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PHYSICAL FUNCTION AND MOBILITY IN CHILDREN WITH CONGENITAL MYOTONIC DYSTROPHY

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ABSTRACT: Introduction: Congenital myotonic dystrophy (CDM) occurs when symptoms of myotonic dystrophy present at birth. In this study we evaluated the relationship between physical function, muscle mass, and age to provide an assessment of the disease and help prepare for therapeutic trials. Methods: CDM participants performed timed functional tests (TFTs), the first 2 minutes of 6-minute walk tests (2/6MWTs), and myometry tests, and also performed dual-energy X-ray absorption (DEXA) scans. Healthy controls (HCs) performed TFTs, 6MWTs, and myometry. Results: Thirty-seven children with CDM and 27 HCs (age range 3–13 years) participated in the study. There were significant differences in the 10-meter walk (11.3 seconds in CDM vs. 8.8 seconds in HC) and 2MWT (91 meters in CDM vs. 193 meters in HCs). DEXA lean mass of the right arm correlated with grip strength (r = 0.91), and lean mass of the right leg correlated with 6MWT (r = 0.62). Conclusion: Children with CDM have significant limitations in strength and mobility. The tests performed were reliable, and lean muscle mass may serve as a useful biomarker.

Myotonic dystrophy (DM1) is the result of a trinucleotide CTGn repeat expansion in the 3’ untranslated region of the DMPK gene.1–4 This CTG repeat can expand markedly between generations, particularly when the mother is affected. Significant repeat expansions may lead to symptoms at birth, known as congenital myotonic dystrophy (CDM).5,6

Children with CDM have high mortality in the newborn period and display significant impairments in physical function throughout childhood.7–16 Clinical features in children with CDM include hypotonia, weakness, feeding difficulties, cognitive impairment, and respiratory failure requiring intubation and ventilation immediately after birth.8,10,14,16–19

A cross-sectional study has identified hand weakness and difficulty with ambulation as affecting quality of life in CDM.20,21 Despite this, few data have been collected for functional outcome measures in CDM.22,23 One study attempted to measure isometric muscle strength using handheld myometry in children with CDM.22 However, the investigators were unable to collect sufficient data due to the participants having difficulty following directions.22 Another study measured timed functional tests, manual muscle tests, and pulmonary function tests in 17 individuals with CDM > 10 years of age.24 Physical ability in children with CDM had been measured previously using the motor function measure (MFM)25 and a similar motor function scale.22 However, the earlier studies were limited by sample size, age restriction, and a smaller subset of functional measures.22,23

In this study we aimed to comprehensively evaluate available outcome measures for use in therapeutic trials. Accordingly, the study goals were to: (1) compare timed functional tests for healthy controls (HCs) and children with CDM; (2) determine the feasibility, reliability, and agreement of functional measures; and (3) identify any relationships between dual-energy X-ray absorption (DEXA)}
lean mass and functional measures for children with CDM.

METHODS

Participants with CDM between 3 and 13 years of age were enrolled at the University of Utah (n = 34) and the University of Western Ontario, Canada (n = 3). The institutional review boards at both institutions approved all study procedures, and informed consent was obtained. Participants were included if they met the research definition for CDM and had no other major medical illnesses. CDM was defined as: (1) symptoms present at birth; (2) newborn symptoms, including hypotonia, feeding difficulties, talipes equinovarus, or respiratory failure; and (3) confirmed genetic testing revealing a CTG repeat in the DMPK gene with >200 repeats. Subjects were excluded if they had any non-DM1 illness that would interfere with their ability to complete study procedures. HCs (n = 27) between 3 and 13 years of age were included if they had no major medical problems and were not currently on any medications.

Timed Functional Testing. Timed functional tests (TFTs) were performed in accordance with previous pediatric studies of neuromuscular disorders. Activities included: time to climb 4 stairs (4SC); time to rise from the floor starting in a supine position; 10-meter (m) run; and 10-m self-selected walking speed. A stopwatch was used, and participants were given a maximum of 60 seconds (s) to complete all tasks. If a subject was unable to complete the task, the time was not recorded. Correlations were analyzed for children with CDM between TFTs and age, and also for TFTs and number of CTGn repeats.

6-Minute and 2-Minute Walk Tests. The 6-minute walk test (6MWT) was conducted in HCs and children with CDM along a 25-m course using criteria cited in previous studies. The distance at 2 minutes (min) was recorded during the 6MWT and was referred to as the 2-minute walk test (2MWT). Orthotics and assistive devices for ambulation were allowed. Continuous verbal encouragement was given from the evaluators and parents during the test to ensure the subjects remained attentive. The 6MWT was performed over 2 consecutive days in children with CDM for reliability testing. HCs performed the walk test on a single day. Subjects who were physically unable to walk were given a distance of 0 m from the 6MWT and 2MWT.

