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Outcome Reliability in Non Ambulatory Boys/Men with Duchenne Muscular Dystrophy

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Abstract

Background—Therapeutic trials in Duchenne muscular dystrophy (DMD) often exclude non-ambulatory individuals. Here we establish optimal and reliable assessments in a multicenter trial.

Methods—Non-ambulatory boys/men with DMD (n=91;16.7± 4.5 years) were assessed by trained clinical evaluators. Feasibility (percentage completing task) and reliability [intra-class correlation coefficients (ICCs) between AM and PM tests] were measured.

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Results—Forced Vital Capacity (FVC, 100% of subjects) showed a mean 47.8 ± 22% predicted (ICC 0.98). Brooke upper extremity functional rating (Brooke) and Egen Klassifikation (EK) scales in 100% of subjects showed ICCs from 0.93-0.99. Manual muscle testing, range of motion, nine-hole peg, and Jebsen-Taylor Hand function testing (JHFT) had variable feasibility (99% to 70%) with ICC also ranging from 0.99 to 0.64. We found beneficial effects of different forms of corticosteroids for Brooke Scale, %predicted FVC, and hand and finger strength.

Conclusion—Reliable assessment of non-ambulatory boys/men with DMD is possible. Clinical trials will have to consider corticosteroid use.

Keywords

Duchenne muscular dystrophy; Non-ambulatory; Strength; Pulmonary function; Corticosteroids; Quality of Life

Introduction

Duchenne Muscular Dystrophy (DMD) is a progressive disabling disease affecting boys and men. It is caused by an X-linked mutation in the gene for dystrophin which results in the absence of dystrophin [1]. Without therapy, boys and young men become weaker and lose function and mobility. Advances in medical management, including corticosteroid use, contracture treatment, cardiac therapy, and ventilatory support, have increased life expectancy for young men with DMD[2,3].

Many therapeutic trials in DMD exclude non-ambulatory boys and men. Consensus has not been reached for what measures are most feasible, reliable, and sensitive to change. Furthermore, effective treatment should demonstrate improved function and quality of life. Therefore, function, strength, and quality of life must be understood and standardized. The primary goal of this study was to determine which clinical outcomes are feasible and reliable for therapeutic trials involving non-ambulatory boys and men with DMD. In addition, a better understanding of the progression of DMD in non-ambulatory boys and men may also lead to better medical treatment[3-5]. Approximately half of the boys and men were taking corticosteroids at the time of the evaluation and therefore their effect was also analyzed.

Pulmonary function is known to decline over the second decade of life in boys with DMD [6-8,3,9]. This decline is a major source of disability and shortened life span and can be collected reliably [10]. Pulmonary dysfunction in DMD is restrictive in nature; it is best measured by forced vital capacity (FVC), which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration. McDonald et al followed 162 patients with a clinical diagnosis of DMD who were not treated with corticosteroids and found the decline in FVC over time varied by age. Boys ages 7-10 years showed a decline of 0.3%/year, while boys ages 10-20 years who were not on corticosteroids showed a decline in FVC of 8.5%/year [11]. Kohler et al. also documented an exponential decline in FVC with age [12].

Muscle strength and function of upper extremities is maintained for variable periods of time once boys with DMD become non-ambulatory. Arm function correlates directly with the ability to manage activities of daily living including feeding, bathing, and brushing teeth. While function is lost with disease progression, precise rates of loss have not been established in the non-ambulatory DMD population. Use of the Brooke Upper Extremity Functional Rating (Brooke) scale and the Egen Klassifikation (EK) scale may provide more information about a subject's ability to manage activities of daily living[13-16]. The EK scale was designed to evaluate the progressive loss of function in 10 tasks in individuals with DMD and Spinal Muscular Atrophy [15]. The EK scale has been shown to have a positive correlation with age and a negative correlation with FVC and MRC scores in DMD[16].

Direct measurement of strength can be performed several ways. Manual Muscle Testing (MMT) of boys with DMD using the Medical Research Council (MRC) scale has been found to have good intra-rater reliability if clinical evaluators have been trained carefully [17]. However there was some variability from muscle to muscle, and the reliability was greater when a combined total muscle score was calculated[17]. In a study with 31 ambulatory DMD boys where FVC, QMT, timed function tests, and MMT were collected, MMT was found to be the least reliable of all assessments with an ICC of 0.61 [1018] . The reliability of using MMT in the non-ambulatory DMD patients has not been studied extensively. In a study where 12/20 DMD subjects were non-ambulatory, MMT scores correlated with a decrease in the Motor Function Measure (MFM) scores over a 6 month period [19].

Hand Held Dynamometry (HHD) has been proposed as an alternative to MMT. There are many hand held devices available for dynamometry testing, but there are limited reports of experience with them [20]. Stuberg and Metcalf studied hip and knee extension, elbow flexion, and shoulder abduction in 14 boys with DMD and healthy controls and found intra-rater correlation coefficients of 0.88 to .99[20]. Some excellent studies have used fixed quantitative muscle testing in ambulatory boys with DMD [18,21]. Grip strength has been studied well in DMD and has been shown to correlate with disability in boys over age 10 [22]. The MRC scale assessment of individual hand strength correlates with grip strength [22].

Hand function and dexterity become critically important as boys and men with DMD lose ambulation. Numerous outcome tools are available to assess hand function, including the Jebsen-Taylor Test of Hand Function (JHFT) and the 9-Hole Peg Test. The JHFT was developed in 1969[23]. It is a timed test with 7 subtests that mimic functional tasks. The JHFT has been found to be a sensitive assessment of hand in 23 patients with DMD [24]. Hand function as measured by the JHFT was later shown to be affected negatively by increasing age and by wrist contractures [25]. The 9-Hole Peg Test (9-HPT) has been established as a valid and reliable way to measure manual dexterity in healthy individuals and those with weakness between the ages of 3-83,[26-29] but it has not been reported in patients with DMD.

Variable degrees of contracture may cause boys with DMD to have different functional abilities, even if they have similar strength. Goniometry is a well-established procedure for the assessment of range of motion and has been used in a variety of conditions affecting the upper extremities to document the extent of the contracture [30] and also shows sensitivity to change [31,32]

Finally, the ability to quantify the quality of life for the young men with DMD may be useful in future treatment/intervention trials. The PedsQol was recently studied in children with DMD[33]. The Individualized Neuromuscular Quality of Life Questionnaire (INQoL) has been designed for and studied in adults with neuromuscular disease, but it has not been studied extensively in men with DMD [34].

