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Quantifying Passive Muscle Stiffness in Children with and without Cerebral Palsy Using Ultrasound Shear Wave Elastography

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Abstract

Aim—The aim of this study was to compare passive muscle stiffness in children with cerebral palsy (CP) and typically developing (TD) children using a novel ultrasound technique – ultrasound shear wave elastography (SWE).

Method—We conducted a prospective study of 13 children with CP (6 females and 7 males, ages 68.7 (28.3) months) and 13 TD children (6 females and 7 males, ages 67.3 (35.0)). Demographic information and physical exam measurements were obtained in addition to shear modulus measurements (passive muscle stiffness) of the lateral gastrocnemius muscle at 20° plantar flexion (PF), 10° PF, and 0° PF using SWE.

Results—Children with CP had significantly greater shear modulus measurements at all three foot positions ($P<0.05$). When the shear modulus values were normalized to the baseline value for each child, there was no significant difference between the two groups.

Interpretation—Passive muscle stiffness, measured without the influence of spasticity, is greater in children with CP as compared to TD children when a muscle is at slack and at stretch. When shear modulus was normalized, the results indicate that muscle in children in both groups respond

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similarly to passive stretch. Further work includes evaluating effect of botulinum toxin on passive muscle properties.

In individuals with cerebral palsy (CP), spasticity is thought to contribute not only to increased active muscle stiffness due to co-contraction of antagonist muscles during volitional movement, but also increased passive muscle stiffness. Advancing our understanding of passive muscle stiffness in children with CP is critical to enhancing active functioning. Passive muscle stiffness leads to muscle adaption and decreased passive joint range of motion (ROM), contributing to the worsening motor impairment in CP over time. For example, many children with CP have a decrease in their ability to ambulate as they age into adolescence and adulthood.(1) While this is likely multifactorial, one critical factor appears to be a loss of passive ROM(2) and thus a decline in the efficiency of walking.(1) This loss of ROM has been attributed to increased passive muscle stiffness (3, 4), with passive stiffness possibly related to spasticity. (5) While, one study has used SWE to measure passive stiffness in children with hemiplegic CP, the authors did not report on spasticity severity, joint ROM, or monitor EMG in all subjects.(6)

Measuring muscle biomechanical properties, including passive muscle stiffness is important as rehabilitation interventions, including stretching, strengthening, and spasticity treatments, rely on altering muscle biomechanical properties. Many current measurements of muscle biomechanical properties are either qualitative (palpation, Ashworth scale, or manual muscle testing) or too complex to perform in a clinic setting (dynamometry). In addition, none of these tests isolate the muscle. For example, dynamometry measures the force (torque) required to move a joint through a specific ROM. It is known that greater torque is required for passive ROM in children with CP as compared to typically developing (TD) children.(7, 8) The increased torque for passive joint movement is suggestive of increased passive muscle stiffness. However, dynamometry does not distinguish passive muscle stiffness from tendon or joint capsular stiffness. Advances in ultrasound elastography techniques provide an opportunity for direct quantification of passive muscle stiffness. Specifically, ultrasound shear wave elastography (SWE) has been used to provide direct, quantitative measurements of muscle stiffness, including individuals as young as 2 years of age through elderly.(9-11) As information on passive muscle stiffness in children with CP is lacking and the ability to measure passive muscle stiffness in a real-time setting has recently been established, the goal of this study was to measure passive muscle stiffness (shear modulus) in children with CP and compare these measurements to TD children, hypothesizing that passive muscle stiffness will be greater in children with CP.

Methods

Participants

Fourteen children aged 2 to 12 years of age with spastic cerebral palsy were recruited from Mayo Clinic's Cerebral Palsy Clinic. Children were excluded if they had 1) any surgery to the tibia or fibula, gastrocnemius/soleus, or Achilles tendon, 2) any other orthopedic surgery to the lower limb in the previous 6 months, 3) any phenol injection to the limb of interest in the previous 6 months, 4) botulinum neurotoxin injection to the lower limb of interest in the previous 3 months, 5) planned active titration of systemic anti-spasticity medications during

the study period, 6) serial casting of the lower limb of interest in the previous 6 months, 7) or inability to tolerate positioning for the study. These children were compared to thirteen age and sex-matched typically developing (TD) children who were recruited from the community. The typically developing children were a subset of a group of children who have been previously reported.(10) Mayo Clinic Institutional Review Board approval was obtained before initiating the study. Written informed consent was obtained from a parent or guardian of each child, with written assent obtained from children if older than 7 years and cognitively able to provide assent.

