Neuromuscular activation differences during gait in patients with Ehlers-Danlos syndrome and healthy adults

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ABSTRACT

Objective: Ehlers-Danlos syndrome (EDS) is a group of genetic disorders affecting connective tissue and symptoms include joint and ligament laxity. The objectives were to compare muscle activation, joint angles, and spatiotemporal parameters during gait, and isometric strength between participants with EDS (hypermobility and classical subtypes) and healthy adults.

Methods: Participants with EDS (n=14) and healthy adults (n=14) were recruited for this cross-sectional study. Lower extremity muscle activation, sagittal joint angles, and spatiotemporal parameters during gait were measured using surface electromyography, motion capture, and force plates. Isometric strength of the lower extremity joints were measured with an isokinetic dynamometer. Important characteristics (principal components) were determined from electromyography and angle waveforms using principal component analysis; relationships between principal component scores and groups were examined using multilevel linear models, after accounting for gait speed. Spatiotemporal parameters and strength were compared using independent t-tests and effect sizes (d). **Results:** EDS group was associated with delayed vastus lateralis (b=16.69) and medialis activation (b=11.33), higher rectus femoris (b=28.34) and tensor fascia latae (b=-11.06) activation, prolonged gluteus medius activation (b=-32.78), and lower medial gastrocnemius activation (b=-27.18). Joint angles were similar between EDS and healthy groups. EDS group had slower gait speeds, shorter stride lengths, and greater percentage of time in stance (d=-1.05 to 0.96). EDS group had weaker hip and ankle muscles (d=-0.83 to -0.97).

Conclusion: Alterations in muscle activation and spatiotemporal parameters during gait in patients with EDS may be a result impaired proprioception and balance, and muscle weakness. Interventions should target these deficits.

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Significance and Innovations

- There is limited research examining gait in patients with Ehlers-Danlos syndrome.
- Patients with Ehlers-Danlos syndrome have altered lower extremity muscle activation during gait and muscle weakness compared to healthy adults.
- Patients with Ehlers-Danlos syndrome have lower gait speeds, shorter stride lengths, and spend a greater percentage of time in stance.
- These alterations in gait are likely due to the impaired proprioception, compromised balance, and muscle weakness commonly seen in these patients.

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of rare genetic disorders that affects the connective tissue (1). There are 13 subtypes with the most common being hypermobility and classical (1). Clinical criteria for a hypermobility EDS diagnosis is generalized joint hypermobility, systemic signs of a generalized connective tissue disorder, and exclusion of other EDS subtypes/alternative diagnoses (1).

Models of joint stability highlight that impairments in passive (ligaments, joint capsule), active (muscles), or neural subsystems could lead to system disruption and joint injury (2). The passive subsystem is disrupted in patients with EDS which is highlighted by severe ligament laxity making them more prone to dislocations (3). There are active subsystem deficits including reduced upper and lower extremity muscle strength (4,5). For instance, patients with EDS hypermobility subtype had lower concentric knee extensor and flexor strength at 60 and 180^{o}/s compared to healthy adults (4). Finally, neural subsystem impairments in these patients have been found including proprioception and balance deficits (5-8). Patients with EDS hypermobility subtype had greater sway during standing balance tests and greater errors during a knee movement detection paradigm compared to healthy adults (5-7). These deficits likely contribute to joint instability and may negatively affect the functional activities of these patients.

Patients with EDS have altered gait compared to healthy adults. Gait speed and step length were significantly reduced in patients with EDS hypermobility subtype compared to healthy adults (9). Patients with EDS have demonstrated increased pelvic tilt excursions and increased ankle and hip joint range of motion (ROM) during gait compared to healthy adults (9).

Patients with EDS hypermobility subtype had increased plantarflexion at initial contact with reduced dorsiflexion in both stance and swing phase (9,10). Thus, deficits in stability subsystems may have resulted in these altered gait kinematics.

Although previous studies have examined joint angles and spatiotemporal parameters during gait in patients with EDS, no study has examined muscle activation. Considering the deficits in passive and neural subsystems, it is unclear how muscle function compensates during gait to maintain joint stability. This is even more important to consider due to the muscle weakness that has been demonstrated in these patients, which is related to activity limitations (4,5). Thus, the primary objective was to compare lower extremity muscle activation, joint angles, and spatiotemporal parameters during gait between participants with EDS and healthy adults. The secondary objective was to compare isometric strength and clinical outcomes between these groups. It was hypothesized that participants with EDS would have higher muscle activation, increased joint angles, and slower speeds compared to healthy adults. Furthermore, participants with EDS would have decreased strength, increased pain intensity, and increased fatigue.

PATIENTS AND METHODS

Research Participants

Participants with EDS were recruited from the Lethbridge-Layton-MacKay Rehabilitation Centre in Montreal, Canada by convenience sampling between May 2018 and July 2018 for this cross-sectional study. Inclusion criteria were diagnosis of either EDS classical or hypermobility subtype by a rheumatologist, between 18 to 80 years old, and able to walk a city block. EDS diagnosis was made using the Villefranche Nosology criteria (11) or the updated

International EDS Consortium criteria depending when the diagnosis was completed (1). Exclusion criteria were participants that required the use of braces during ambulation that would hinder electrode placement, recent leg surgery or trauma (within one year), neurological conditions (e.g. previous stroke), severe cardiorespiratory conditions, and pregnancy. In addition, healthy adults were recruited by word of mouth and advertisements. They had the same exclusion criteria, although additional exclusion criteria included history of joint hypermobility disorders, recurrent joint dislocations, and family history of EDS. Research ethics was approved by the Centre de recherche interdisciplinaire en réadaptation du Montréal métropolitain research ethics board. Written, informed consent was obtained from participants.

