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Unraveling upper extremity performance in Duchenne muscular dystrophy: A biophysical model

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Abstract

This study aimed to identify critical physiological outcome variables underlying reduced upper extremity task performance in Duchenne muscular dystrophy (DMD). These critical variables were used to propose an explanatory biophysical model of the upper extremity working mechanisms in DMD. Twenty-three DMD patients (8–21 years) participated in this study. Correlations with Brooke scale and Performance of Upper Limb (PUL) score were very high for maximal active joint angle, high for maximal muscle torque and maximal surface electromyography amplitude, and moderate for mean echogenicity and maximal passive joint angle. Multivariable regression analysis showed that maximal active joint angle and maximal muscle torque were significantly associated with Brooke score ($R^2 = 0.91$). Maximal active joint angle, maximal passive joint angle, and maximal muscle torque were significantly associated with PUL score ($R^2 = 0.94$). Based on the most critical physiological outcome variables, we constructed an exploratory biophysical model of the working mechanisms leading to limitations in upper extremity task performance. Better insights in these working mechanisms could support clinical management of upper extremity limitations and facilitate the development of interventions. In addition, the model could form the basis for new multi-layered outcome measures for clinical trials.

Keywords: Duchenne muscular dystrophy; Upper limb; Electromyography; Range of motion; Biophysical model.

1. Introduction

Duchenne muscular dystrophy (DMD) is an x-linked neuromuscular disorder that affects 1 in 5000 live-born boys [1]. DMD is characterized by progressive muscle weakening. First the pelvic girdle is affected and later on, all muscles become affected. Boys with DMD lose the ability to walk around the age of 13 when using corticosteroids [2] and their arm function also weakens around that age [3]. Consequently, DMD patients are in a wheelchair for the largest parts of their lives, and the ability to perform activities with their upper extremities (UE) becomes more and more difficult. As a result, focus of clinical practice and research in DMD has shifted toward preservation of UE function, and a growing amount of UE interventions have become available. These interventions focus on treatment of different physiological aspects of the disease. For example, UE splinting or surgery can be used for contracture management, while corticosteroid treatment aims to improve muscle strength, arm supports attempt to increase UE range of motion, and physical exercise training aims to improve both range of motion and muscle strength [4,5]. Ultimately, all these interventions try to improve or retain UE task performance in daily life. In order to optimize clinical management and select appropriate interventions, the working mechanisms that critically constitute a person's UE function are very important.

The clinical assessment of UE function in boys and men with DMD is commonly done using functional scales, such as the Brooke upper extremity functional rating scale [6], the Performance of Upper Limb (PUL) scale [7], and the Motor Function Measure (MFM) [8]. In research, outcome

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measures related to muscle strength, muscle composition, or the ability to move the arms are sometimes performed [9–15]. These outcome measures, separately, give good insight in someone's ability to perform UE tasks, but they do not give insight into the underlying biophysical mechanisms leading to those impairments. A better understanding of these mechanisms, however, is important to support individual clinical decision making and optimize clinical management. For the lower extremity, the working mechanisms underlying reduced walking performance are assessed using gait analysis, in a clinical setting as well as in research [16]. Until now, there is no standardized assessment for evaluating the working mechanisms of the UE in DMD patients.

In a previous study, we described UE function in boys and men with DMD using a wide variety of physiological outcome measures and functional scales [17]. Although this study gave new insights into UE decline across the different stages of the disease, this study was descriptive and did not aim to identify the critical biophysical mechanisms resulting in UE limitations. Therefore, the aim of this study was to identify critical physiological outcome variables underlying reduced UE task performance in DMD. These critical variables were used to propose an explanatory biophysical model of the UE working mechanisms in DMD.

2. Methods

2.1. Population

The study population consisted of 23 boys and men with DMD. Patients were included if they had a DNA established DMD diagnosis, a Brooke scale of 1–5 [6], and if they were older than 6 years. Patients were recruited through the Radboud University Medical Center outpatient clinic and by an advertisement on the website of the Dutch Duchenne Parent Project (organization run by parents of DMD patients). This study was approved by the medical ethical committee Arnhem–Nijmegen in the Netherlands (Registration number 2012/135, NL nr.: 39126.091.12). Informed consent was obtained from all subjects and from their parents when subjects were under 18 years of age.