Study Methods

For each child, demographic information collected included date of birth, weight, height, sex, medical and surgical history, medications, and previous botulinum toxin or phenol injections. Physical examination measurements collected were spasticity using the Modified Ashworth Scale (MAS) (children with CP only), ankle ROM, Gross Motor Function Classification Scale (GMFCS) level (children with CP only), and type of CP (children with CP only). MAS testing for the ankle were performed with the child either seated or supine, depending on child's ability and preference. The reliability of the MAS for measuring spasticity has come into question.(12) However, the complexity of administering the Tardieu Scale makes it less applicable for use in the clinical setting and the Modified Tardieu Scale has similar inter- and intra-rater reliability as the MAS.(13, 14) Maximum passive joint ROM of the ankle for foot dorsiflexion (DF) and plantar flexion (PF) was performed using a goniometer with the child in supine position. When supine, the child's hip was positioned at 0° extension and knee was placed in full extension (0° flexion). If the child did not have the ROM at the hip or knee to accommodate this positioning, the nearest position that the child could comfortably tolerate was used. Maximum passive ankle ROM was achieved when either the child demonstrated discomfort, either verbally or through other indications or a solid end point was reached with stretch.

Following the physical exam measurements, measurements of bilateral lateral gastrocnemius stiffness were performed using SWE. An Aixplorer ultrasonic scanner (version 4.0; SuperSonic Imagine, Aix-en-Provence, France) with a linear array transducer (SL15-4; SuperSonic Imagine, Aix-en-Provence, France) was used with musculoskeletal preset (SWE Optimization: Standard, HD/Frame Rate: Balanced, Zoom: 120%, Smoothing: 5, Persistence: High). The physics and mathematical approach for these measurements are described elsewhere.(9, 15, 16) Briefly, the ultrasound probe generates transient shear waves in muscle by transmitting ultrasound push beams.(9) The same probe then detects the shear waves travelling along the muscle fiber, the speed of which can be used to calculate the Young's modulus.(15, 17) Young's modulus is the output of the Aixplorer.

SWE measurements were obtained as previously described.(10) For the SWE measurements, each child was assisted into a prone position with feet over the edge of the examination table. With a tape measure, circumferential measurements of each calf were obtained, and the area of greatest muscle bulk was marked on the skin. The ultrasound transducer was positioned on the lateral gastrocnemius muscle over the area of greatest muscle bulk. The transducer was aligned with the direction of the muscle fiber. The distance from the fibular

head to the proximal end of the ultrasound probe was measured and recorded to maintain positioning of the ultrasound transducer for the repeated measures. B-mode imaging was used to confirm positioning and alignment of the transducer. Appropriate transducer alignment was achieved when several fascicles of the lateral gastrocnemius could be traced (Figure 1).(18) The transducer was held in place with minimal pressure on skin by one of the examiners. Surface electromyography (U-Control; Thought Technology Ltd, Québec, Canada) was used to ensure muscle relaxation. The Ucontrol was set at lowest scale range (X1, upper threshold 3.0) for detecting muscle activation. Electrodes were placed over the posterior calf near the area of the SWE measurement. Goniometer was used to identify foot position with 20° PF, 10° PF, and 0° PF being the positons of interest. The goniometer was aligned with the shaft of the tibia or fibula and the calcaneus. The examiner then applied pressure along the plantar surface of the foot, using calcaneal movement as the dorsiflexion measurement and observing for inadvertent foot rotation or inversion/eversion. When correct foot position and sufficient muscle relaxation were present, SWE measurement was performed. Measures were obtained at three positions and then repeated twice. The three measures for each foot position were averaged to generate a single value for further analysis.