Grip and Pinch Myometry. The average of 3 trials of grip and pinch measurements for maximum voluntary isometric contraction (MVIC) was collected from both hands in HCs and children with CDM. Handgrip was collected using a digital hand dynamometer (Jamar Plus+; Sammons Preston, Bolingbrook, Illinois). Jaw chuck pinch and lateral pinch were collected using a digital pinch gauge (Jamar Plus+). Participants were instructed to grip and pinch as hard as they were able with the hand and forearm resting at their sides in 90° of elbow flexion and neutral pronation/supination.

Handheld Myometry. Strength testing was collected in HCs and children with CDM (age range 4–13 years) on 4 muscle groups, bilateral shoulder abductors and ankle dorsiflexors using a Commander Muscle Tester (PowerTrack II; JTECH Medical, Midvale, Utah). A make test was conducted. Shoulder abduction was collected with the patient in the seated position with the shoulder abducted to 90° and the elbow flexed a few degrees with a dynamometer placed proximal to the lateral humeral epicondyles. Ankle dorsiflexion was tested in the seated position with the legs flexed over the edge of the table with shoes off, lower leg stabilized above the ankle joint, and the myometer placed on the dorsum of the foot over the metatarsals. Dorsiflexion with inversion was allowed, because many children with CDM had difficulty isolating pure dorsiflexion. Three trials were collected per muscle, and the average was recorded.

Dual-Energy X-Ray Absorptiometry. Whole-body DEXA scans were performed on children with CDM using a Hologic Discovery (Hologic, Inc., Marlborough, Massachusetts) machine running Apex version 3.2 software. HCs did not undergo DEXA scans. Children were positioned according to manufacturer recommendations. On occasion, when cooperation could not be solicited from a few of the children, a cotton sheet was used to swaddle the child to minimize movement artifact. Scans of the lean mass of the right arm and leg were acquired and analyzed by a licensed and certified technician from the International Society for Clinical Densitometry.

Bruininks-Oseretsky Test of Motor Proficiency—2nd Edition. The Bruininks-Oseretsky Test of Motor Proficiency—2nd edition (BOT-2) fine motor control and manual coordination subtests were attempted in 25 of the children with CDM between 4 and 13 years of age. Each subject’s percentile rank was calculated in relation to previously established standardized and norm-referenced values.

Statistical Analysis. Independent-sample t-tests or Wilcoxon 2-sample tests were used to compare the differences in functional measures between CDM and the control group. Pearson correlation was used to determine the relationship between the
upper and lower extremity outcome measures and the DEXA lean mass. Intraclass correlation (ICC) and Bland–Altman analyses were used to test the reliability between days 1 and 2 of the 6MWT and 2MWT. Family-wise error was corrected for by using Holm–Bonferroni methods. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) statistical software, and \( P < 0.05 \) was considered significant.

**RESULTS**

**Participant Demographics.** This study included 37 participants with CDM and 27 HCs. Detailed demographic data, including age, gender, ethnicity, race, and CTG\(_n\) repeat number, are presented in Table 1.

**Timed Function Testing.** When comparing TFTs, children with CDM performed significantly lower than HCs on all 4 measures (10-m walk, 10-m run, time to rise from floor, 4SC), after adjusting for age. Findings were as follows (mean ± standard deviation): 10-m walk: CDM \((n = 31)\) 11.3 ± 6.9 s, HCs \((n = 26)\) 6.8 ± 1.8 s \((P < 0.001)\); 10-m run: CDM \((n = 29)\) 6.1 ± 3.1 s, HCs \((n = 25)\) 3.2 ± 0.5 s \((P < 0.001)\); time to rise from the floor: CDM \((n = 26)\) 9.4 ± 6.3 s, HCs \((n = 25)\) 2.0 ± 0.6 s \((P < 0.001)\); and 4SC: CDM \((n = 29)\) 7.0 ± 7.6 s, HCs \((n = 26)\) 1.5 ± 0.9 s \((P < 0.001)\).

Some participants with CDM were unable to complete the test for physical, behavioral, or cognitive reasons. Behavioral difficulties included participants with CDM being easily distracted, uncooperative, or sometimes refusing to perform the tests. A time was recorded only if the participant was able to complete the test. The percentages of participants with CDM who were scored for the TFTs were: 10-m walk, 83.8%; 10-m run, 78.4%; 4SC, 78.4%; and time to rise from floor, 74%. Figure S1 (refer to Supplementary Material, available online) provides an analysis of TFT results versus age as a function of CTG\(_n\) repeat length (>100 or <1,000) in children with CDM.