2.2. Outcome measures

The outcome measures and procedures used in this study are concisely described below. For full details on the outcome measures, procedures and reference values, we refer to Janssen et al. [17].

The Brooke upper extremity functional grading scale [6] and the Performance of Upper Limb (PUL) scale [7] were used to assess UE task performance. The physiological outcome measures we used were: maximal muscle torque, maximal surface electromyography (sEMG) amplitude, muscle thickness, echogenicity, and maximal active and passive joint angles. Maximal muscle torque (measured with a static frame myometer (Fig. 1)), and maximal sEMG amplitudes (Zerowire EMG, Aurion, Italy) were recorded

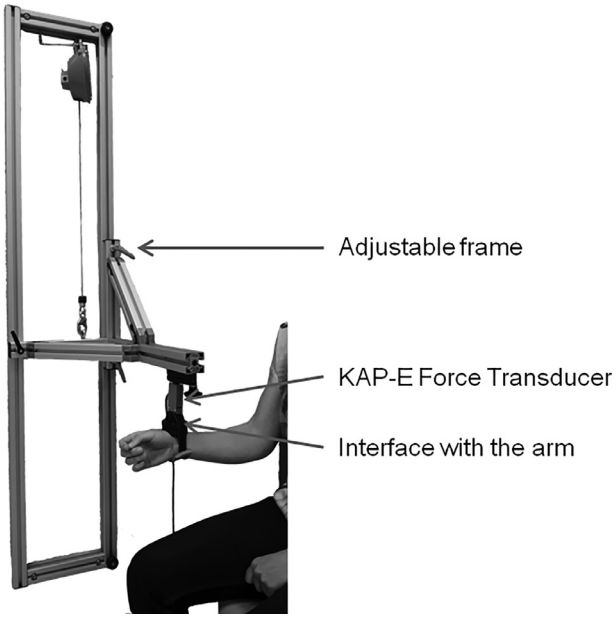

Fig. 1. Static frame myometer. Consisting of a KAP-E Force Transducer, measurement range 0.2–2000 N (Angewandte System Technik, Dresden, Germany), and a height and position adjustable frame (designed and custom made by mechanical engineers from the VU medical centre, Amsterdam, the Netherlands).

during maximal voluntary isometric contractions (MVICs) of 7 muscles of the right arm (Trapezius (descending part), Biceps Brachii (long head), Triceps Brachii (long head), Deltoid (lateral part), Pectoralis Major (clavicular head), wrist flexors and wrist extensors). Forces measured by the static frame myometer were converted to torques by factoring in the length of the lever arm based on anthropometric measurements of the subject. Echogenicity and muscle thickness were calculated for the same muscles except for the Pectoralis Major, because the location of this muscle did not allow for reliable ultrasound measurements. Echogenicity is the extent to which a structure reflects ultrasound of a surface. High echogenicity means that more ultrasound is reflected, for example when high levels of fatty and connective tissue are present in a muscle. Passive and active joint angles were obtained using three-dimensional motion analysis (Vicon, Oxford Metrics, Oxford, UK.), in combination with the kinematic model of Jaspers et al. [18]. Passive joint angles were determined for: 'shoulder abduction', 'elbow flexion', 'elbow extension', 'pronation', 'supination', 'wrist flexion', 'wrist extension', 'ulnar deviation' and 'radial deviation'. Similar active joint angles were determined, including two more shoulder angles: 'shoulder flexion' and 'horizontal shoulder adduction'. All data were collected by an experienced researcher (MJ).

2.3. Statistical analysis

Ultrasound results were compared to muscle-specific reference values (collected from 60 healthy subjects) and expressed as *Z*-scores (representing the number of standard deviations from the mean) [19]. Echogenicity and muscle

Table 1
Spearman correlation coefficients of sum scores.

	1	2	3	4	5	6	7	8
1. Brooke scale ($N=23$)	1							
2. PUL score ($N=22$)	−0.95**	1						
3. Muscle torque ($N=19$)	−0.64**	0.71**	1					
4. sEMG amplitude ($N=20$)	−0.72**	0.67**	0.15	1				
5. Echogenicity ($N=22$)	−0.54*	0.56**	0.31	0.50*	1			
6. Muscle thickness ($N=8$)	−0.26	0.48	0.50	−0.26	0.14	1		
7. Active joint angle ($N=22$)	−0.93**	0.91**	0.55*	0.78**	0.57**	0.38	1	
8. Passive joint angle ($N=22$)	−0.58**	0.47*	0.33	0.51*	0.34	−0.31	0.69**	1

*Statistical significant correlation (p-value < 0.05).
**Statistical significant correlation (p-value < 0.01).

thickness were corrected for age, weight, and height if necessary using the method described by Scholten et al. [20].