The output for each SWE measurement is a 2-dimensional elastogram (Figure 1). On this elastogram, a region of interest over the lateral gastrocnemius muscle was selected such that muscle fascial borders, tendon, and blood vessels were excluded. As previously described, (9, 11) we used an open-source imaging plug-in for the DICOM reader (OsiriX Imaging Software, Geneva, Switzerland) to measure the mean Young's modulus for the circular region of interest (mean diameter: 4.8 to 5.0 mm) within the SWE elastogram. The Young's modulus is related to shear wave speed via Equations 1(19):

$$E=3G=3{c_s}^2\rho \quad (1)$$

where E is Young's modulus, G is shear modulus, c_s is shear wave propagation velocity, and ρ is density, which can be assumed to be 1000 kg/m3 for all soft tissues. Note that Eq. (1) assumes an isotropic, purely elastic, and homogeneous medium, which is not the case for skeletal muscles, and therefore, shear wave speed is the more appropriate variable to describe muscle stiffness measured from ultrasound SWE. (20) To be consistent with our previous *in vitro* muscle study (17) and the healthy control study (10), in this paper we elected to report shear modulus, which can be conveniently converted to shear wave speed using Eq. (1). (17, 20) For further assessment of the passive stiffness changes as the muscle is stretched, a normalized shear modulus value was created for each child. This was done by dividing the shear modulus value at each foot position by the base line shear modulus value for each child. For the purpose of this study, the baseline shear modulus value was the value when the foot was 20° PF.

Statistical Analysis

Differences between lateral gastrocnemius shear modulus at each foot position for the same side between children with CP and TD children was of primary interest. For children with CP, the involved leg for children with hemiplegia or the most affected leg for all others was

used. Most affected leg was the side with greater gastrocnemius spasticity or less dorsiflexion ROM. For the matched TD children, the same-side (as their matched CP child) leg was used. Categorical variables (i.e. Sex, GMFCS, MAS, CP type) were summarized using frequency and percentages with Chi-squared tests used to assess differences between the comparison groups. Continuous variables (i.e. Age, BMI, calf circumference, maximal ankle DF, shear modulus) were summarized using median, interquartile range (Q1, Q3) and range. Do to the limited sample size, Wilcoxon rank sum tests (a non-parametric approach) were used to assess differences between two groups with Kruskal Wallis tests used when comparing across three groups (GMFCS, MAS, and history of botulinum toxin injections). Spearman Rank Correlations were used to explore the relationship between pairs of continuous variables. The level for significance for any p-value was set at less than 0.05. All analyses were conducted using SAS for Unix (version 9; SAS Institute Inc).

Results

A total of 27 children participated in this study; 14 children with CP and 13 TD children. One child with CP was unable to achieve sufficient muscle relaxation despite multiple attempts at alternative positioning. This child was excluded from the study, resulting in 26 children used for analysis. One child with CP was missing data on leg circumference. Demographic characteristics and comparisons between the sexes for children with CP are described in Table 1. Demographic characteristics and comparisons between children with CP and TD children are in Table 2. There were slightly more boys (7 (53.8%)) than girls in both groups. Of the children with CP, 6 (46.2%) had hemiplegia and 7 (53.8%) had diplegia or triplegia. All children with CP had some ambulatory ability. MAS of the ankle ranged from 1 to 3.

With regard to the children with CP, there was no significant difference between the sexes for age, BMI, calf circumference, GMFCS level, MAS, CP type, or ankle ROM, or most shear modulus values (Table 1). Girls with CP had a significantly lower shear modulus at 10° PF only, as compared to boys. There was also no association between shear modulus and GMFCS level, MAS, or history of botulinum toxin injection to the calf muscle.

When compared to age and sex matched TD children, there was a significant difference with regard to ankle ROM and shear modulus at all ankle positions (Table 2, Figure 2). Children with CP also had greater variability in their shear modulus values as indicated by the larger standard deviation of their measurements at all ankle positions (Figure 2). There was no significant difference between children with CP and TD children for BMI, leg circumference, or *normalized* shear modulus.