At the time of the design of this study, we attempted to incorporate hand and upper extremity outcome measures that were established and had been shown to be reliable and useful in the assessment of upper extremity strength and function in DMD and a variety of other disorders. Since then there has been increased activity in regard to the topic of upper limb assessment in boys with DMD [35-39]. Due to the time our study was designed, these assessments were could not be incorporated. The objective of this study was to determine the reliability and feasibility of the JHFT test, 9-Hole Peg Test, EK scale, Brooke scale, HHD (elbow, grip and pinch), goniometry (active and passive of UE only), Manual Muscle testing (MRC), FVC, and InQoL in non-ambulatory boys and men with DMD.

Methods

Study Subjects

The design was set up to be as inclusive as possible. Subjects were required to have a confirmed clinical diagnosis of DMD based on biopsy, dystrophin mutation analysis, or a confirmed family history of DMD. All subjects were required to be greater than age 7 years and be non-ambulatory (unable to walk without braces or assistive devices) for greater than 1 year. Glucocorticoid treatment in any form and ongoing treatment with cardiac medications was acceptable. Subjects were excluded if they required daytime ventilatory assistance, were unable to cooperate with or understand testing, had undergone a major surgical procedure within 1 month prior to the start of the study and if they had been exposed to any investigational treatment. In all, 93 subjects were screened, and 91 were enrolled. The 2 who failed screening were unable to complete FVC testing. All 5 MDA-DMD research centers received human studies approval, and informed consent/assent was obtained for each participant prior to enrollment in the study.

Training and time of assessment—Clinical Evaluators from the 5 MDA-DMD Clinical Research Network (CRN) centers were trained in all outcome measures. The training took place at a two-day meeting at Washington University in Saint Louis under the direction of JMF. All clinical evaluators were certified prior to enrollment of study subjects. The clinical assessments included are summarized in Table 1. In order to establish intra-rater reliability, the tests were repeated after a break of at least 1-hour. Total testing time was generally 90-150 minutes in the morning and again in the afternoon testing session.

Test Measures

The assessments were performed in the order given in Table 1.

Vital signs—Height, weight, Body Mass Index, blood pressure, and heart rate were obtained or calculated. Height was calculated with 2 methods. Ulnar length of all participants was measured using segmometer, and this length was used to calculate a predicted height (100% of subjects) [40]. Segmental height was measured on the right side of the subject while he was lying supine on an exam table or in his wheelchair if the chair could recline fully. Attempts were made to straighten the subject's spine and lower extremities as much as possible. Using a straight edge, the following segments were measured: top of the head to the right greater trochanter, right greater trochanter to the right femoral condyle, right femoral condyle to the distal point of the calcaneus. The mean of 3 measurements was recorded. Segmental height calculation was only possible in 56 subjects willing and able to assume this position (71%).

Spirometry—All subjects performed FVC while supported in an upright position[41]. Standardized testing guidelines were followed (ATS guidelines 2005), and calculations were determined using the normative data based on the United States population [42]. The height used in the calculation of percent-predicted pulmonary function values was calculated from the subject ulnar length, as this was captured in all subjects [40]. FVC and FEV1 values were captured for 3 trials, and a percent predicted was collected based on the best result.

Brooke Upper Extremity Functional Scale—The Brooke scale was developed specifically for use in DMD. [14] It scores upper extremity function from “0”, which is full range, to 6 (no use of hands). This scale has been used frequently as an outcome measure in DMD [43].

Egan Klassifikation Scale (EK scale)—The EK ordinal scale ranges from 0 to 30 points, and higher scores are associated with lower function. The scale consists of 10 categories (each scored from 0 to 3) involving the following domains: 1) wheelchair use, 2) transfer from a wheelchair, 3) standing, 4) balance in a wheelchair, 5) move the arms, 6) use the hands and arms when eating, 7) turn in bed, 8) cough, 9) speak, and 10) physical well-being. The EK scale is administered by interviewing the subject. For items 4, 5, and 8 the interviewer must observe the subject performing the task. A higher score indicates a lower level of function.

Manual Muscle Testing—Manual muscle testing (MMT) was performed using the MMRC (Modified Medical Research Council) Scale[44]. Shoulder abduction, elbow flexion/extension, and wrist flexion/extension were evaluated.

Quantitative Myometry—The muscle strength in Newtons (1 kg is approximately 10 N (9.80665 N) was measured using a hand-held dynamometer (Type CT 3001, CITEC, C.I.T. Technics BV, Groningen, Netherlands). Maximal isometric force was calculated. The CITEC was used to measure grip, key pinch, finger pinch, biceps, and triceps. The CITEC measures force in Newtons and is sensitive to force from 0 to 500.

Jebsen-Taylor Hand Function Test (JHFT)—The JHFT has been used as an objective assessment of arm and hand function in adults with hemiplegia, rheumatoid arthritis, and subjects with C6-C7 traumatic tetraplegia[23]. It has also been used to assess hand and arm function in children with tetraplegia [45] and cerebral palsy[46]. The original JHFT test includes 7 subtests that are performed with each hand: writing, turning cards over, picking up small commonly encountered objects, simulated eating, stacking checkers, and moving light and heavy objects. Each test for each hand is timed, and subjects start with the non-dominant hand. Additional subtests that were added to the standard JHFT included stacking of large (light and heavy) objects.

Nine Hole Peg Test (9HPT)—The 9HPT is a quantitative test of upper extremity function. It was administered following the standardized manufacturer's guidelines. Subjects were timed while placing and removing the 9 pegs with each hand.

Goniometry—Passive and active goniometry was performed. Passive goniometry measures joint restriction, while active goniometry measures how far a person can move into the available range independently. All active range of motion measures were performed moving against gravity. Passive measures were captured with the subject relaxed with gravity eliminated if possible. Active/Passive shoulder abduction, elbow flexion, elbow extension, wrist flexion, and wrist extension were measured. Passive measurements followed standard goniometry placement and measurement [32]. Active goniometry captured the active arc of motion.

