specifically report the corticosteroid use in his subject population, the study was performed in the 90s when corticosteroids was not considered standard of care.

Although corticosteroid treatment is considered the standard of care in DMD and has been associated with improvements in muscle strength and a delay of loss of ambulation, it does have some side effects. Common reported side effects include weight gain, Cushingoid, loss of bone mass and behavioral deficits^{25,26}. Presently, new drugs are under development that strive to provide some of the same positive effects, such as reduction in inflammation, while minimizing the side effects typically associated with corticosteroid use^{26,27}.

Evaluating the relationship between strength and function longitudinally

The ability to perform ambulatory timed tasks was more strongly correlated to strength in the proximal KE group compared to the distal PF group. These findings indicate that these timed performance tasks, commonly used in clinical trials, are more dependent on proximal muscle strength. Of all the timed functional performance tests, 6MWT showed the weakest correlation with muscle strength. While the 6MWT is well accepted by the FDA as a primary outcome measures, it may not directly assess lower limb muscle performance. The 6MWT was initially developed as cardiopulmonary assessment test and has been criticized for its potential dependence on motivation, especially in a pediatric population. However, given the limited number of clinically relevant outcome measures available it remains a valuable endpoint in clinical trials targeting ambulatory DMD patients.

Despite a strong cross-sectional relationship between KE strength and performance on timed functional tasks, only a modest correlation was found between change in strength and change in function over two years. Similarly, Beenaker et al (2005)¹⁴ reported that the declines in strength and loss of functional ability do not mirror one another. These findings emphasize that a decrease in functional ability is not solely dependent on strength of the lower extremities; other factors such as strength of the trunk musculature²⁸, compensatory strategies^{28,29}, and contractures³⁰ may play an important role. Interestingly, PF strength was a relatively better predictor of loss of the ability to perform all functional tasks, except for supine to stand. Based on these findings, we speculate that patients with extensive

involvement of the knee extensors can potentially still complete ambulatory tests, and only after significant decline in PF strength, do they lose the ability to perform the test altogether.

This study provides an account of changes in proximal and distal lower limb strength in a large cohort of subjects with DMD over a period of two-years and examines the relationship with decline in performance on timed functional tests. Our findings support the concept that change in lower limb strength alone does not account for the decline in functional ability in DMD. Based on these findings future studies should examine how changes in other factors, such as neural drive, strength of postural muscles, and compensatory strategies affect overall functional ability in this patient population.

Acknowledgments

Funding: Magnetic Resonance Imaging and Biomarkers in Muscular Dystrophy (NIAMS, NINDS: R01 AR056973); Wellstone Grant (NIAMS: U54AR052646).

The authors would like to acknowledge the contributions of Dr. Steve Chrzanowski and Ms. Catherine Powers, University of Florida, for their guidance and assistance in refining this paper.

References

1. 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. *Archives of Physical Medicine and Rehabilitation*. 2010; 91(7):1051–1058. [PubMed: 20599043]
2. Sussman M. Duchenne Muscular Dystrophy. *J Am Acad Orthop Surg*. 2002; 10(2):138–151. [PubMed: 11929208]
3. Eagle M, Chandler C, Baudouin SV, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. *Neuromuscular Disorders*. 2002; 12(10):926–929. [PubMed: 12467747]
4. Ishikawa Y, Miura T, Ishikawa Y, et al. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. *Neuromuscul Disord*. 2011; 21(1):47–51. [PubMed: 21144751]
5. McDonald CM, Abresch RT, Carter GT, et al. Profiles of neuromuscular diseases. Duchenne muscular dystrophy. *American journal of physical medicine & rehabilitation/Association of Academic Physiatrists*. 1995; 74(5 Suppl):S70.
6. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018; 17(3):251–267. [PubMed: 29395989]
7. Cirak S, Arechavala-Gomez V, Guglieri M, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. *The Lancet*. 2011; 378(9791):595–605.
8. Blankinship MJ, Gregorevic P, Chamberlain JS. Gene Therapy Strategies for Duchenne Muscular Dystrophy Utilizing Recombinant Adeno-associated Virus Vectors. *Mol Ther*. 2006; 13(2):241–249. [PubMed: 16361117]
9. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *Lancet Neurol*. 2018
10. Lerario A, Bonfiglio S, Sormani M, et al. Quantitative muscle strength assessment in duchenne muscular dystrophy: longitudinal study and correlation with functional measures. *BMC Neurology*. 2012; 12(1):91. [PubMed: 22974002]
11. McDonald CM, Henricson EK, Abresch RT, et al. THE 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle & Nerve*. 2013; 48(3):343–356. [PubMed: 23681930]

12. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. *American journal of physical medicine & rehabilitation*. 2005; 84(11):843–850. [PubMed: 16244521]
13. Stuberger WA, Metcalf WK. Reliability of quantitative muscle testing in healthy children and in children with Duchenne muscular dystrophy using a hand-held dynamometer. *Physical Therapy*. 1988; 68(6):977–982. [PubMed: 3375322]
14. Beenakker EAC, Maurits NM, Fock JM, Brouwer OF, van der Hoeven JH. Functional ability and muscle force in healthy children and ambulant Duchenne muscular dystrophy patients. *European Journal of Paediatric Neurology*. 2005; 9(6):387–393. [PubMed: 16102988]
15. Akima H, Lott D, Senesac C, et al. Relationships of thigh muscle contractile and non-contractile tissue with function, strength, and age in boys with Duchenne muscular dystrophy. *Neuromuscular Disorders*. 2012; 22(1):16–25. [PubMed: 21807516]
16. McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. *Muscle & Nerve*. 2010; 41(4):500–510. [PubMed: 19941337]
17. Gehan EA, George SL. Estimation of human body surface area from height and weight. *Cancer Chemother Rep*. 1970; 54(4):225. [PubMed: 5527019]
18. Andres PL, English R, Mendoza M, et al. Developing normalized strength scores for neuromuscular research. *Muscle & Nerve*. 2013; 47(2):177–182. [PubMed: 23168880]
19. Willcocks RJ, Arpan IA, Forbes SC, et al. Longitudinal measurements of MRI-T2 in boys with Duchenne muscular dystrophy: Effects of age and disease progression. *Neuromuscular Disorders*. 2014; 24(5):393–401. [PubMed: 24491484]
20. Whipple RH, Wolfson LI, Amerman PM. The relationship of knee and ankle weakness to falls in nursing home residents: an isokinetic study. *J Am Geriatr Soc*. 1987; 35(1):13–20. [PubMed: 3794141]
21. Jonkers I, Stewart C, Spaepen A. The complementary role of the plantarflexors, hamstrings and gluteus maximus in the control of stance limb stability during gait. *Gait Posture*. 2003; 17(3):264–272. [PubMed: 12770640]
22. Willcocks RJ, Rooney WD, Triplett WT, et al. Multicenter prospective longitudinal study of magnetic resonance biomarkers in a large duchenne muscular dystrophy cohort. *Ann Neurol*. 2016; 79(4):535–547. [PubMed: 26891991]
23. Vohra RS, Lott D, Mathur S, et al. Magnetic Resonance Assessment of Hypertrophic and Pseudo-Hypertrophic Changes in Lower Leg Muscles of Boys with Duchenne Muscular Dystrophy and Their Relationship to Functional Measurements. *PLOS ONE*. 2015; 10(6):e0128915. [PubMed: 26103164]
24. Jaric S. Muscle strength testing. *Sports Medicine*. 2002; 32(10):615–631. [PubMed: 12141882]
25. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016; (5):CD003725. [PubMed: 27149418]
26. Hoffman EP, Reeves E, Damsker J, et al. Novel approaches to corticosteroid treatment in Duchenne muscular dystrophy. *Phys Med Rehabil Clin N Am*. 2012; 23(4):821–828. [PubMed: 23137739]
27. Dillingham BC, Knoblach SM, Many GM, et al. VBP15, a novel anti-inflammatory, is effective at reducing the severity of murine experimental autoimmune encephalomyelitis. *Cell Mol Neurobiol*. 2015; 35(3):377–387. [PubMed: 25392236]
28. Martini J, Voos MC, Hukuda ME, Resende MB, Caromano FA. Compensatory movements during functional activities in ambulatory children with Duchenne muscular dystrophy. *Arq Neuropsiquiatr*. 2014; 72(1):5–11. [PubMed: 24637975]
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. [PubMed: 29171337]
30. Connolly AM, Schierbecker J, Renna R, Florence J. High dose weekly oral prednisone improves strength in boys with Duchenne muscular dystrophy. *Neuromuscul Disord*. 2002; 12(10):917–925. [PubMed: 12467746]