Discussion

Absolute passive muscle stiffness was greater in children with CP as compared to TD children at similar ankle joint positions. However, when the passive muscle stiffness was normalized (i.e. passive stiffness that is normalized to each child's 20° PF), this difference was eliminated. This indicates that the passive stiffness of muscle in children with CP is greater than TD children, though passive stiffness increases similarly between children with

CP and TD children when the muscle is stretched. This increased passive stiffness in children with CP may be related to differences in the muscle fibers, extracellular matrix, or both. Studies of in vivo muscle properties in children with CP who have muscle contractures requiring orthopedic surgery, show increased sarcomere length and increased passive mechanical stiffness.(21, 22) However, whether this increased passive stiffness is directly related to differences in the muscle fiber or the collagen content of the extracellular matrix appears to vary between muscles, and is not predictable based on the muscle architecture.(21, 22) The timing and cause of the development of these maladaptive muscle properties is not clear. Thus, the underlying mechanisms for the increased muscle stiffness in CP are not well understood. With SWE, it is possible to longitudinally follow muscle stiffness, thus quantifying how muscle stiffness evolves over a lifetime in individuals with and without neuromuscular disorders.

We did not find an association between passive muscle stiffness in children with CP and history of previous botulinum toxin injections, spasticity severity, or GMFCS level. While we cannot make definitive conclusions due our study size and limitations of some of the measurements used, our results are consistent with other studies on the microscopic muscle architecture.(21, 22) Studies using SWE to evaluate effect of botulinum toxin injections and selective dorsal rhizotomy on passive muscle stiffness in children with CP are underway.

Our children with CP were well-matched with the group of TD children. This is important as age, sex, body mass, and muscle mass are possible influences on muscle properties.(11, 23) In our previous study of TD children, we did not find a correlation between age and sex on passive muscle properties.(10) When comparing sexes in the children with CP we did find a significant difference in shear modulus at one foot position. With the small numbers of children with CP in each group and variability of measurements, the relevance of this significance is uncertain. Further evaluation of this with more children with CP and additional muscle groups is necessary.

Lastly, we found greater variability in the shear modulus measurements at all foot positions in children with CP as compared to TD children. This variability is likely two-fold. First, it is well-known that musculoskeletal measurements in children with CP are more heterogeneous than TD children. Second, as stiffness increases, SWE also has greater variability inherent with capturing high-speed shear waves.(9) As children with CP had greater passive muscle stiffness than TD children, this also contributed to some of the greater variability in shear modulus measurements. However, despite this variability, we still found a significant difference in passive muscle stiffness between CP and TD children. In the future, studying the variability of measurements between children with CP may be helpful for individualizing rehabilitation with a focus on optimizing muscle properties.

Limitations

This study has some limitations. First, while we did not exclude children of GMFCS levels IV and V, we had difficulty recruiting children with these greater functional impairments as the parents felt their child would not tolerate positioning or cooperate with testing. Children with CP had greater difficulty with muscle relaxation (as monitored with surface EMG), requiring longer study visits and occasional breaks. However, as sufficient relaxation was

eventually achieved, we do not feel this impacted the results. Another limitation is that we imaged one muscle. While our results appear consistent with other studies looking at musculoskeletal properties, further investigation of passive muscle properties in other key muscles is warranted. To measure ankle ROM, we used a goniometer, which has approximately 5° to 14° variability in children with CP. (24, 25) The goniometer was chosen due to ease of use in a clinical setting and to maintain clinical applicability and translation of this study. Some children with CP who had maximal ankle dorsiflexion of less than 0° during their initial goniometric testing (which was always performed before SWE) were subsequently able to achieve 0° dorsiflexion. This was either due to response to initial stretch for goniometric measurement, inherent variability in goniometric measurements, in advert ankle rotation during dorsiflexion, or some combination of these. While we recorded whether or not children had previous botulinum toxin injections and timing of the most recent injection, we did not record the number of injections these children had, which may impact passive muscle stiffness. With our sample size, statistically reporting comparisons of number of previous injections, dose, and passive muscle stiffness would not be possible. Lastly, shear modulus is reported as an acceptable measure for muscle elasticity. (16, 17) However, muscle is anisotropic, viscoelastic, and heterogeneous, which violates the common assumptions used to convert shear wave speed to shear modulus and Young's modulus (Eq. 1). The assumptions of Eq. 1 currently remain a noted limitation for musculoskeletal ultrasound SWE until more representative models are developed for musculoskeletal tissues.