Statistical analysis was performed on individual outcome measures (scores per muscle/joint) as well as on sum scores. The sum scores were calculated by adding the results of all values of individual muscles/joints for one outcome measure. If one or more values were missing, the sum score was also reported as missing. If values were missing because patients were physically unable to perform the activity, a score of 0 was used for the calculation of the sum scores. Spearman correlation coefficients were calculated between all sum scores, and between functional scales and individual physiological outcome measures. Correlations of the Brooke scale and PUL sum score with physiological outcome measures (muscle torque, sEMG amplitude, echogenicity, muscle thickness, and active and passive joint angels) were used to identify the critical outcome variables responsible for reduced UE task performance. Stepwise multivariable linear regression analysis using functional scales (Brooke and PUL scale) as dependent variables and sum scores of physiological outcome measures as independent variables was used to determine which physiological measures were significantly associated with task performance. The statistical significance level was set at a p-value smaller than 0.05. However, when multiple comparisons were made regarding the same dependent variable (correlation of functional scales and individual physiologic scores) we corrected the p-value using false discovery rate (FDR) [21,22]. SPSS Statistics Version 20 (IBM, Somers, USA) was used for statistical analysis.

3. Results

The median age of the study population was 14.9 (range 8.1–21.7) years. The median age at diagnosis was 3.75 years (range 0–7 years) and 74% of the patients were non-ambulant (median age of losing ambulation was 10 (range 7–13) years). Thirteen percent of the patients had a mild scoliosis, and 22% had a severe scoliosis, of which 40% was surgically corrected. Corticosteroids were used by 74% of the patients, 12% used Deflazacort on a daily basis and 88% uses Prednisone/Prednisolone on a 10-days-on/10-days-off basis. Dosages vary between 0.14 and 0.74 mg/kg.

Table 1 describes the Spearman correlation coefficients between all sum scores. Correlations with Brooke scale and PUL score were very high ($r_s > 0.800$) for maximal active joint angle sum score, high ($r_s = 0.600$–0.799) for maximal muscle torque and maximal sEMG amplitude sum scores, and moderate ($r_s = 0.400$–0.599) for mean echogenicity Z-score and maximal passive joint angle sum score. No significant relation was found between mean muscle thickness Z-score and Brooke and PUL scale, respectively.

Multivariable regression analysis (Table 2) showed that both maximal active joint angle sum score and maximal muscle torque sum score were significantly associated with Brooke scale and together explained 91% of the variance in Brooke scale. In addition, maximal active joint angle sum score, maximal passive joint angle sum score, and maximal muscle torque sum score were significantly associated with PUL score, and together these variables explained 94% of the variance in PUL score.

Significant correlations between sum scores of physiological outcome measures were found for maximal active joint angle sum score with maximal muscle torque, maximal sEMG amplitude, maximal passive joint angle sum scores and echogenicity Z-score ($r_s = 0.55$, 0.78, 0.67 and 0.57); and for sEMG amplitude with echogenicity Z-score and passive joint angle sum score ($r_s = 0.50$ and 0.51).

The Spearman correlation coefficients between functional scales and individual (muscle/movement specific) physiological outcome measures are shown in Table 3. Muscle torques of the Biceps, Triceps, Pectoralis major and Wrist extensors showed high correlation coefficients ($r_s > 0.6$) with both Brooke scale and PUL score, as did maximal Deltoid torque with PUL score ($r_s = 0{,}684$). Maximal sEMG amplitudes of the Triceps, Deltoid and Pectoralis major muscles correlated strongly with both Brooke scale and PUL score, while maximal Trapezius sEMG amplitude correlated strongly only with Brooke scale. Regarding echogenicity, moderate but significant correlations were found of Deltoid and Wrist flexor echogenicity with Brooke scale and PUL score. For muscle thickness, only the Triceps muscle significantly correlated with Brooke scale ($r_s = -0{,}642$). Maximal active joint angles of the shoulder movements (flexion, abduction, adduction) correlated very strongly ($r_s > 0.8$) with both Brooke scale and PUL score.