Considering the rarity of EDS, a formal sample size calculation was not performed. All available patients with EDS at our facility were invited to participate. This resulted in the recruitment of 14 participants (12 women, 2 men; 2 classical, 12 hypermobility) with EDS. One participant could not complete gait testing due to severe symptoms. An equal number of healthy participants were recruited (n=14; 12 women, 2 men) and were matched based on sex. Demographic variables were collected from both groups (Table 1).

Clinical Outcomes

The 36-item Short Form Survey (SF-36) provided a measure of overall health (12). Scores for the eight subscales (Table 2) were converted to a 100 scale with higher scores representing better outcomes. Fatigue was measured with the Fatigue Severity Scale (FSS) and higher scores represented increased fatigue severity (13). Pain intensity was measured with a 100-mm visual analogue scale (VAS) for both pain intensity on the day of the study and average pain over the previous week (14). Higher scores represented greater pain intensity. Quality of life was measured with the EQ-5D-5L QoL measure (15) and scores where then converted to a single

index value with the Canadian Value Set, ranging between -0.148 (worst) and 0.949 (best) health states (16). The EQ-5D-5L QoL also includes a VAS where participants score their health on a vertical VAS between 'best imaginable health state' and 'worst imaginable health state', with higher scores indicating a better state of health. All clinical outcomes have demonstrated acceptable reliability and validity in patients with EDS or in other patient populations (12-14,17,18).

Gait Data Collection

Methods for collecting gait data have previously demonstrated acceptable test-retest reliability (ICC=0.73 to 0.97) in patients with knee osteoarthritis (19,20). Muscle activation was collected using surface electromyography (EMG) sampled at 2000 Hz (Trigno, Delsys Inc.; common mode rejection ratio >80 db at 60 Hz, bandwidth 20–450 Hz). Electrodes were placed over ten muscles of the participant's dominant leg according to standard guidelines and included: gastrocnemius (medial and lateral heads), rectus femoris, vastus medialis, vastus lateralis, lateral hamstring, gluteus maximus, gluteus medius, tibialis anterior, and tensor fascia latae (21). Preparation included shaving the area and cleaning the skin with alcohol. Muscle contractions were elicited after electrode placement to confirm the appropriate placement.

Lower extremity joint angles were measured using 3-dimensional motion capture. This included eight cameras (OQUS 300+, Qualisys) sampled at 100 Hz and two synchronized force plates (BP400600, AMTI) sampled at 2000 Hz. Forty reflective markers were placed according to published guidelines (22). Markers were placed bilaterally on the acromion, anterior and posterior iliac spine, femoral greater trochanter and lateral epicondyle, lateral malleoli, 1st and 5th metatarsal head and calcaneus. Marker clusters (four markers/cluster) were placed mid-thigh and mid-shank bilaterally for segment tracking. In addition, markers were placed on the medial

epicondyle (knee), medial malleolus (ankle) and 3rd metatarsal head during a static trial to determine joint centers, but were removed during dynamic trials.

Once electrodes and reflective markers were applied, participants were asked to stand on the force plate to measure mass and create joint definitions (static trial). Next, participants performed hip flexion/extension and abduction/adduction while standing on one leg in order to determine hip joint centre. Lastly, participants were asked to walk in a straight line along an 8-meter walkway at self-selected speeds. They were instructed to walk at their normal speed. They were not informed about the force plates and they were not instructed to target them. At least two practice trials were allowed. Finally, eight gait trials were collected with adequate force plate strikes, although only five trials were analyzed. Additional trials were collected to account for potential collection errors. All participants wore their normal footwear because many participants in the EDS group reported foot deformities and did not want to ambulate without shoes. Participants were allowed to rest at any time during testing if they expressed fatigue.

Maximum Voluntary Isometric Contractions

Following gait testing, participants underwent a series of maximal voluntary isometric contractions (MVIC). This data were used to normalize gait EMG waveforms. The following exercises were chosen: 1-hip extension in prone with the hip in neutral (gluteus maximus), 2-hip abduction in side-lying with the upper test leg in neutral (gluteus medius, tensor fascia latae), 3-hip flexion with the hip in 20 degrees of flexion (tensor fascia latae), 4-ankle plantarflexion in supine (gastrocnemius) with the ankle in neutral, 5-ankle dorsiflexion in supine (tibialis anterior) with the ankle in neutral, 6-knee extension in sitting with the knee in 45 degrees (vastus medialis, vastus lateralis, rectus femoris), 7-knee flexion in a sitting position with knee flexed to 55 degrees (lateral hamstring), 8-standing plantarflexion (gastrocnemius). These exercises have

been used in previous MVIC protocols in various patient populations (20,23-26). Resistance for exercises one to seven was provided by an isokinetic dynamometer (Cybex). Exercise eight was performed on a step and resistance provided by a researcher through the shoulders. Participants performed one practice trial followed by two test trials (5 seconds each) for each exercise. A 1 min rest was provided between trials. If a large discrepancy between the two trials was noted, then a third trial was performed. Peak values from the dynamometer torque signal from the two or three trials for exercises 1-7 were identified and represented isometric strength. Peak values were identified over a 0.5 s steady state window and were normalized to body mass.