**6-Minute and 2-Minute Walk Tests.** The total 6MWT distance has been previously reported.\(^{30}\)
Behavioral difficulties prevented some participants (11%) from completing the full 6MWT, but all participants were able to complete at least the first 2 minutes. Similar to the 6MWT, 2MWT results were significantly different in the CDM population (CDM $91 \pm 58.9$ m vs. HC $193 \pm 22.7$ m; $P < 0.0001$), as shown in Figure 1. Both walk tests had high test–retest reliability (2MWT ICC = 0.94, 6MWT ICC = 0.96). Bland–Altman plots of test–retest reliability are presented in Figure 2. For the 6MWT, the mean difference between days 1 and 2 was close to 0, 1.46 m/min or 8.52 m over 6 min, and thereby indicates our 6MWT had test–retest reliability. Likewise, for the 2MWT, the mean difference between days 1 and 2 was 0.66 m/min or 1.32 m over 2 min. The 2MWT overall has a smaller mean difference than 6MWT. No systematic change was noted, as the Bland–Altman plot shows random changes in the mean values between the 2 test occasions.

**Correlation of Timed Functional Tests and Walk Tests.** The first 2 minutes of the 6MWT correlated highly with the overall 6 MWT distance (Table 2). Gait speed items, 10-m run and 4SC, and 10-m run and 10-m walk had strong correlations. Modest correlations were found between all other comparisons (Table 2).

**Handheld Myometry.** Handheld myometry results are reported in Supplementary table S1, available online. The average age of children with CDM able to complete shoulder abduction myometry was 9.51 years and 9.98 years for ankle dorsiflexion myometry.

**Dual-Energy X-Ray Absorptiometry.** DEXA lean mass results by age and gender for children with CDM ($n = 29$) are shown in Supplementary figure S2, available online. The mean DEXA total lean mass for males (15,058 g/cm$^2$) was higher than that for females (15,013 g/cm$^2$), but the difference was not significant ($P = 0.539$). The total lean mass correlated significantly with age for children with CDM ($r = 0.808, P < 0.001$). DEXA lean mass of the right arm correlated well with all 3 measures of hand strength (Table 3). However, when comparing DEXA lean mass of the lower extremity and total lean body mass with 10-m walk or 2MWT/6MWT performances, only modest correlations were found for each measure (2MWT, $r = 0.59$; 6MWT, $r = 0.62$; 10-m walk, $r = -0.38$; Tables 2 and 3).

![Figure 2](image.png)

**Figure 2.** Bland–Altman graphs of 2MWT and 6MWT test–retest reliability.

<table>
<thead>
<tr>
<th>Measure</th>
<th>DEXA total lean mass</th>
<th>2MWT</th>
<th>6MWT</th>
<th>10-m walk</th>
<th>4-stair climb</th>
<th>Rise from floor</th>
<th>10-m run</th>
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<tr>
<td>DEXA total lean mass</td>
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<td>2MWT</td>
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<td>($P = 0.001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
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<td>1.00</td>
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<td>($P = 0.066$)</td>
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<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
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<td>($P = 0.0012$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
</tr>
<tr>
<td>Rise from floor</td>
<td>-0.28</td>
<td>-0.66</td>
<td>-0.66</td>
<td>0.57</td>
<td>0.55</td>
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<td>($P = 0.239$)</td>
<td>($P = 0.0003$)</td>
<td>($P = 0.0006$)</td>
<td>($P = 0.0025$)</td>
<td>($P = 0.0042$)</td>
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<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
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<tr>
<td>10-m run</td>
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<td>0.82</td>
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<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P &lt; 0.0001$)</td>
<td>($P = 0.0003$)</td>
</tr>
</tbody>
</table>

**Table 2.** Pearson coefficients for walk tests and timed functional tests.
**Exploratory Measures.** The BOT-2 assesses fine motor control and manual dexterity. It was administered to 25 children with CDM between 4 and 13 years of age (average age 8.1 years). Ninety-four percent of participants scored in the 0 to 2nd percentile when compared with norm-referenced values for fine motor control, manual coordination, and fine motor composite. One subject scored in the 8th percentile for fine manual control.