Table 2
Stepwise multivariable regression analysis.

	Brooke scale β (95% CI)	R^2 change	PUL score β (95% CI)	R^2 change
Max. muscle torque sum score (Nm)	−0.015 (−0.028; −0.003)	0.04	0.181 (0.025; 0.338)	0.03
Max. sEMG amplitude sum score (mV)				
Mean echogenicity *Z*-score				
Mean muscle thickness *Z*-score				
Maximal active joint angle sum score	−0.004 (−0.005; −0.003)	0.88	0.066 (0.049; 0.083)	0.85
Maximal passive joint angle sum score			−0.054 (−0.093; −0.016)	0.06
	R^2 = 0.907 ($p < 0.001$)		**R^2 = 0.938** ($p < 0.001$)	

Passive maximal elbow extension angle showed a high correlation with both Brooke and PUL score, and passive maximal shoulder abduction angle showed a moderate correlation with these scales.

4. Discussion

This study aimed to identify critical physiological outcome variables underlying reduced UE task performance in DMD. Based on these critical variables we propose an explanatory biophysical model of the UE working mechanism. Critical physiological outcome variables were chosen based on the strength of their associations with functional scales (Brooke and PUL scale) as shown in this study, and on their ability to discriminate between DMD patients in different stages of the disease, as shown in our previous study [17]. Based on these results, we conclude that 'maximal active joint angle', 'maximal muscle torque', 'maximal sEMG amplitude' and 'maximal passive joint angle' are the most critical variables underlying reduced UE task performance in DMD.

Maximal active joint angle sum scores showed the strongest correlation with both Brooke and PUL score and uniquely contributed to their explained variance in the multivariate model. In addition, maximal active joint angle sum score significantly discriminated between DMD patients in different stages of the disease [17]. The etiological interpretation is that – from a geometrical point of view – the attainable joint positions will directly affect the position of the end effector (task performance). Maximal muscle torque sum score also showed high correlations with both Brooke and PUL scores and uniquely contributed to their explained variance in the multivariate model. Moreover, maximal muscle torque sum score discriminated between DMD patients in different disease stages [17]. Maximal sEMG amplitude sum score was also identified as a critical variable, because it showed similar correlations and discriminative ability as maximal muscle torque sum scores. Maximal sEMG amplitude sum score, however, was not independently associated with Brooke and PUL scale (Table 2). Maximal passive joint angle sum score was critical for UE task performance due to its ability to discriminate between DMD patients in different stages of the disease and its moderate correlation with both Brooke and PUL score. In addition, maximal passive joint angle sum score was significantly associated with PUL score. Both echogenicity *Z*-scores and muscle thickness were not identified as critical outcome variables, as they only showed moderate correlations with Brooke and PUL score. Moreover, we previously found that both ultrasound variables were not able to discriminate between patients with different Brooke scales [17]. Although these measures are intuitively appealing, our results question whether the capacity of a muscle to generate force in DMD can be validly measured using either muscle thickness or echogenicity obtained by ultrasound. Ultrasound has the disadvantage that it is unable to measure deeper muscles, and the high attenuation of ultrasound images, especially in DMD patients with more fatty infiltration in their muscles, reduce the feasibility and reliability of ultrasound in this population [23,24].

When looking more specifically into the individual muscles and movements that are critical for UE task performance, we found that the maximal muscle torque and maximal sEMG amplitude of mainly proximal and midlevel muscles showed strong correlations with UE task performance. Proximal and midlevel muscles are of great importance for movements involving the shoulder and elbow, which is the case in most UE tasks [25,26]. The large association between proximal muscles/movements and task performance becomes also apparent from the large correlations between maximal active joint angles of the shoulder and UE task performance. This association was not seen between midlevel muscles and elbow movements. It must be realized that even a small decrease in shoulder angle will result in large effects on the hand position at the end of the kinematic chain. Nevertheless, we expect that the function of distal muscles and the ability to perform distal (hand) movements becomes critically important when the disease is progressing. Therefore, clinicians should mainly focus on retaining strength and range of motion of muscles and movements that are most relevant at specific stages of the disease. In other words, clinicians should not focus on abilities that are already lost, but on abilities that can still be retained or potentially improved. Regarding maximal passive joint angles, we see that the joints that are most prone to develop contractures are also most strongly related to task performance. From the literature and previous research we know that passive elbow extension and passive forearm supination are most often restricted [27,28], and indeed these movements show a moderate but significant relation with UE task performance. In addition, passive shoulder abduction angle is surprisingly related to UE task performance. Shoulder contractures are not often described in the literature and the passive range of motion is usually still larger than the

Table 3
Spearman correlation coefficients between functional scales and physiologic outcome measures (individual scores).