Data Processing

Gait and MVIC EMG signals were band-pass filtered (20-500 Hz) with a 4^{th} order, recursive Butterworth filter, corrected for resting bias, and full-wave rectified (20). Maximum EMG amplitudes obtained from MVIC exercises were calculated using a 100 ms moving average window. Gait EMG waveforms were further processed by creating a linear envelope with a low-pass (6 Hz), 4^{th} order, recursive Butterworth filter and amplitude normalized to maximum MVIC EMG.

Data from reflective markers and force plate were low pass filtered with 4^{th} order, recursive Butterworth filter with cut-off frequencies of 6 Hz and 20 Hz respectively. The following spatiotemporal parameters were calculated and averaged over the five trials for each participant: 1) gait speed of the posterior superior iliac spine (PSIS) markers in the direction of forward progression; 2) step length (normalized to body height); 3) step width; and 4) stance duration as a percentage of gait cycle. Hip, knee, and ankle angle waveforms were calculated about the joint co-ordinate system of the dominant lower extremity (27). Only sagittal angles

were examined and hip flexion, knee flexion, and ankle dorsiflexion represented positive values. Gait EMG and joint angle waveforms were time normalized to 100% of the gait cycle.

Principal Component Analysis

Important waveform characteristics were identified using principal component analysis (PCA) (28). The benefits of PCA is that it can reduce the complexity of gait waveforms to a few parameters that capture important variability in these waveforms and it considers the time content (28). However, clinical interpretation of these characteristics may be difficult on occasion. Alternatively, selecting discrete parameters from gait waveforms (e.g. peak angle, angle at initial contact) is a common approach. However, selecting these discrete parameters is subjective, they might ignore important variability in the data, and they often disregard temporal information in the waveforms (28). Thus, separate PCAs were conducted for each gait EMG and joint angle waveform variable (e.g. knee flexion angle, vastus lateralis EMG) in order to evaluate the impact of EDS on each muscle or joint angle separately. Waveforms from all participants for the variable of interest, which included five trials for each participant, were entered into a data matrix. Covariance matrices were determined from data matrices, and an eigenvector decomposition of these covariance matrices produced principal components (*PC*). These *PCs* represented waveform characteristics such as amplitude or shape characteristics. Only the first thee PCs were retained. Next, trial waveforms were scored against *PCs* to produce principal component scores (*PC-scores*). These *PC-scores* are indicative of how closely a trial waveform (e.g. knee flexion) matched the shape of the waveform characteristics (*PC*). These *PC-scores* were the dependent variable in statistical analyses.

Statistical Analysis

Descriptive statistics were calculated for group demographics, clinical outcomes, and spatiotemporal variables. Independent t-tests and effect sizes (Cohen's d) compared demographic, spatiotemporal variables, and isometric strength between groups. Effect sizes (d) were interpreted as small (d=0.20), medium (d=0.50), and large (d=0.80) (29). Clinical outcomes were not normally distributed, and thus nonparametric statistics (Mann-Whitney U-tests) compared these variables between groups. Likewise, nonparametric effect sizes ($r=Z/\sqrt{N}$) were determined for clinical measures and interpreted as small (r=0.10), medium (r=0.30), and large (r=0.50) (29).

Multilevel linear models examined if gait EMG and joint angle *PC-scores* were related to group (healthy vs. EDS). Dependent variables were gait *PC-scores* and separate analyses were conducted for each *PC* (e.g. *PC1* for vastus lateralis EMG). Data were clustered within the participants because they contributed five gait trials to each model. Following the intercept, the number of the gait trial (1 to 5) was entered which accounted for potential fatigue. Next, gait speed over each individual trial was entered to account for potential differences in gait speed between trials and between groups. Finally, a dichotomous variable for group (0=healthy, 1=EDS) was entered. Model parameters with 95% confidence intervals were presented and statistical significance ($p<0.05$) was determined from the Wald statistic. The intercept and participant were entered as random effects and remaining variables were entered as fixed effects. Degrees of freedom were calculated using the Satterthwaite method, parameter estimates were determined using full maximum-likelihood, and variance components was chosen as the covariance structure. The appropriateness of the models were assessed by examining linearity, normality, homoscedasticity, and multicollinearity. A threshold of $p<0.05$ was used for statistical significance. Statistical analyses were completed with IBM SPSS Statistics 24 (IBM, Armonk).

RESULTS

There were no significant differences in demographic variables between EDS and healthy groups (Table 1). Analyses of the clinical measures revealed the EDS group had statistically significant worse health outcomes, greater pain intensity, greater fatigue, and lower quality of life (Table 2). These differences represented large effect sizes (Table 2).