Individualized Neuromuscular Quality of Life Questionnaire (INQoL)—The INQoL, a self-administered tool, was given to all participants who were 18 years and older. It consists of 45 questions within 10 sections. Four sections focus on the impact of muscle disease symptoms (including weakness, locking, pain, and fatigue), 5 sections examine the impact that muscle disease has on particular areas of life, and 1 section asks about the positive and negative effects of treatment [34]. Each of the 45 questions is responded to using a 7-point Likert scale, with 7 being the highest detrimental impact on quality of life. The final score is presented as a percentage of the maximum detrimental impact, and therefore higher percentages are associated with more detrimental impact.

Statistical Methods

A centralized data management repository at Nationwide Children's Hospital was used for this study. The intra-class correlation coefficient (ICC) was calculated for all measures collected twice in the same day by each clinical evaluator for each subject. Morning results were used for descriptive statistics and for comparison of age and corticosteroid treatment effects. Descriptive statistics and paired statistical comparisons were performed with GraphPad Prism (GraphPad Software, La Jolla, CA). ANOVA with Tukey post analysis was used to compare steroid treatment groups. A Spearman correlation was used to analyze effects of age. *P*-values are all 2-tailed.

Results

Subjects

Ninety-one boys and men were enrolled (Supplementary Table1). Every site enrolled at least subjects; Washington University (N=20), Nationwide Children's (N=17), University of California-Davis (N=28), University of Minnesota (N=18), Boston Children's (N=8).

Mutations in the *DMD* gene were defined in 86 subjects or a brother (94%). Five subjects (6%) had a diagnosis by muscle biopsy only (Supplementary Table 1).

Age, Vital signs and baseline corticosteroid use—The average age was 16.7 ± 4.5 years, range 9.8 - 32.1. Forty-four were using oral corticosteroids; 19 were using twice weekly dosing, and 25 were using daily dosing. Precise length of time on corticosteroid use was not captured, but all had started corticosteroids while still ambulatory. There was no significant difference in the mean age of those using corticosteroids versus those not (16.0 ± 4.0 versus 17.5 ± 4.7 unpaired *t*-test, P =.09). Segmental height was only measured in 56 (61%). Ulnar length was obtained in all subjects, and therefore this value was used to calculate the BMI and the percent predicted FVC. The mean BMI was 23.8 ± 6.8, range 11.0 - 39.5. There was not a meaningful association between BMI and age (r = -0.22). Average systolic and diastolic blood pressures did not differ significantly between the groups.

Feasibility and reliability (Tables 2-7)

Average, range, and Vital capacity, as it was an inclusion criterion, had 100% participation (Table 2). Manual muscle testing feasibility ranged from 97% (elbow flexion) to 70% (wrist flexion); fixed wrist flexion contractures made this test not possible for some (Table 3). Intra-rater reliability was very good (all ICCs >0.87; elbow flexion showed the highest ICCs at 0.99 and 0.98 for right and left sides). The ranges of MRC scores for arm abduction, elbow flexion, and elbow extension were 4- to 0. The range of MRC scores for wrist extensors was 0-4+.

We quantified strength using HHD. HHD feasibility ranged from 70% for elbow flexion and extension (not possible to evaluate if subject did not fully recline or get out of the wheel chair to lie supine) to 99% for key pinch and 95 % for Grip assessment (Table 4). Intra-rater reliability was very good (ICCs 0.87 to 0.97). Key pinch was on average slightly stronger and also had higher feasibility compared to pinch.

Range of Motion was feasible in most muscle groups (80 to 96%) with the lowest percent from the elbow extension, in part related to inability to assume the supine position required (Table 5). Intra-rater reliability varied between different joint (ICCs ranged from 0.69 for passive elbow extension to 0.99 for active elbow flexion). The values for active range of motion for each joint varied widely (0 to145 degrees, depending on the joint) and, as expected, reflected the degree of weakness. For example, subjects with 3+ or better MRC strength of arm flexion always had elbow flexion more than 90 degrees. Values for passive range of motion were greater than active range of motion. The most common fixed contractures measured were at the elbow and wrist.

The 9 HPT showed relatively low feasibility with only 69% completing all 9 pegs with the dominant hand and 70% completing with the non-dominant hand in order to give an overall time (Table 6). In some cases this was related to workable space/reach and in others because of weakness. In some cases, subjects could not complete the task (all 9 pegs) in the allotted time (2 minutes). Feasibility did increase slightly if one calculated a time per peg (77% for both dominant and non-dominant hand).

The JHFT varied widely from task to task (Table 7). While 97% were able to write with the dominant hand, only 67% were able to simulate feeding with the non-dominant hand. Feasibility was higher by a few percent for the dominant hand in most subtest sections (Table 7). ICCs also varied widely from 0.58 - 0.73 (simulate feeding) to 0.94 - 0.95 (lifting small common objects).

Effect of age

We compared the effect of age in the most reliable and feasible subtests. These included percent predicted FVC, Brooke and EK scales, and grip and key pinch strength. We expected and found a clear negative correlation between predicted vital capacity and increasing age (Figure 1). Both Brooke scale and EK scale also worsened (higher scores) with age (Figures 2 and 3). Strength of grip (Figures 4 and 5) and key pinch strength (Figures 6 and 7) also declined with age. As this cohort is being followed across time, responsiveness to change will be determined.

Outliers

We noticed that there were outliers who performed better than most subjects their age (Figures 1-7). For example, the percent predicted of the FVC showed a decrease across all ages, but 3 subjects were outliers on this test (Figure 1). One, age 11 years (subject 6), was the brother of subject 76, who had been diagnosed by a muscle biopsy that showed no dystrophin. Subject 6 was taking weekly corticosteroids and had a FVC of 107% predicted. The second was age 12.1 years (Subject 11) with an out of frame mutation (exon 52-54); he was taking daily corticosteroids and had an FVC of 99% predicted. The third, age 19 years (subject 66), had a duplication of exon 3-4 which was predicted to be in frame. He was on daily corticosteroids and stopped ambulating at age 15 years. His biopsy showed <5% residual dystrophin. He also was an outlier on the Brooke and EK scales. We also looked at the stronger outliers for grip (right and left) and key pinch grip (right and left) (Figures 4-7). Five subjects accounted for these outlier values: Subject 46 (age 15.9 years, out of frame deletion of 45-54, on daily corticosteroids); subject 63, (age 18.5 years, out of frame deletion of exons 8-11, on daily corticosteroids); subject 66 (age 19 years, in-frame duplication of exon 3-4, on daily corticosteroids); subject 79 (age 21.1years, out of frame deletion exon 45-52 on daily corticosteroids), and subject 88 (age 25.8 years, out of frame duplication of exons 17-50, on no corticosteroids). Subject 88 was also an outlier on the Brooke Scale.