	Brooke scale (r_s)	N	PUL score (r_s)	N
Maximal muscle torque (Nm)				
Trapezius	−0,595*	22	0,591*	21
Biceps	−0,755*	22	0,816*	21
Triceps	−0,730*	21	0,673*	21
Deltoid	−0,583*	20	0,684*	20
Pectoralis major	−0,723*	22	0,768*	21
Wrist flexors	−0,485*	20	0,508	20
Wrist extensors	−0,640*	20	0,648*	20
Maximal sEMG amplitude (mV)				
Trapezius	−0,642*	23	0,542*	22
Biceps	−0,557*	22	0,443	21
Triceps	−0,767*	23	0,722*	22
Deltoid	−0,661*	21	0,674*	20
Pectoralis major	−0,738*	23	0,752*	22
Wrist flexors	−0,564*	23	0,522*	22
Wrist extensors	−0,482*	23	0,398	22
Z-scores Echogenicity (1/3 ROI)				
Trapezius	−0,270	22	0,364	21
Deltoid	−0,586*	23	0,573*	22
Biceps	−0,367	23	0,365	22
Triceps	−0,431*	23	0,346	22
Wrist flexors	−0,637*	22	0,593*	21
Wrist extensors	−0,320	22	0,408	21
Z-scores Muscle Thickness				
Trapezius	−0,180	17	0,260	17
Deltoid	−0,214	15	0,236	14
Biceps	0,077	17	−0,043	16
Triceps	−0,642	12	0,529	12
Wrist flexors	−0,003	17	0,028	17
Wrist extensors	0,124	21	0,005	21
Maximal active joint angles				
Shoulder flexion	−0,866*	23	0,842*	22
Shoulder abduction	−0,866*	23	0,846*	22
Shoulder adduction†	−0,884*	23	0,904*	22
Elbow flexion	−0,472*	23	0,321	22
Elbow extension	0,056	23	−0,241	22
Pronation	−0,407	23	0,288	22
Supination	0,565*	23	−0,481	22
Wrist flexion	0,471*	22	−0,450	21
Wrist extension	−0,574*	22	0,411	21
Radial deviation	0,494*	22	−0,467	21
Ulnar deviation	−0,401	22	0,230	21
Maximal passive joint angles				
Shoulder abduction	−0,569*	22	0,528*	22
Elbow flexion	−0,131	23	−0,015	22
Elbow extension	0,672*	23	−0,609*	22
Pronation	0,004	23	−0,109	22
Supination	0,463*	23	−0,310	22
Wrist flexion	0,462*	23	−0,406	22
Wrist extension	−0,309	23	0,067	22
Radial deviation	0,413	23	−0,294	22
Ulnar deviation	−0,125	23	−0,008	22

*Statistical significant correlation after correction based on false discovery rate (p-value <0.0303 for Brooke scale and p value <0.0127 for PUL scale).
† Shoulder adduction in the horizontal plane.

functional range of UE task performance. However, although the passive range is not critically restricted, increased stiffness of the muscle near its maximal elongation will increase the amount of force needed to move the arms. Although passive range of motion if not primarily responsible for limited task performance, it may be an important factor for task performance, especially when interventions to improve arm function, such as dynamic arm supports, are applied.

The critical physiological outcome measures we identified are grossly in line with the literature. Bartels et al. stated that UE muscle strength and passive range of motion are strongly associated with UE function [27], and Uchikawa et al. and Beenakker et al. showed that activities of daily living in patients with DMD are related to age and muscle strength [11,29]. Furthermore, Han et al. and Lowes at al. showed that reachable workspace, which is comparable to the active range of motion of the shoulder, is correlated with task performance in DMD [9,10]. In addition, active range of motion, however, has proven to predict UE function in post-stroke patients [30]. To our knowledge, there are no studies published on the relation of maximal sEMG amplitude with UE task performance.