One participant from the EDS group could not complete gait or MVIC testing due to severe symptoms and was not included in analyses of gait or strength variables. EDS group had statistically significant lower isometric strength for hip flexion, hip abduction, ankle plantarflexion, and ankle dorsiflexion, which represented large effect sizes (Table 1). None of participants used braces during testing. Two participants from the EDS group required the use of Canadian crutches (e.g. forearm crutch) during gait testing. They both used a 2-point gait pattern where a crutch moved in unison with the contralateral lower extremity. Both participants did not feel comfortable ambulating without the crutches. They were both included in all primary statistical analyses. However, a sensitivity analysis was also completed (see Sensitivity Analysis below).

Analysis of the spatiotemporal parameters for the entire sample revealed the EDS group had statistically significant slower gait speeds, shorter stride lengths, and spent a greater percentage of time in stance, which represented large effect sizes (Table 1).

Electromyography

Model parameters (e.g. slopes) for the multilevel linear models of the EMG *PC-scores* are provided in Table 3. The group variable (healthy vs. EDS) was not statistically significantly related to EMG *PC-scores* for the lateral hamstrings, gluteus maximus, lateral gastrocnemius,

and tibialis anterior. Statistically significant findings for the relationship between group and EMG *PC-scores* for the remaining muscles are reported below. Figures to assist with interpreting the *PCs* are provided in the supplemental.

Vastus Medialis. After accounting for the number of trials and gait speed, group was significantly (p=0.01) associated with vastus medialis *PC3-scores*. This *PC* represented a time shift in vastus medialis EMG. EDS group was associated with higher *PC3-scores* indicating delayed vastus medialis onset (Figure 1).

Vastus Lateralis. Group was associated with vastus lateralis *PC3-scores*. Similar to vastus medialis, EDS group was significantly (p=0.01) associated with higher *PC3-scores* indicating delayed vastus lateralis onset (Figure 1).

Rectus Femoris. Group was significantly (p=0.05) associated with rectus femoris *PC1-scores* and *PC1* represented the overall amplitude and shape of rectus femoris EMG. EDS group was associated with higher *PC1-scores* indicating higher rectus femoris EMG amplitudes (Figure 1).

Gluteus Medius. Group was significantly (p=0.01) associated with gluteus medius *PC2-scores*. This *PC* represented the difference in gluteus medius EMG amplitude during loading response/terminal swing versus mid-stance. EDS group was associated with lower *PC2-scores* indicating lower gluteus medius amplitudes during loading response/terminal swing and higher amplitudes during mid-stance (Figure 2).

Tensor Fascia Latae. Group was significantly (p=0.04) associated with tensor fascia latae *PC3-scores*. This *PC* represented the difference in tensor fascia latae EMG during mid-stance relative to terminal stance. EDS group was associated with lower *PC3-scores* indicating

smaller differences in tensor fascia latae EMG between these times, which was due to higher tensor fascia latae EMG amplitudes during mid-stance. (Figure 2).

Medial Gastrocnemius. Group was significantly (p=0.02) associated with medial gastrocnemius *PC3-scores*. This *PC* represented medial gastrocnemius EMG amplitudes during loading response/mid-stance. EDS group was associated with lower *PC3-scores* indicating lower EMG amplitudes during these times, although this difference was small visually (Figure 2).

Joint Angles

Model parameters for the multilevel linear models of the joint angle *PC-scores* are provided in Table 4. The group variable (healthy vs. EDS) was not statistically significantly related to any joint angle *PC-score* after accounting for the number of trials and gait speed. Joint angle figures are provided in the supplemental.

Sensitivity Analysis

A sensitivity analysis was completed, which excluded the two participants from the EDS group that used Canadian crutches. For the majority of EMG and joint angle *PC-scores*, relationships between the *PC-scores* and group did not substantially change (Supplemental) compared to when all available data were included. The only difference was group was no longer statistically significantly (p=0.11) associated with rectus femoris *PC1-scores* (overall amplitude). Likewise, a sensitivity analysis compared healthy adults and participants with EDS hypermobility subtype. Thus, participants with EDS classical subtype were excluded. Again, relationships between *PC-scores* and group did not substantially change compared to when all available data were included. The only difference was group was no longer statistically significantly (p=0.10) associated with rectus femoris *PC1-scores* (overall amplitude).

DISCUSSION

This is one of the first studies to examine muscle activation during gait in patients with EDS. Considering the deficits in the passive subsystem (e.g. ligament laxity) in these patients, it is important to understand how the active (i.e. muscles) subsystem might compensate to prevent joint instability. Participants with EDS were associated with alterations in muscle activation during gait including: delayed vastus medialis and lateralis activation; higher rectus femoris activation; prolonged gluteus medius activation; higher tensor fascia latae activation; and lower medial gastrocnemius activation during loading response/mid-stance. Despite these findings, sagittal joint angles during gait were similar between EDS and healthy groups. Additionally, the EDS group had hip and ankle muscle weakness. Thus, deficits in the active subsystem are apparent in patients with EDS which may further negatively impact joint stability and contribute to injury. Understanding muscle strength and function deficits in patients with EDS will lead to improved functional rehabilitation programs that can target specific neuromuscular impairments.