Conclusion

Muscle properties have been previously investigated and quantified through invasive measures (muscle biopsy) or inferred from complex measurements performed in a lab based setting (dynamometry). This study demonstrates that passive muscle stiffness in children can be measured in a clinical setting with passive muscle stiffness being greater in children with CP. Directly measuring muscle properties with SWE has potential to become an extension of the physical exam, as use of ultrasound in clinical practice is growing. In the future, SWE may be a useful clinical tool for diagnosis of CP and longitudinal monitoring of passive muscle stiffness to assist with treatment decisions and response of passive muscle stiffness to therapeutic interventions.

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What this paper adds

- Passive muscle stiffness can be directly measured and quantified in children with CP using SWE.
- Passive muscle stiffness is greater in children with CP.
- There was no association between passive muscle stiffness and spasticity severity, history of botulinum toxin injections, or GMFCS level.

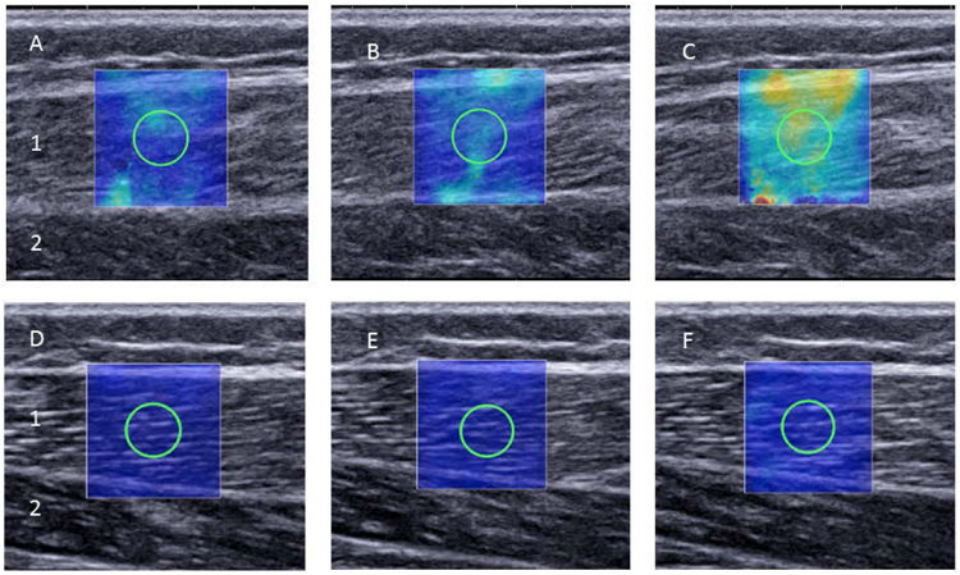

Figure 1.

Representative B-mode Ultrasound Image with Super-Imposed 2-Dimensional (2-D) Elastograms from Right Lateral Gastrocnemius of a Child with Cerebral Palsy and the Matched Typically Developing Child. Figure shows ultrasound images of a child with CP (top) and a typically developing child (bottom). A) 20° plantar flexion, B) 10° plantar flexion, C) 0° plantar flexion, D) 20° plantar flexion, E) 10° plantar flexion, and F) 0° plantar flexion. The colored box, located over the B-mode image of the lateral gastrocnemius muscle (1), represents the 2-D Elastogram which is the area of shear wave capture. The circle inside the box represents the region of interest, which is the area of shear wave measurement. The soleus muscle (2) is also shown. The 2-D Elastogram colors are a visual representation of shear-wave speed: purple-blue indicates tissue with low shear-wave speed (softer tissue) and yellow-red indicates tissue with high shear-wave speed (more stiff tissue).