Fig. 1.

(A). Longitudinal alteration in Absolute KE and PF peak torque (B). Normalized PF and KE Peak Torque by age group. * significant different at $p < 0.05$; ** significantkly different at $p < 0.001$

Table 1

Baseline characteristics and demographics of control group and DMD subjects.

	Control		DMD			
	All		5-6.9 years	7-8.9 years	9-10.9 years	11+ years
Number	46	77	18	24	19	16
Age (years)	9.2±2.2	8.9±2.1	6.4±0.5	8.1±0.5	9.9±0.6	11.8±0.9
Body Weight(kg)	33.3±12.4	29.5±10.4	21.4±3.6	26.5±9.2	29.9±6.3	42.1±8.6
Height (cm)	137.5±12.3	121.4±16.6	111.2±5.5	120.7±25.3	123.3±6.4	131.5±7.4
BSA (kg/cm ²)	1.1±0.3	1.0±0.2	0.8±0.1	0.9±0.1	1.0±0.1	1.2±0.2

BSA-body surface area, DMD-Duchenne muscular dystrophy

Table 2

Baseline comparison of muscle strength for Knee extensors (KE) and Plantar flexors (PF) among different age groups for healthy control and DMD subjects.

	KE _{PT}		KE _{PTBSA}		PF _{PT}		PF _{PTBSA}	
	Control	DMD	Control	DMD	Control	DMD	Control	DMD
5–6.9 years	26.6±2.5 n=10	14.3±1.3 n=18	35.8±5.8 n=10	17.6±1.6 n=18	30.2±2.1 n=10	22.2±1.3 n=18	39.3±4.3 n=10	27.2±1.2 n=18
7–8.9 years	44.5±2.3 n=14	11.3±1.6 n=24	51.0±2.9 n=14	12.1±1.6 n=24	43.8±2.2 n=14	26.1±1.4 n=24	50.1±1.4 n=14	27.2±1.3 n=24
9–10.9 years	69.9±5.7 n=13	10.7±1.5 n=19	68.8±5.4 n=13	10.9±1.6 n=19	57.1±3.1 n=13	24.8±0.9 n=19	57.3±4.2 n=13	24.9±1.2 n=19
11+ years	98.5±13.6 n=9	10.7±1.8 n=16	83.5±7.8 n=9	8.4±1.3 n=16	68.3±6.0 n=9	30.7±3.7 n=16	59.1±4.0 n=9	24.5±2.5 n=16

DMD-Duchenne muscular dystrophy, KE_{PT}-absolute torque of knee extensors, KE_{PTBSA}-normalized torque of knee extensor, PF_{PT}- absolute torque of plantar flexors, PF_{PTBSA}-normalized torque of plantar flexors.