Findings for the muscle activation patterns during gait can be partly explained by the muscle weakness in the EDS group. The EDS group was associated with higher levels of rectus femoris and tensor fascia latae activation, which likely compensated for the weak hip flexors and abductors. Increasing both the number of active motor units and the time which they are active, thereby increasing the EMG signal, are potential mechanisms to compensate for muscle weakness. This weakness is likely due to muscle atrophy which has been previously demonstrated in patients with EDS (30); however, another study found no muscle atrophy (4). Although not all of the strength values from MVIC exercises were statistically significantly lower in the EDS group, effect sizes were at least moderate for all exercises (Table 1). Increasing the sample size would have detected additional statistical differences. This muscle weakness is

consistent with a previous study that found knee extensor and flexor weakness during isokinetic exercises in patients with EDS (4). Other alterations in muscle activation patterns during gait in the EDS group might be a result of deficits in the neural subsystem, such as proprioception impairments, that have been previously demonstrated (5,8). Specifically, the EDS group was associated with delayed vastus lateralis and medialis activation, and lower levels of activation during early onset of medial gastrocnemius and gluteus medius. Perhaps these participants with EDS had impaired proprioception or joint position sense due to joint and ligament laxity. This might have led to the delayed muscle activation during the loading phase of gait. These hypotheses explaining the altered muscle activation patterns are speculative, but they provide a rationale for adding strengthening and proprioceptive exercises to EDS treatment programs in an attempt to limit active and neural subsystem deficits.

There were no statistically significant differences in lower extremity sagittal angles during gait between EDS and healthy groups. This is contrary to previous studies that have demonstrated differences (9,10,31). Possible explanations for these contradictory findings include methods to account for gait speed differences between groups and methods to summarize joint angle waveforms (PCA, discrete values). Additionally, other kinematic variables (joint translation, arthokinematics) might have detected differences between groups. Previous findings relating to spatiotemporal parameters are consistent with the current results including decreased gait speed (7) and decreased stride or step length (7,9). These gait adaptations, including the greater percentage of time in stance, would increase the stability during ambulation and might be a compensation for the impaired balance previously demonstrated in patients with EDS (7).

Significant differences in clinical outcomes were present. The EDS group had worse health outcomes, greater pain intensity, greater fatigue, and lower quality of life. These

differences represented large effect sizes. These findings are consistent with previous studies (3,32,33). Energy management techniques, graded activity, strengthening, and aerobic exercises should be considered within a multidisciplinary framework in order to manage the symptoms and activity limitations commonly found in patients with EDS (34).

A study limitation was the small sample size. With the rarity of the condition, it is difficult to recruit a large sample. Most participants with EDS were generally higher functioning patients which could limit the generalizability of the findings to lower functioning patients. Most participants had EDS hypermobility subtype and results cannot be generalized to other EDS subtypes including classical. Isometric strength was assessed since EMG from this test was utilized to amplitude normalize gait EMG. Strength differences should be confirmed during concentric and eccentric testing.

In conclusion, EDS was associated with alterations in lower extremity muscle activation patterns during gait and muscle weakness compared to healthy adults. Participants with EDS also had slower gait speeds and decreased stride length. Alterations in gait may be a result of deficits in the passive, active, and neural subsystems that control joint stability including joint laxity, impaired proprioception and balance, and muscle weakness. Future research should examine if treatment programs can address these deficits.

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Table 1. Means (standard deviation) for demographic variables, spatiotemporal gait parameters, and isometric strength for Ehlers-Danlos syndrome (EDS) and healthy groups.

Variables		EDS group (n = 14, 12 women)	Healthy group (n = 14, 12 women)	p value‡	Effect size (d)
Age (y)		42 (12)	50 (16)	0.17	-0.55
Height (m)*		1.69 (0.08)	1.64 (0.08)	0.16	0.55
Mass (kg)		72.8 (21.0)	63.2 (13.2)	0.16	0.55
Body mass index (kg/m^2)*		25.4 (6.2)	23.5 (4.6)	0.36	0.36
Spatiotemporal gait parameters*	Gait speed (m/s)	1.09 (0.26)	1.32 (0.17)	0.01	-1.05
	Stride length†	0.76 (0.08)	0.82 (0.07)	0.05	-0.80
	Stride width (m)	0.12 (0.03)	0.10 (0.03)	0.19	0.52
	Stance (%)	62.90 (1.80)	61.13 (1.86)	0.02	0.96
Isometric strength (Nm/kg)*	Hip extension	1.03 (0.34)	1.28 (0.46)	0.16	-0.60
	Hip abduction	1.39 (0.44)	1.87 (0.68)	0.05	-0.83
	Hip flexion	1.18 (0.35)	1.49 (0.40)	0.04	-0.84
	Ankle plantarflexion	0.68 (0.32)	1.00 (0.41)	0.04	-0.86
	Ankle dorsiflexion	0.19 (0.07)	0.28 (0.12)	0.03	-0.97
	Knee extension	1.01 (0.22)	1.17 (0.20)	0.06	-0.76
	Knee flexion	0.68 (0.18)	0.77 (0.21)	0.26	-0.45

*Height, body mass index, spatiotemporal gait parameters, and isometric strength were not recorded for one participant in the EDS group due to an inability to complete testing.
†Stride length was divided by body height to account for size differences, and is unitless.
‡p-values were calculated with independent t-tests.