Effect of corticosteroid use

We found no significant differences in BMI or blood pressure for those who were taking corticosteroids compare to those who were not (Table 8). The Brooke Scale was significantly better for those taking daily or twice weekly corticosteroids compared to those taking none (Table 9). Those taking twice-weekly corticosteroids also showed better % Predicted FVC compared to those taking no corticosteroids. Right hand grip and bilateral key pinch were better for those taking daily corticosteroids compared to those taking none (Table 9).

INQoL survey (Figure 8)

Thirty-two young men, age 18 and over (mean age 21.6; Range 18.4-32.1) completed the survey. Eleven (34% mean age 21.7 ±3.8) were taking steroids (7 daily and 4 twice weekly dosing), and 21 (66%; mean age 21.4 ± 3.0) were not. All acknowledged weakness, with total weakness score of 56 ± 23%. Nine (28%) complained of "locking" symptoms with an average score of 33 ± 26%. Fourteen (44%) complained of pain with an average score of 32 ± 19%. Twenty-six men (81%) complained of being tired with average score of 34 ± 20%. 100% of men acknowledged an impact of DMD on independence with an average score of 54 ± 18%. Thirty (94%) noted an impact of DMD on relationships with an average score of 26 ± 20%. The average total INQoL score for these subjects was 25 ± 12%. There was no significant association of total INQoL score or INQoL sub-scores with increasing age or steroid use. Data for age versus weakness, pain, independence and total score are reflected in Figure 8.

Discussion

Baseline characteristics

Most subjects had blood pressures in the normal range, and, as expected, resting heart rates tended to be higher. We noted a striking variation of BMI ranging from 11 to 39.5. We did not find a meaningful association between BMI and age. There was no difference between the reliability of subjects with high or low BMI. While we measured FVC in this study and found a negative correlation with age, maximum inspiratory pressure and maximum expiratory pressure may reflect earlier weakness in boys and men with DMD[47,48]. While we tried to capture the full range of the non-ambulatory DMD population who were not on full-time ventilatory support, we had 2 subjects who failed screening because of inability to perform pulmonary function testing.

Feasibility and intra-rater reliability

Feasibility, defined as the percent of subjects able to perform the task, was influenced by 2 major factors. The first was positioning. Some manual muscle testing, some quantitative strength testing, and proper measurement of segmental length all require that subjects get out of their chair or have a chair that can recline fully. Getting out of the chair was often difficult, and some young men refused, particularly during the afternoon session. Reduced feasibility in some subtests of the JHFT and the nine-hole peg simply relate to weakness and fatigue. Other scales, including the Brooke and EK scales are designed to reflect the entire course of the disease and remain feasible in all subjects. We found excellent feasibility (>95%) for pulmonary function testing, Brooke scale, EK scale, manual muscle testing, grip meter testing, and pinch and key testing. Two subsets of the JHFT (writing with dominant hand and stacking checkers with either hand) also had good participation rates (>90%). Furthermore, all of these measures also had high ICCs. Other subsets of the JHFT and nine-hole peg test had lower participation rates, but ICCs remained high (Tables 2- 7); this was because subjects hit the floor of these tests. For example, the nine-hole peg test (Table 7) had participation rates of only 69-70% but still very good ICC (0.86-.91). The average times for the 9-hole peg for those who completed the task averaged 30 ± 13 for the dominant and 34 ± 13 for the non-dominant. These values are longer than in healthy males aged 21-25 years (mean 16.4 seconds for right hand and 17.5 for left hand) [28]. If the nine-hole peg test was scored as a function of time per peg, participation rate improved slightly (77%).

The time to evaluate all measures once was about 2 hours. However, by permitting subjects to remain in their chairs and eliminating sections of the JHFT that had low feasibility, evaluation time could be reduced to 1 hour. Tests which could not be performed in the upright position included segmental height and elbow extensor HHD for biceps and triceps, gravity eliminated shoulder abduction (MMT), and anti-gravity elbow extension (MMT).

The size of our sample allowed us to look at baseline differences between those on or off corticosteroids. The results show that those who were taking corticosteroids (daily or weekly) had significantly better performance on the Brooke scale than those who were not taking corticosteroids. There was also a positive effect on percent-predicted FVC for those taking twice weekly steroids and better grip and key pinch strength for those taking daily steroids. These results show that a clinical trial must be stratified if those both on and off steroids are to be enrolled. Perhaps more importantly, it supports the position that corticosteroid use should be continued even after ambulation is lost. [49,5,50]

There are several potential variables that may account for outliers in performance at a given age, including the nature of the mutation, ongoing or past corticosteroid use, and genetic modifiers. In our cohort, outliers included individuals with both deletions and duplications, but it should be noted that our assumptions regarding reading frame were based on genomic analysis and not confirmed by mRNA analysis, a particularly important consideration in duplication mutations. Nevertheless, several of the outliers (or their affected relatives) had biopsies consistent with frame-truncating mutations. Our analysis did not take into account the duration of corticosteroid exposure, but only 1 outlier (subject 88) was on no corticosteroids, suggesting that corticosteroids may be continually protective. Finally, we did not analyze *SPP1* or *LTBP4* genotypes; polymorphisms in each have been associated with modification of DMD severity. [51,52] In particular *SPP1* has an association with grip strength [52].