Table 3

Change of strength in DMD subjects over two years

	Absolute Torque (PT)		Normalized Torque (PTBSA)	
	Baseline	Year 1 (%change)	Baseline	Year 1 (%change)
KE	11.8 ±0.8	11.5 ±0.9 (-2.5%)	12.3 ±0.9	11.3 ±0.9 (-8.1%)
		10.7 ±0.9* (-9.3%)		9.9 ±0.8*** (-19.5%)
PF	25.9 ±1.0	25.6 ±1.1 (-1.2%)	26.2 ±0.8	24.3 ±0.9 (-7.3%)
		25.0 ±1.1 (-3.5%)		22.7 ±1.0** (-13.4%)

* significant at p<0.05 from baseline;

** significant at p<0.001 from baseline;

*** significant at p<0.0001 from baseline

KE-knee extensors, PF-plantar flexors,

Spearman correlation between strength and function at baseline, and muscle strength (absolute and normalized) and functional ability (as measured by timed functional tasks) in DMD subjects over two years.

Table 4

	Absolute Torque (PT)						Normalized Torque (PTBSA)					
	Baseline			Baseline to One Year			Baseline			Baseline to One Year		
	KE _{PT}	PF _{PT}	KE _{PT}	PF _{PT}	KE _{PT}	PF _{PT}	KE _{BSA}	PF _{BSA}	KE _{BSA}	PF _{BSA}	KE _{BSA}	PF _{BSA}
10m walk/run	-0.56***	-0.09	-0.24**	-0.20	-0.23**	-0.32*	-0.64***	-0.38**	-0.23**	-0.21	-0.16*	-0.33*
Supine to stand	-0.60***	-0.07	-0.24*	-0.04	-0.17*	-0.25	-0.71***	-0.33**	-0.22*	-0.03	-0.15*	-0.29
Six-minute walk	0.34**	0.18	0.19*	0.08	0.16*	0.30	0.38***	0.27*	0.22*	0.10	0.12	0.34*
Climbing 4 stairs	-0.62***	-0.03	-0.12	-0.03	-0.26**	-0.19	-0.69***	-0.28**	-0.13	-0.04	-0.22**	-0.22

* significant at p<0.05;

** significant at p<0.01;

*** significant at p<0.001

DMD-Duchenne muscular dystrophy, KE_{PT}- Knee extensors absolute torque, KE_{PTBSA}- knee extensors normalized torque, PF_{PT}- plantar flexors absolute torque, PF_{PTBSA}- plantar flexors normalized torque.

ROC curve estimates to assess muscle strength (absolute and normalized) as a predictor of loss of functional ability on timed performance tasks.

Table 5

Strength Variable	Function variable	Threshold	Sensitivity	Specificity	Area under curve	95%CI (UL, LL)
KE (ftlb)	10m walk/run	6.8	70.1	87.0	0.78	0.68,0.87
	4 Stairs	6.7	71.9	84.5	0.81	0.72,0.88
	Six-min	6.9	83.3	65.7	0.75	0.65,0.85
	SUP	7.5	74.7	78.3	0.78	0.68,0.87
PF (ftlb)	10m walk/run	18.3	82.7	68.6	0.73	0.56,0.88
	4 Stairs	19.4	80.3	68.6	0.74	0.59,0.86
	Six-min	17.9	83.4	66.8	0.73	0.55,0.87
	SUP	23.1	63.4	54.2	0.58	0.46,0.69
Normalized KE (ftlb/cm ²)	10m walk/run	5.8	73.0	87.0	0.81	0.72,0.90
	4 Stairs	5.7	76.0	86.6	0.85	0.77,0.91
	Six-min	5.9	71.9	81.7	0.79	0.71,0.87
	SUP	6.6	77.6	75.1	0.83	0.75,0.90
Normalized PF (ftlb/cm ²)	10m walk/run	18.1	83.6	85.6	0.87	0.77,0.95
	4 Stairs	18.8	83.5	87.4	0.87	0.78,0.94
	Six-min	18.1	83.3	87.8	0.87	0.77,0.95
	SUP	22.1	72.5	70.6	0.75	0.67,0.82

KEPT- Knee extensors absolute torque, KEPTBSA - knee extensor normalized torque, PFPT- plantar flexors absolute torque, PFPTBSA - plantar flexors normalized torque.