For a better understanding of the working mechanisms that could lead to limitations in UE task performance, we constructed an explanatory biophysical model (Fig. 2). The construction of this model was based on common knowledge of UE anatomy and physiology and supported by the author's interpretation of the statistical results of this study. Due to the relatively large amount of variables and the limited number of participants in this study, we were not able to construct a reliable model solely based on statistics.

As indicated in the model, we consider task performance to be dependent on several biophysical characteristics, of which active range of motion is most closely related to task performance. Active range of motion is dependent on passive range of motion and the available muscle torque minus the external load and the passive joint torque. Passive joint torque is defined as the intrinsic torque that develops in the joint when moving due to the elastic properties of the muscles around the joint [31,32]. The available joint torque is based on the muscle capacity, where maximal muscle force is influenced by the maximal muscle activation, by the muscles cross-sectional area (CSA) and the unit of force that can be delivered per area of muscle [33,34]. In DMD patients, CSA does not significantly differ from healthy subjects, although some muscles show signs of either atrophy or hypertrophy [35–38]. The ability to generate force per area of muscle, however, is much lower compared to healthy controls [17]. Possible explanations for this reduced ability to generate force are: contractile muscle tissue wastage due to absence or shortage of dystrophin and infiltration of fatty and connective tissue [36,39] and impaired contraction efficiency due to time delay in force transmission [40]. As a result, we expect the influence of CSA on muscle strength in DMD patients to be much lower compared to healthy subjects.

The biophysical model was constructed based on a limited amount of data and variables. So, with the growing amount of knowledge that becomes available regarding UE function in DMD patients, it is possible that other critical variables for UE task performance will be added to the model in the future. Furthermore, the critical variables are determined

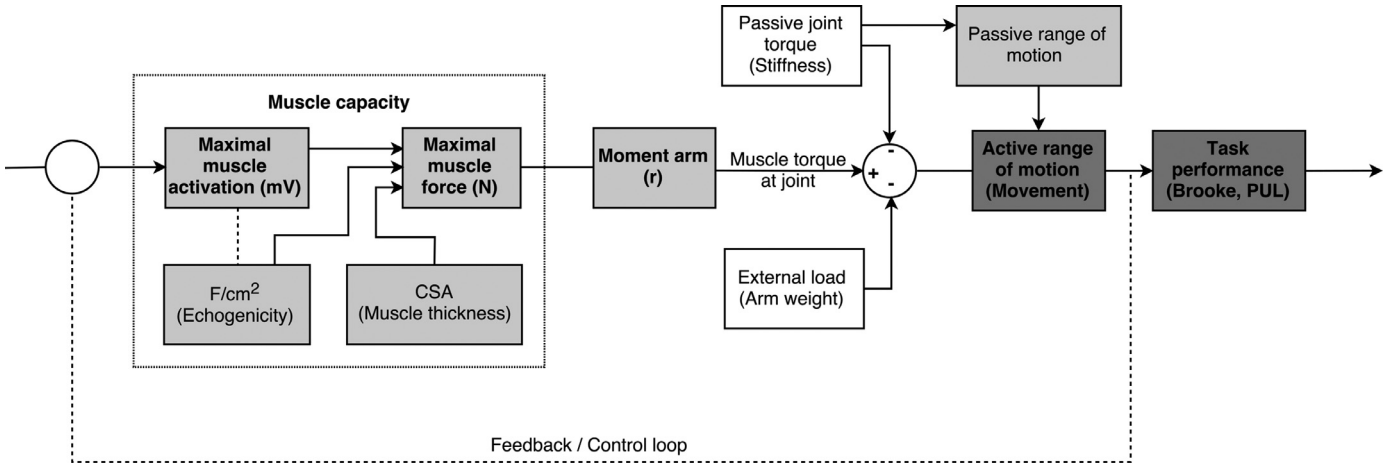

Fig. 2. Explanatory biophysical model of the UE working mechanism in DMD. Note: mV = millivolt, N = Newton, F/cm^2 = force per square centimeter of muscle, CSA = cross sectional area, r = radius.