As expected, the INQoL demonstrated that DMD impacts many aspects of life, including weakness, pain, and independence. However, there was no clear association with increasing age or the use of corticosteroids. The results reflect differential tolerance between subjects, which may result from other variables not specifically addressed in this study, including socioeconomic status and education. Some clinical trials currently planned or underway are being extended to include non-ambulatory boys and men. It is important to look at those subjects who have enough hand/arm function to be able to measure change. While most of the measures showed high or excellent ICCs, not all subjects could perform all measures. Feasibility can clearly be increased if subjects are selected who have some baseline hand and arm strength. However, even in this very inclusive set of subjects we were able to measure differences according to age. Follow-up of this cohort will determine responsiveness to change within subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

Brooke Scale	Brooke Upper Extremity Functional Rating Scale
CE	Clinical Evaluators
DMD	Duchenne Muscular Dystrophy
EK Scale	Egen Klassifikation
JHFT	Jebsen-Taylor Test of Hand Function
FVC	Forced Vital Capacity
HHD	Hand Held Dynamometry
ICC	Interclass Correlation
MMT	Manual Muscle Testing
MRC	Medical Research Council
9-HPT	9-Hole Peg Test
ROM	Range of Motion
INQoL	Individualized Neuromuscular Quality of Life Questionnaire

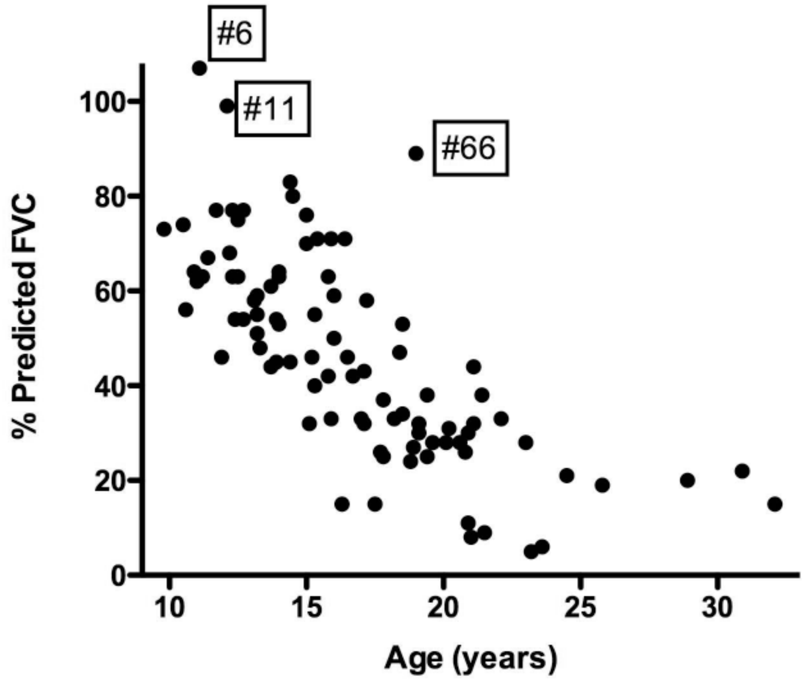

Figure 1. Percent Predicted FVC versus Age

Spearman correlation, r = -0.78, P = <.0001. Three outliers are discussed in text.

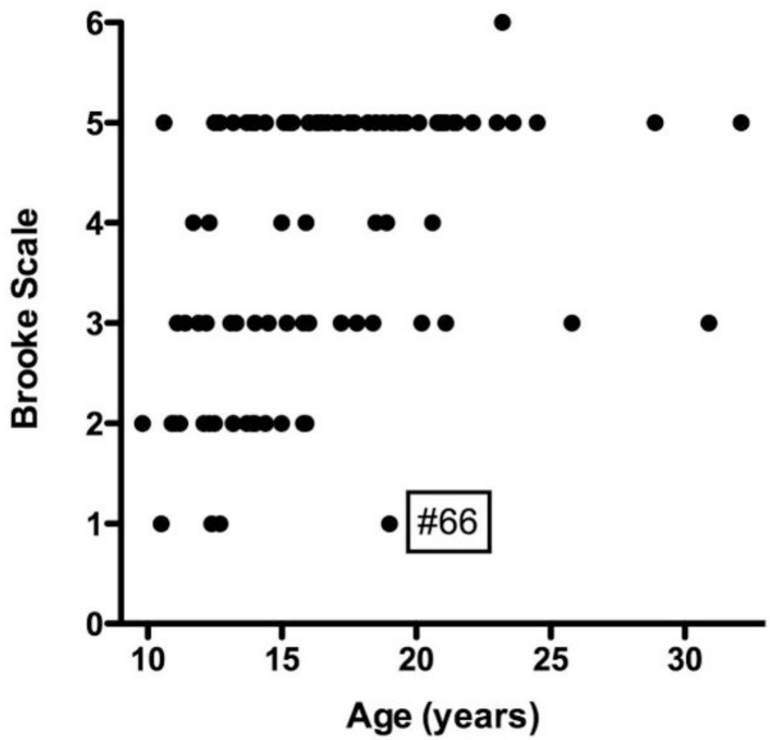

Figure 2. Brooke Scale versus Age

Spearman correlation, $r = +0.52$, $P < .0001$. The outliers, subjects #66, age 19 years, and #88, age 25.8 years are discussed in text.

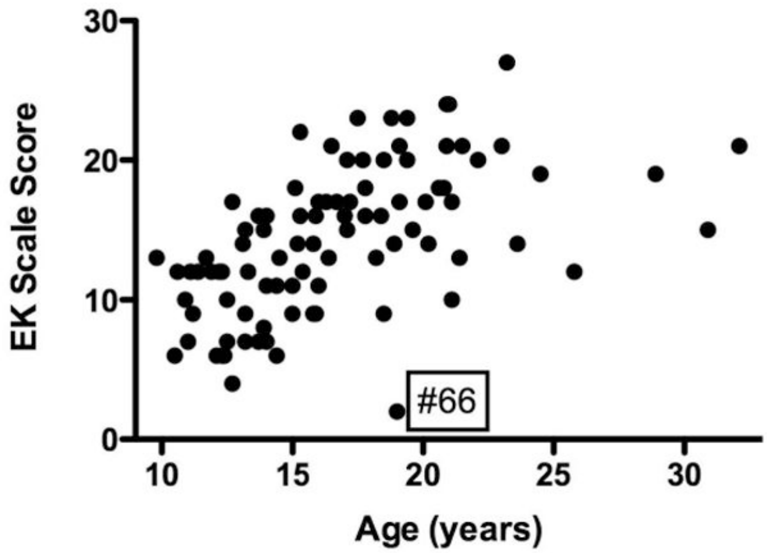

Figure 3. EK Scale Score versus Age

Spearman correlation, $r = +0.63$, $P < .0001$. The outlier, subject #66 is discussed in the text.