Table 2. Median (minimum, maximum) of clinical outcome measures for Ehlers-Danlos syndrome (EDS) and healthy groups

Outcome measures	Subscale	EDS group	Healthy group	p-values†	Effect Size (r)
Short-Form 36 (/100)	Physical functioning	35 (0, 70)	100 (85, 100)	<0.01	-0.87
	Role limitations due to physical health	0 (0, 100)	100 (0, 100)	<0.01	-0.72
	Role limitations due to emotional problems	33 (0, 100)	100 (0, 100)	<0.01	-0.57
	Energy/fatigue	30 (0, 45)	75 (45, 100)	<0.01	-0.84
	Emotional well-being	64 (24, 80)	84 (28, 92)	<0.01	-0.49
	Social functioning	38 (25, 75)	100 (25, 100)	<0.01	-0.75
	Pain	28 (0, 90)	100 (78, 100)	<0.01	-0.83
	General health	35 (0, 65)	88 (40, 100)	<0.01	-0.75
Fatigue Severity Scale (/63)		51 (21, 63)	22 (10, 50)	<0.01	0.67
Pain Visual Analog Scale	Today (/10)	5.5 (2.0, 8.0)	0.0 (0.0, 2.0)	<0.01	0.86
	Previous week (/10)	7.0 (0.5, 10.0)	1 (0, 5)	<0.01	0.76
EQ-5D-5L QoL	Index (/1.0)*	0.47 (0.15, 0.91)	0.95 (0.87, 0.95)	<0.01	-0.83
	Visual analog scale (/100)	65 (25, 90)	90 (60, 99)	<0.01	-0.69

*EQ-5D-5L QoL was converted to a score using the Canadian Value Set (16).
†p-value were calculated with Mann-Whitney U-tests

Table 3. Model parameters (95% confidence intervals) for the multilevel linear model analyses of the gait electromyography principal component (*PC*) scores.*

Muscle	*PC*	Trial Number	Speed	Group
Vastus Medialis	1	-1.30 (-2.98, 0.38)	**135.92 (89.29, 182.55)**	-4.40 (-40.00, 31.20)
	2	-0.52 (-1.29, 0.25)	-4.65 (-27.12, 17.82)	13.18 (-5.96, 32.31)
	3	-0.81 (-2.17, 0.55)	16.04 (-1.08, 33.15)	**11.33 (2.64, 20.03)**
Vastus Lateralis	1	-0.58 (-1.76, 0.61)	**92.26 (56.36, 128.17)**	4.16 (-29.29, 37.61)
	2	-0.55 (-1.25, 0.15)	20.13 (-0.01, 40.27)	13.75 (-2.74, 30.23)
	3	-0.59 (-1.83, 0.66)	19.65 (-1.12, 40.42)	**16.69 (5.52, 27.86)**
Rectus Femoris	1	-0.27 (-1.10, 0.55)	**34.88 (8.99, 60.78)**	**28.34 (-0.03, 56.72)**
	2	-0.53 (-1.35, 0.30)	13.26 (-8.75, 35.27)	5.26 (-10.62, 21.15)
	3	-0.26 (-1.02, 0.50)	**40.81 (24.05, 57.57)**	-2.35 (-12.43, 7.74)
Lateral Hamstring	1	1.30 (-0.20, 2.80)	**61.39 (15.66, 107.12)**	-24.58 (-72.33, 23.16)
	2	-1.08 (-2.27, 0.11)	**-57.68 (-84.94, -30.43)**	11.96 (-5.43, 29.36)
	3	-0.39 (-2.10, 1.32)	-2.39 (-35.49, 30.72)	9.55 (-9.61, 28.72)
Gluteus Medius	1	0.39 (-2.63, 3.40)	-74.67 (-155.70, 6.36)	-22.96 (-81.36, 35.44)
	2	0.61 (-1.70, 2.92)	**57.99 (16.11, 99.85)**	**-32.78 (-55.54, -10.01)**
	3	0.04 (-2.58, 2.65)	21.74 (-25.55, 69.02)	0.10 (-25.62, 25.83)
Gluteus Maximus	1	0.23 (-1.25, 1.71)	-28.68 (-76.08, 18.71)	40.90 (-13.02, 94.83)
	2	0.32 (-1.06, 1.70)	9.58 (-27.37, 46.52)	-9.67 (-33.52, 14.18)
	3	1.17 (-0.26, 2.60)	-12.88 (-36.11, 10.35)	0.89 (-10.02, 11.80)
Tensor Fascia Late	1	-0.45 (-1.68, 0.77)	-23.29 (-60.68, 14.11)	9.17 (-26.70, 45.05)
	2	0.64 (-0.26, 1.55)	**36.92 (13.88, 59.97)**	-0.68 (-16.34, 14.98)
	3	0.52 (-0.60, 1.65)	7.17 (-12.08, 26.43)	**-11.06 (-21.48, -0.64)**