**Seventy-two percent of children with CDM were able to complete the fine manual control and manual coordination subsets of the BOT-2.**

**DISCUSSION**

In this study we have provided a cross-sectional assessment of physical function in children with CDM. There is evidence that strength improves throughout childhood, albeit at different rates, depending on the outcome measure used. However, despite improvement, the children with CDM who were evaluated scored lower than their healthy peers. In general, the improvement between age groups on the measures assessed stands in contrast to findings from adults with DM1, where strength declined over time. It is possible that CDM is a developmental disorder, and that natural muscle maturation may partially compensate for the underlying pathophysiology. Future studies should attempt to compare individuals with adult-age CDM to adults with DM1 and, likewise, children with CDM to individuals with childhood-onset DM1.

This study was designed to prepare for clinical trials in children with CDM by evaluating the feasibility, reliability, and validity of functional outcome measures. Overall, the measures assessed met criteria for inclusion in clinical trials in that they were reliable and generally completed. The 6MWT and 2MWT were found to have excellent test-retest reliability. It appears that children with CDM have decreased performance on TFTs if they possess >1,000 CTG<sub>n</sub> repeats when compared with their peers with CDM who have <1,000 CTG<sub>n</sub> repeats (see Supplementary Fig. S1). DEXA lean body mass may be an effective clinical tool to utilize in future studies for predicting functional upper extremity strength and may be a potential biomarker to monitor functional changes in disease progression.

Given the association of intellectual impairment in children with CDM, functional outcomes may have variable completion rates. The TFTs and 6MWT described had acceptable rates of completion. Future studies may consider using the 2MWT rather than the 6MWT, because more children were able to complete the first 2 minutes of the 6MWT than the full 6MWT. Tests with the lowest completion rates for children with CDM included spirometry, BOT-2, and myometry of the ankle dorsiflexors. We also found that children with CDM displayed a floor effect on the BOT-2, whereby no subjects who were able to complete the test scored above the 8th percentile on any of the subtests of fine manual control and manual coordination.

There are limitations to our study. First, the study is cross-sectional in nature. Future longitudinal studies will be required to obtain within-participant comparisons. Second, many of our participants were remote from the study center and required travel, which may have contributed to fatigue. Third, intellectual impairment and

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**Table 3. Pearson correlation for DEXA results compared with functional tests**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Total body lean mass</th>
<th>Lean mass of right arm</th>
<th>Right grip</th>
<th>Right pinch</th>
<th>Right jaw chuck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body lean mass</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Right grip</td>
<td>0.84 (P &lt; 0.001)</td>
<td>0.91 (P &lt; 0.0001)</td>
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<tr>
<td>Right lateral pinch</td>
<td>0.76 (P &lt; 0.001)</td>
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<td>0.94 (P &lt; 0.0001)</td>
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<tr>
<td>Right jaw chuck</td>
<td>0.73 (P &lt; 0.001)</td>
<td>0.77 (P = 0.0000)</td>
<td>0.86 (P &lt; 0.0001)</td>
<td>0.78 (P &lt; 0.0001)</td>
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<table>
<thead>
<tr>
<th>Measure</th>
<th>Total body lean mass</th>
<th>Lean mass of right leg</th>
<th>2MWT</th>
<th>6MWT</th>
<th>10-m walk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body lean mass</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2MWT</td>
<td>0.62 (P = 0.001)</td>
<td>0.59 (P = 0.0047)</td>
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<td>6MWT</td>
<td>0.62 (P = 0.001)</td>
<td>0.62 (P = 0.0034)</td>
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<tr>
<td>10-m walk*</td>
<td>-0.39 (P = 0.066)</td>
<td>-0.38 (P = 0.1345)</td>
<td>-0.73 (P &lt; 0.0001)</td>
<td>-0.76 (P &lt; 0.0001)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*An inverse correlation is found between lean mass of the right leg and 10-m walk, as increasing lean mass should result in less time to complete the 10-m walk.*
behavioral problems in some children with CDM limited the completion rate of some tests. Finally, the first 2 minutes of the 6MWT were used rather than a separate 2MWT. Future results may vary with the use of the actual 2MWT as a stand-alone measure.

Overall, this study has defined some of the limitations of physical function during childhood in children with CDM. Due to the nature of CDM, there was a degree of variability between each subject’s ability to complete the full battery of physical function assessments. Children with CDM may display autism-like characteristics. Despite these obstacles we found that most children with CDM were able to complete the walk tests, TFTs, and DEXA scans. Future studies should continue to examine and seek to validate various measures of functional mobility in children with CDM to better understand disease progression and prepare for clinical trials.

The authors thank Hillarie Slater (DEXA scan technician at the University of Utah), Heather Hayes, PT, PhD, and Wei Chen, PhD (both from the University of Utah), for their contributions to this work.

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