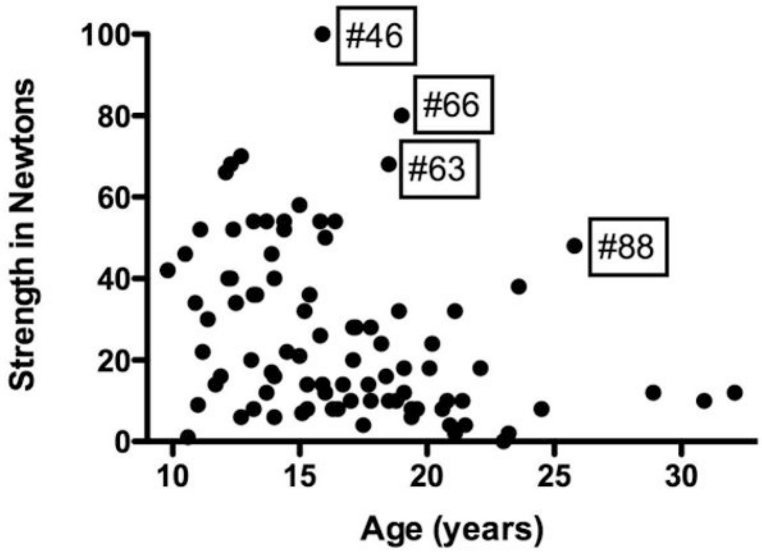

Figure 4. Right Hand Grip versus Age

Spearman correlation, r = -0.38, P = 0.0002. The 4 outliers are discussed in the text.

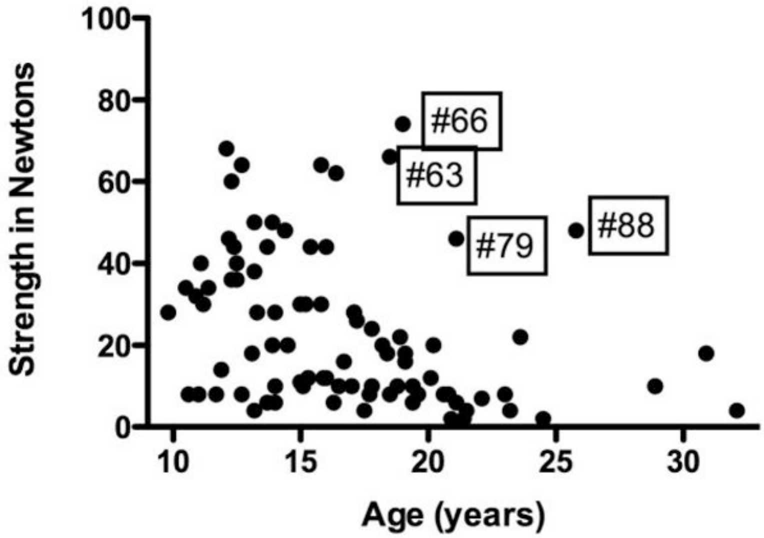

Figure 5. Left Hand Grip versus Age

Spearman correlation, r = -0.40, P=.0001. Outliers are discussed in text.

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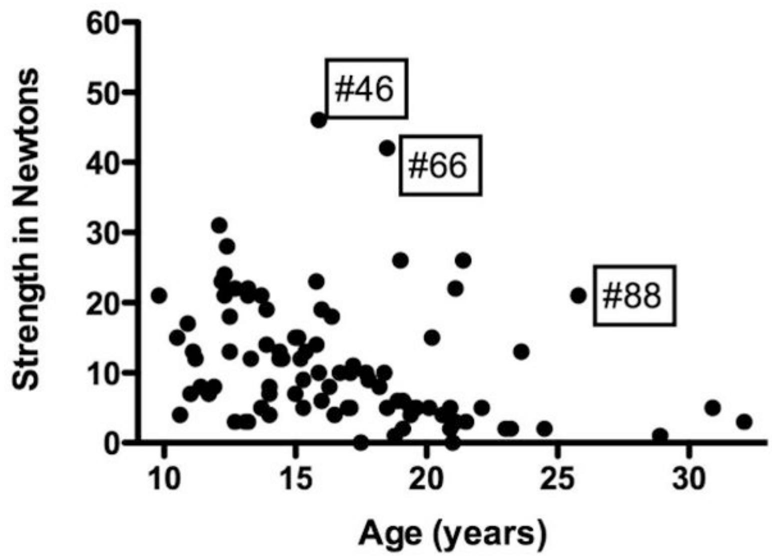

Figure 6. Right Key Pinch versus Age

Spearman correlation, $r = -0.42$, $P<.0001$. Outliers are discussed in text.

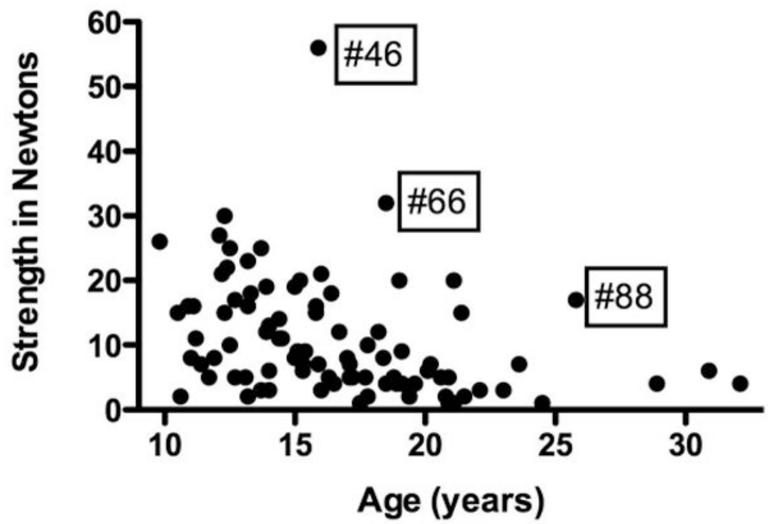

Figure 7. Left Key Pinch versus Age

Spearman correlation, $r = -0.46$, $P < .0001$.