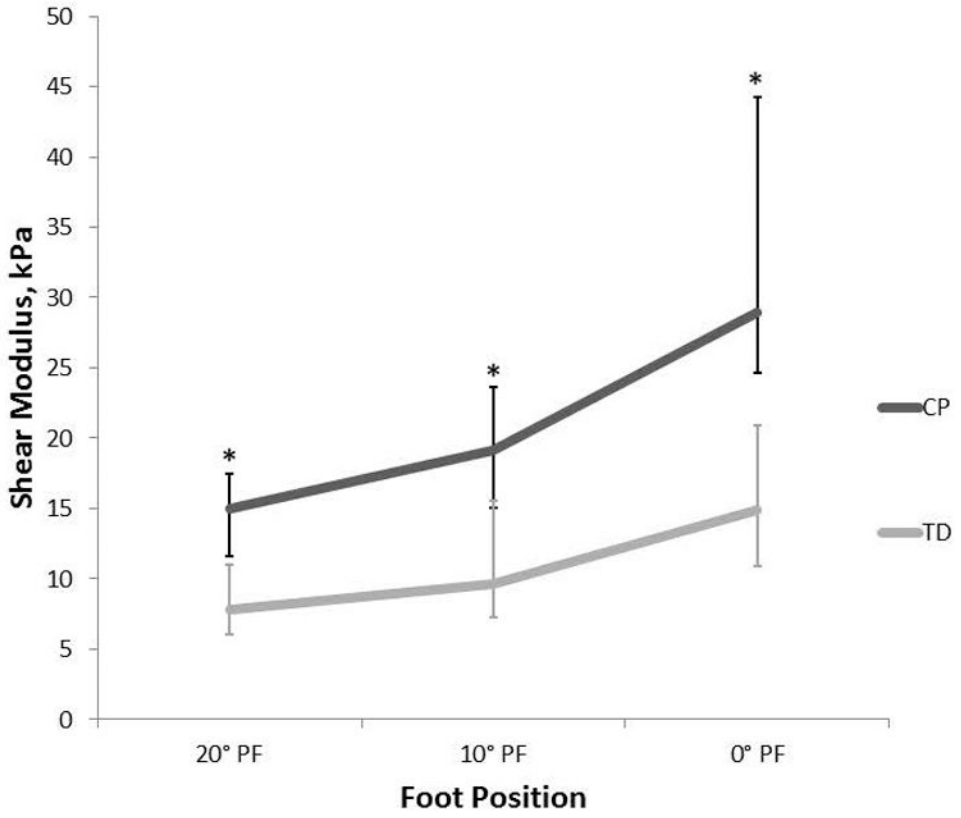

Figure 2.

Stiffness of Lateral Gastrocnemius Muscle in Children with and without Cerebral Palsy. Abbreviations: kPa, kilopascals; CP, cerebral palsy; TD, typically developing; PF, plantar flexion. * indicates that values for each foot position for children with CP differed significantly from each foot position for TD children (P<.01). The bars indicate Q1 and Q3 from median value for each foot position. Foot position is in degrees of PF, with 0° PF being the neutral position.

Table 1

Demographic Characteristics, Physical Measurements, and Shear Modulus of Children with Cerebral Palsy With Respect to Sex

	Participants		
Characteristic[a], median (Q1, Q3)	**Girls (n=6)**	**Boys (n=7)**	**p-value [b]**
Age, mo	56.0 (35.0, 60.0)	86.0 (61.0, 100.0)	.153
Age range, mo	25.0-110.0	34.0-105.0	
BMI, kg/m^2	17.3 (16.2, 18.6)	15.8 (15.0, 17.1)	.063
BMI range, kg/m^2	15.9-19.9	13.8-18.5	
Calf circumference, cm	20.5 (20.1, 21.0)	22.2 (20.0, 26.1)	.626
Calf circumference range [c], cm	20.0-30.0	16.5-27.2	
GMFCS level [d], n (%)			.344
I	2 (33.3)		
II	1 (16.7)	3 (42.9)	
III	3 (50.0)	3 (42.9)	
Modified Ashworth Scale [e], n (%)		1 (14.3)	.360
1			
2	0 (0.0)		
3	1 (16.7)	2 (28.6)	
Cerebral palsy type, n (%)	5 (83.3)	1 (14.3)	.391
Diplegic/Triplegic		4 (57.1)	
Hemiplegic			
	4 (66.7)		
	2 (33.3)	3 (42.9)	
		4 (57.1)	
Maximal ankle DF, degrees	13.0 (5.0, 20.0)	3.0 (0.0, 4.0)	.085
Maximal ankle DF range, degrees	-12.0-20.0	-2.0-12.0	
Shear modulus, kPa			
20 PF	12.6 (9.0, 15.1)	16.8 (12.1, 18.7)	.253
10 PF	14.8 (11.6, 16.0)	22.5 (19.1, 23.7)	.046
0 PF	21.8 (16.6, 28.9)	36.1 (26.7, 45.8)	.087