based on statistical models that assume a linear relation, while in reality, the relations might not be linear. Different critical variables may, for example, apply to different stages of the disease. Unfortunately, the limited number of participants in this study did not allow for examining the disease stage dependent relation between task performance and physiological outcome measures. When more data becomes available through future research, non-linear modeling should be considered. Nevertheless, we believe that our model has several important clinical applications and, to the best of our knowledge, it is the first model attempting to explain the underlying mechanisms causing UE limitations in boys and men with DMD. The model can support the diagnosis of UE impairments at the International Classification of Functioning, Disability and Health (ICF) [41] level of body functions and structures instead of at the ICF activity level. In addition, this model can help to identify the mechanisms by which interventions, such as medication, may affect UE task performance. Based on the most critical physiological variables influencing UE task performance, new outcome measures for clinical trials can be developed and the selection of appropriate interventions can be based on biophysical characteristics.

New outcome measures regarding UE function are of great importance for clinical trials in non-ambulant DMD patients. The model presented in this study could form the basis for new multi-layered outcome measures for clinical trials. This research shows that range of motion and maximal muscle force are the most important physiological variables for UE task performance. Therefore we suggest to include both functional scales and physiological outcome measures in clinical trials. Muscle force of different muscle groups (proximal and distal) can, for example, be measured using a hand-held dynamometer, although this method is not always reliable in weak patients. For UE range of motion, recently new tools have been developed using the Microsoft Kinect [9,10]. These tools are relatively cheap and easy to apply in clinical practice and they might be suitable to implement in clinical trials as well.

Regarding the selection of appropriate interventions to improve UE function, we would also like to make recommendations. This study showed that range of motion is the most critical biophysical aspect underlying UE task performance, and literature showed that the ability to perform activities of daily living (ADL) requires sufficient range of motion in multiple joints [25,26]. As a result, we believe that interventions for improving UE function should be aimed at retaining the ability to use functional range of motion. For this purpose, contracture prevention is of importance, as severe contractures can reduce the reachable workspace and make the performance of ADL more difficult [27,42]. Despite the fact that research on the prevention of UE contractures is limited, it is recognized that stretching and splinting may be helpful, and that in severe and fixed contractures surgical intervention may be required [4,43]. In addition, prolonged static positioning of the limb should be prevented [43]. Another intervention that can possibly retain UE range of motion is the use of a dynamic arm support. Dynamic arm supports reduce the effort that is needed to move the arms (mainly against gravity), which in turn reduces the muscle capacity that is needed to perform movements. As a result, the active range of motion of the arms increases and task performance improves. Improving or retaining muscle strength is also very important for UE task performance, and clinicians should consider interventions that can improve muscle strength. Corticosteroid treatment has proven to retain muscle strength [44–46], and also physical exercise training may improve muscle strength of DMD patients [5].

Next to the physiological factors described above, there are some other variables that may influence UE task performance. For example, chronic pain is known to have a negative impact on general physical functioning [47]. In addition, intrinsic and environmental factors such as muscle/joint stiffness, nutrition, motivation, and other emotional aspects may influence task performance. Other important factors that may affect UE task performance are fatigue and muscle contraction efficiency. Unfortunately, we did not measure the influence of these factors on UE task performance directly and therefore they

were not included in the model. Future research should, however, focus on the relation between these variables and UE task performance.

There are some limitations to this study that should be mentioned. The sample size was relatively small, in particular regarding the DMD patients in the more advanced disease stages (Brooke 4 and 5). The small sample size disallowed stratification of possible confounders, such as ambulation, corticosteroid use, and scoliosis. In addition, no longitudinal data were available. Therefore, we could not include in the model data related to changes in variables over time. Nevertheless, we found significant cross-sectional correlations and consider this model valid for a wide range of DMD patients, but further validation studies are necessary. The correlation coefficients we found were based on a linear relationship between variables, while some of these relations may not be linear. Future validation studies should attempt to gain insight into the order of these correlations. Longitudinal data of a large group of DMD patients in different stages of the disease should be collected to establish causal relations between the biophysical variables and to see whether there are other variables that might be added to the model. In this study, we only included participants with a Brooke scale of 1–5. In order to see if the model is also valid for the most severely affected patients, future studies should also include patients with a Brooke scale of 6. To this end, measurement instruments might need to be adapted to the residual capacity of these patients, for example by focusing on strength and range of motion of the hands.

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