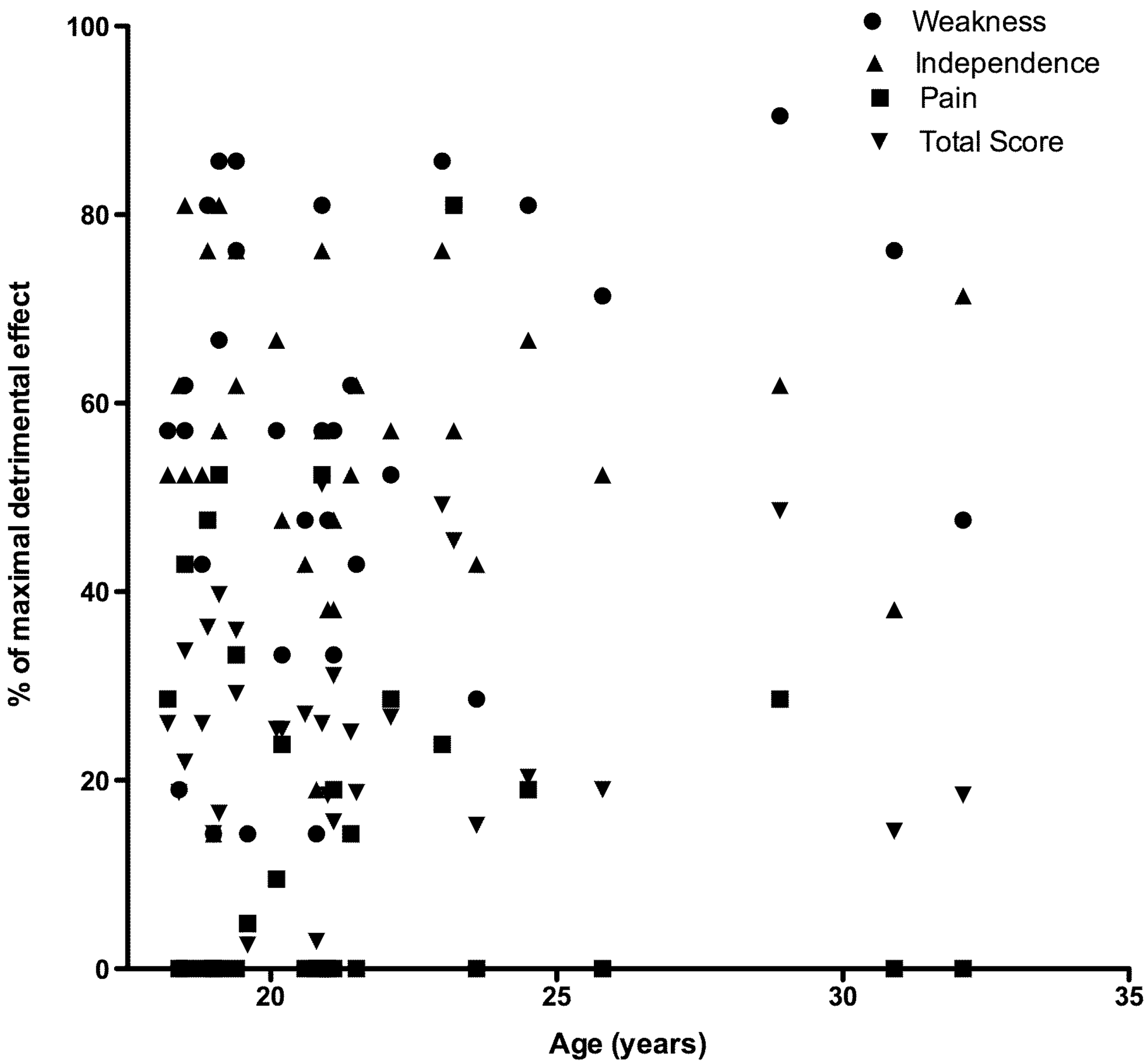

Figure 8. Individual Neuromuscular Quality of Life Scores versus Age

Thirty-two subjects over age 18 completed the INQoL survey. Spearman correlation analysis showed no subscore or the total score correlated with age. Weakness, *r* =+ 0.19, *P*=.3; Independence, *r* = - 0.08, *P*=.66; Pain *r* = - 0.06; *P*=.41; and Total Score, *r* = -0.07; *P*= 0.67.

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Table 1

Clinical assessments used to test non-ambulatory boys and men with DMD.

Test	Test Administration	Time to administer
Caregiver Burden	Parent or primary caregiver	10 minutes
Ulnar Length and Segmental Height	Trained clinical evaluator	5 minutes
Jebsen-Taylor Hand Function Test *	Trained clinical evaluator	40 minutes
9-Hole Peg Test	Trained clinical evaluator	Up to 20 minutes
Egen Klassifikation Scale	Trained clinical evaluator	10 minutes
Brooke Upper Extremity Functional Rating Scale	Trained clinical evaluator	5minutes
Hand Held Myometry	Trained clinical evaluator	15 minutes
Goniometry	Trained clinical evaluator	20 minutes
Manual Muscle Testing	Trained clinical evaluator	20 minutes
FVC	Trained clinical evaluator	5-10 minutes
InQoL	Subject ≥18 years old	15 minutes

Table 2

Pulmonary Function testing

100% (91 subjects) were assessed twice with excellent intra-rater reliability.

TEST	Mean	Range	ICC
FVC percent predicted	47.78 ± 22.42	3.67-103.67	0.98
FEV1 percent predicted	43.55 ± 20.91	3.33-102.00	0.94
Vital Capacity	1.70 ± 0.70	0.22-4.17	0.95
FEV1	1.38 ± 0.60	0.17-3.67	0.93

Table 3

Manual Motor Testing Intra-rater Reliability

Manual muscle testing was both feasible and reliable, with the exception of wrist flexion, where fixed contractures prevented assessment in about 30% of subjects.