Lateral Gastrcos	1	0.04 (-3.12, 3.20)	**167.67 (77.38, 257.96)**	19.07 (-53.75, 91.89)
	2	1.10 (-1.52, 3.71)	-41.64 (-99.25, 15.97)	31.55 (-3.13, 66.23)
	3	0.43 (-2.47, 3.34)	**55.29 (13.20, 97.39)**	-0.03 (-21.91, 21.85)
Medial Gastrocs	1	-2.49 (-5.73, 0.76)	53.35 (-36.68, 143.39)	-2.79 (-71.41, 65.84)
	2	-0.94 (-3.96, 2.08)	**-76.90 (-144.13, -9.67)**	-1.50 (-42.30, 39.29)
	3	2.47 (-0.60, 5.53)	**-89.27 (-131.81, -46.74)**	**-27.18 (-49.13, -5.23)**
Tibialis Anterior	1	-0.73 (-2.67, 1.21)	**60.99 (11.41, 110.57)**	-26.36 (-56.28, 3.55)
	2	-0.27 (-2.76, 2.21)	**-58.13 (-105.12, -11.13)**	-0.39 (-23.56, 22.78)
	3	0.20 (-1.41, 1.81)	-11.15 (-43.35, 21.06)	15.33 (-0.93, 31.58)

*Bolded values are statistically significant at $p \leq 0.05$.

Table 4. Model parameters (95% confidence intervals) for the multilevel linear model analyses of the gait joint angle principal component (*PC*) scores.*

Angle	*PC*	Trial Number	Speed	Group
Hip Flexion	1	-1.13 (-2.26, 0.01)	33.53 (-3.60, 70.66)	-14.98 (-66.70, 36.74)
	2	-0.34 (-0.92, 0.25)	**59.10 (44.00, 74.20)**	3.88 (-6.51, 14.27)
	3	0.17 (-0.94, 1.27)	-0.61 (-19.89, 18.66)	9.65 (-0.84, 20.13)
Knee Flexion	1	**-1.31 (-2.58, -0.04)**	**64.45 (26.26, 102.65)**	-4.27 (-39.07, 30.53)
	2	1.71 (-0.40, 3.82)	**-71.82 (-107.27, -36.38)**	6.54 (-12.54, 25.62)
	3	0.11 (-1.00, 1.22)	**27.05 (2.53, 51.58)**	7.60 (-7.25, 22.45)
Ankle Dorsiflexion	1	**-0.87 (-1.69, -0.05)**	-7.47 (-33.75, 18.81)	12.45 (-19.04, 43.94)
	2	0.33 (-0.58, 1.23)	**-63.41 (-87.05, -39.77)**	12.84 (-3.68, 29.36)
	3	-0.44 (-1.25, 0.36)	19.69 (2.41, 36.96)	8.47 (-1.77, 18.71)

*Bolded values are statistically significant at $p \leq 0.05$.

Robbins SM, Cossette-Levasseur M, Kikuchi K, Sarjeant J, Shiu YG, Azar C, Hazel EM (2020). Neuromuscular activation differences during gait in patients with Ehlers-Danlos syndrome and healthy adults. Arthritis Care & Research, 72(11), 1653-1662. doi: 10.1002/acr.24067.