Abbreviations: BMI, body mass index; GMFCS, Gross Motor Function Classification System; DF, dorsiflexion; kPa, kilopascal; PF, plantar flexion.

[a] Values are presented as median and 1^{rst} and 3rd interquartile range (Q1, Q3) unless specified otherwise.

[b] p-values for shear modulus are form one-way analysis of variance, other continuous variables are from Wilcoxon rank sum tests and categorical variables are from chi-squared tests.

[c] Calf circumference value was missing from one girl.

[d] GMFCS ranges from I-V. However no there were no children in the study in IV and V.

[e] Modified Ashworth Scale ranges from 1 to 4. However no there were no children in the study in level 4.

Table 2

Demographic Characteristics, Physical Measurements, and Shear Modulus of Children with Cerebral Palsy Compared to TD Children

	Patients		
Characteristic [a], median (Q1,Q3)	**CP (n=13)**	**TD (n=13)**	***P* Value [b]**
Age, mo	61.0 (52.0, 92.0)	63.0 (52.0, 112.5)	1.000
Age range, mo	25.0-110.0	24.0-138.0	
Female, n (%)	6 (46.2)	6 (46.2)	1.000
BMI, kg/m^2	16.2 (15.8, 17.9)	17.8 (15.5, 18.8)	.398
BMI range, kg/m^2	13.8-19.9	14.6-26.1	
Calf circumference, cm	21.3 (20.1, 25.6)	25.7 (22.2, 27.8)	.077
Calf circumference range, cm	16.5-30.0	19.5-33.8	
Maximal ankle DF, degrees	4.0 (0.0, 12.0)	12.0 (10.0, 13.0)	.044
Maximal ankle DF range, degrees	-12.0-20.0	5.0-31.0	
GMFCS level [c], n (%)			
I	5 (38.5)	na	
II	4 (30.8)	na	
III	4 (30.8)	na	
Modified Ashworth Scale [d], n (%)			
1	2 (15.4)	na	
2	2 (15.4)	na	
3	9 (69.2)	na	
Cerebral palsy type, n (%)			
Diplegic/Triplegic	7 (53.8)	na	
Hemiplegic	6 (46.2)	na	
Previous botulinum toxin injection, n (%)			
Yes	7 (53.8)	na	
No	6 (46.2)	na	
Shear modulus, kPa			
20 PF	15.0 (11.6, 17.5)	7.8 (6.1, 11.0)	.001
10 PF	19.1 (15.0, 23.6)	9.6 (7.3, 15.6)	.002
0 PF	28.9 (24.6, 44.2)	14.9 (10.9, 20.9)	.001
Normalized shear modulus [e]			
20 PF	1.0 (0.0)	1.0 (0.0)	1.000
10 PF	1.3 (1.2, 1.4)	1.4 (1.1, 1.5)	0.555
0 PF	2.2 (1.9, 2.6)	1.9 (1.8, 2.5)	0.398

Abbreviations: BMI, body mass index; GMFCS, Gross Motor Function Classification System; DF, dorsiflexion; kPa, kilopascal; PF, plantar flexion.

[a] Values are presented as median and 1rst and 3rd interquartile range (Q1, Q3) unless specified otherwise.

[b] p-values for continuous variables are from Wilcoxon rank sum tests and from chi-squared tests for categorical variables.

[c] GMFCS ranges from I-V. However no there were no children in the study in IV and V.

[d] Modified Ashworth Scale ranges from 1 to 4. However no there were no children in the study in level 4.

[e] To normalize, each child's shear modulus was divided by their baseline (20 PF) shear modulus value.