TEST	n=(Right/left)	Percent Completed (%)	MRC Range	ICC
Shoulder abduction	160/161	88/89	4 to 0	0.95/0.95
Elbow Flexion	176/175	97/96	4 to 0	0.99/0.98
Wrist Flexion	130/128	71/70	4+ to 0	0.92/0.93
Wrist Extension	174/174	95/95	4+ to 0	0.87/0.90

Table 4

Hand Held Dynamometry (HHD)

For accurate assessment of elbow flexion and extension, the subject must lay supine. In some cases, the subject was unable or unwilling to do this. This accounts for the low feasibility for these measures. In contrast, evaluation of Grip, Pinch, and Key strength had good feasibility (88/91; 86/91 and 90/91 respectively). ICCs were very high.

HHD	n= Right/Left (%R/L)	Mean± s.d. (Newtons) Right/Left	Range (Newtons) Right/Left	ICC (R/L)
Supine Elbow Flexion	130/127 (71/70)	12 ± 11 11 ± 8	47-0 40-0	0.95/0.97
Supine Elbow extension	135/133 (74/73)	11 ± 9 12 ± 9	39-0 45-0	0.96/0.94
Grip	176/176 (97/97)	26 ± 21 25 ± 21	100-0 126-2	0.94/0.94
Pinch	172/172 (94/94)	8 ± 5 7 ± 5	30-0 25-0	0.87/0.89
Key	180/180 (99/99)	11 ± 9 11 ± 9	46-0 56-0	0.95/0.95

Table 5

Range of Motion

Active and Passive range of motion showed very high ICC, but feasibility of some joints was affected by ability and willingness to assume the full supine position.

Joint	n=(R/L)	% of Subjects	ICC
Shoulder Abduction (Active)	171/172	94/94	0.90/0.98
Shoulder Abduction (Passive)	154/154	85/85	0.97/0.97
Elbow Flexion (Active)	170/169	93/93	0.99/0.99
Elbow Flexion (Passive)	179/179	98/98	0.96/0.89
Elbow Extension (Active)	147/145	81/80	0.89/0.89
Elbow Extension (Passive)	175/175	96/96	0.72/0.69
Wrist Extension (Active)	157/157	86/86	0.96/0.96
Wrist Extension (Passive)	164/164	90/90	0.96/0.96

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Table 6

9-Hole Peg Test Feasibility and Reliability (Average of 2 trials)

Feasibility increased slightly if time per peg was calculated, allowing those who could not complete the task to be included.

Test	n	% of Subjects	Time (seconds)	ICC
Dominant Hand time*	125	69	30±13*	0.86
Non-Dominant time*	128	70	34±13*	0.91
Dominant Hand time per peg	140	77	1.7±0.7*	0.81
Non-Dominant Hand time per peg	141	77	1.9±0.7*	0.98

*Calculated using only trials with all 18 pegs completed.

Table 7

JHFT Feasibility and Reliability

Individual Test	N (of 182)	% of subjects	Mean (secs) ± SD	Range	ICC
Writing Non Dom hand	159	87	58.2 ± 23.4	17-120	0.79
Writing Dom hand	177	97	28.1 ± 19.1	8-99	0.87
Simulated page turning Non Dom hand	156	86	15.6 ± 19.9	3-120	0.70
Simulated page turning Dom hand	155	85	12.1 ± 13.6	3-84	0.90
Lifting small common objects Non Dom hand	139	76	23.4 ± 23.2	5-120	0.95
Lifting small common objects Dom hand	141	77	20.9 ± 20.0	5-103	0.94
Simulated feeding Non Dom hand	122	67	38.0 ± 26.8	9-118	0.58
Simulated feeding Dom hand	139	76	31.3 ± 24.0	7-106	0.73
Stacking Checkers Non Dom hand	168	92	8.9 ± 9.4	2-54	0.82
Stacking Checkers Dom hand	168	92	6.6 ± 6.1	1-37	0.91
Lifting light objects Non Dom hand	145	80	15.7 ± 19.4	2-110	0.88
Lifting light objects Dom hand	147	81	17.4 ± 25.1	2-120	0.85
Lifting heavy objects Non Dom hand	134	74	19.2 ± 22.2	2-112	0.92
Lifting heavy objects Dom hand	139	76	19.2 ± 22.2	2-120	0.80
Stacking large light objects Non Dom	81	45	18.9 ± 25.9	3-120	0.95
Stacking large light objects Dom	92	51	17.5 ± 24.9	2-120	0.74
Stacking large heavy objects Non Dom	59	32	20.2 ± 26.0	2-120	0.81
Stacking large heavy objects Non Dom	66	36	18.1 ± 24.3	1-120	0.93

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Table 8
Effect of Steroid use on BMI, Blood Pressure and Pulse Rate

With the exception of pulse rate, which was slightly higher (*P*<.05 ANOVA) in the group taking twice weekly corticosteroids, there were no significant differences between groups.

Steroid Use	BMI	Systolic BP	Diastolic BP	Pulse
Daily n= 25	25.1 ± 6.6	111 ±12	67±8	91±17
2× week n= 19	25.9 ± 5.2	107±13	70±8	102±18*
None n= 47	22.2 ± 6.7	112 ±16	67±11	88±18

Table 9

Effect of Steroid use on Percent Predicted FVC, Brooke, and EK Scores, Grip and Key grip strength

ANOVA analysis was performed with Tukey post analysis. There were no significant differences between twice weekly and Daily corticosteroids.

Cortico-steroid Use	FVC % Predicted	Age (Yrs)	Brooke Scale	EK Scale	Grip, Right (Newt)	Grip Left (Newt)	Key Right (Newt)	Key Left (Newt)
Daily n= 25	51± 25	16.5± 4.5	**3.2 ± 1.4***	13.1 ± 4.2	**38 ± 23***	34 ± 27	**16 ± 11***	**16 ± 12***
2× week n= 19	**57 ± 20***	15.2 ±3.4	**3.1 ± 1.0***	13.1 ± 3.8	31 ± 18	28 ± 18	13 ± 7	12 ± 7
None n= 47	40± 19	17.5 ±4.7	4.4 ± 1.1	15.7 ± 5.8	19 ± 17	19 ± 17	8 ± 7	7 ± 6

* =P< .05 for values differences that were significant compared to No steroids.