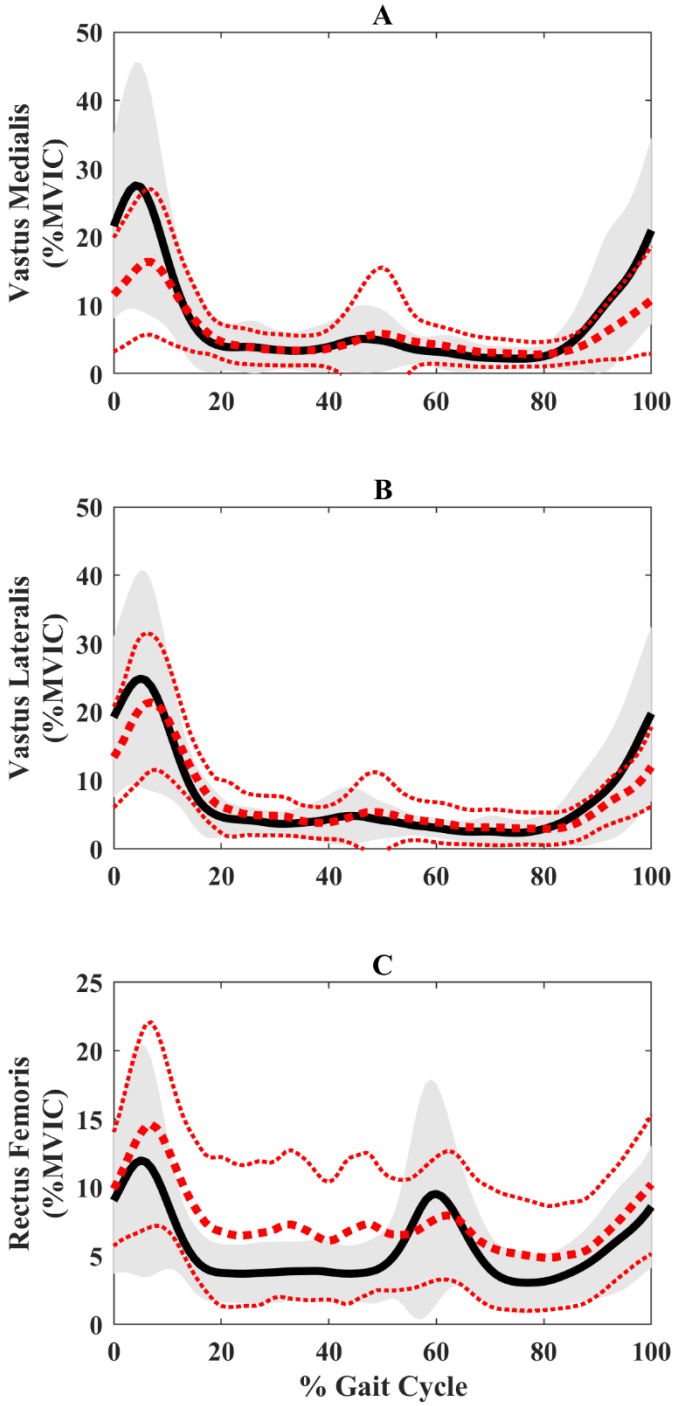

Figure 1. The group ensemble mean EMG waveforms over the gait cycle for (A) vastus medialis, (B) vastus lateralis, and (C) rectus femoris as a percentage of maximum voluntary isometric contractions (%MVIC) for the healthy (solid black line) and Ehlers-Danlos syndrome (thick, dashed red line) groups. The grey shaded area and thin, dashed red lines represent one standard deviation for the healthy and Ehlers-Danlos syndrome groups respectively.

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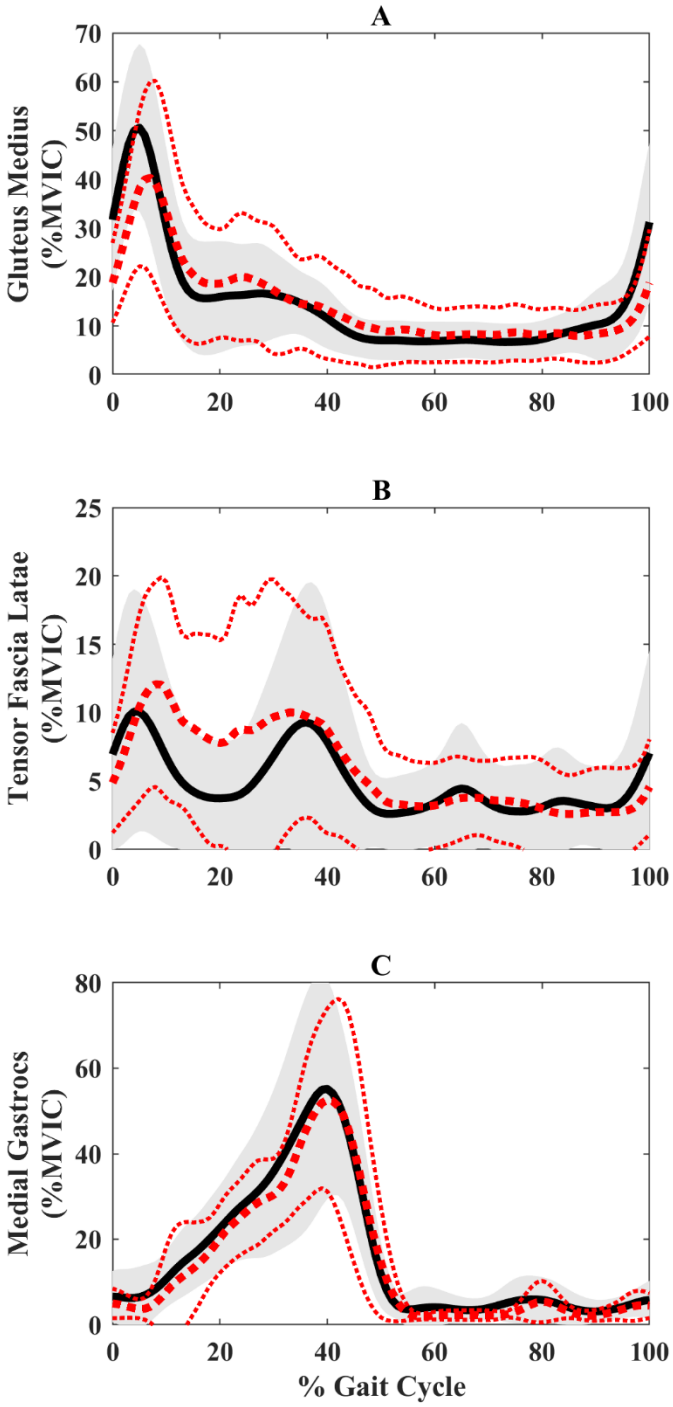

Figure 2. The group ensemble mean EMG waveforms over the gait cycle for (A) gluteus medius, (B) tensor fascia latae, and (C) medial gastrocnemius as a percentage of maximum voluntary isometric contractions (%MVIC) for the healthy (solid black line) and Ehlers-Danlos syndrome (thick, dashed red line) groups. The grey shaded area and thin, dashed red lines represent one standard deviation for the healthy and Ehlers-Danlos syndrome groups respectively.