Altered neural control of gait and its association with pain and joint impairment in adults with haemophilic arthropathy: Clinical and methodological implications

Cruz-Montecinos, Carlos; Maas, Huub; Cerda, Mauricio; Pérez-Alenda, Sofía

published in
Haemophilia
2022

DOI (link to publisher)
10.1111/hae.14517

document version
Publisher's PDF, also known as Version of record

Received: 19 November 2021 | Revised: 29 January 2022 | Accepted: 4 February 2022

DOI: 10.1111/hae.14517

Haemophilia WILEY

ORIGINAL ARTICLE

Muskuloskeletal

Altered neural control of gait and its association with pain and joint impairment in adults with haemophilic arthropathy: Clinical and methodological implications

Carlos Cruz-Montecinos[1,2,3] | Huub Maas[2] | Mauricio Cerda[4,5] | Sofía Pérez-Alenda[1]

[1]Physiotherapy in Motion Multispeciality Research Group (PTinMOTION), Department of Physiotherapy, University of Valencia, Valencia, Spain

[2]Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, The Netherlands

[3]Laboratory of Clinical Biomechanics, Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile

[4]SCIAN-Lab, Programme of Integrative Biology, ICBM, & Center for Medical Informatics and Telemedicine, Faculty of Medicine, University of Chile, Santiago, Chile

[5]Biomedical Neuroscience Institute, Santiago, Chile

Correspondence
Carlos Cruz-Montecinos, Physiotherapy in Motion Multispeciality Research Group (PTinMOTION), Department of Physiotherapy, University of Valencia, Valencia, Spain.
Email: ccmkine@gmail.com

Abstract

Introduction: It is unknown whether altered neural control is associated with clinical outcomes in people with haemophilic arthropathy (PWHA). The dynamic motor control index during walking (Walk-DMC) is a summary metric of neural control.

Aims: The primary aim of this study was to apply the Walk-DMC to assess if people diagnosed with haemophilic arthropathy have impaired neural control of gait and investigate the association of Walk-DMC with pain and joint impairment.

Method: The Walk-DMC was assessed using surface electromyography in 11 leg muscles. Twenty-two PWHA and 15 healthy subjects walked on a 30-m walkway at 1 m/s. In addition, pain (visual analogue scale), knee flexion contracture (degrees) and joint impairment (Haemophilia Joint Health Score, HJHS) were assessed. The clinical outcomes were correlated with the Walk-DMC. Multiple regression analysis was performed to predict the Walk-DMC using the clinical outcomes.

Results: In 13 PWHA the Walk-DMC was beyond the normal range (80–120 pts). PWHA with an altered Walk-DMC showed more years with arthropathy, more pain, higher knee flexion contracture and a higher HJHS score ($P < .05$, effect size $> .8$). Significant negative moderate associations between Walk-DMC and pain, knee flexion contracture and HJHS were found ($P < .05$). The model that best predicted the Walk-DMC was the pain with knee flexion contracture ($R^2 = .44$; $P = .004$).

Conclusions: PWHA with abnormal neural control of gait also has more years with arthropathy, more pain, and more impaired joints. Our results indicate an association between the Walk-DMC index and joint damage, specifically with pain in combination with knee flexion contracture.

KEYWORDS
gait, joint damage, muscle synergy, neuromuscular control, surface electromyography

1 | INTRODUCTION

In people with haemophilia, the most frequent clinical manifestation is haemophilic arthropathy, which results from repetitive intraarticular bleeding, inflamed synovial membrane and irreversible changes in cartilage tissue.[1] Prophylaxis is accepted as the only way to prevent bleeding and preserve musculoskeletal health.[2] Without adequate prophylaxis treatment, the process of joint deterioration in haemophilic

arthropathy can be seen with an aggressive progression rate. However, in many underdeveloped countries, prophylaxis availability is limited.[3]

Haemophilic arthropathy often results in chronic pain and joint impairment, affecting motor function and quality of life.[1,4–7] Clinical examination of joints and muscles, besides examining posture and gait, are the most often used assessments by physiotherapists for haemophilia care.[8] In addition, several tools have been proposed to monitor disease progression, such as ultrasound and magnetic resonance imaging of joints, gait analysis and surface electromyography (sEMG).[9–13]

Using sEMG, a new tool called the Walking Dynamic Motor Control (Walk-DMC) index has been proposed as a summary metric of neural control of gait. The Walk-DMC index has been used to assess synergistic and antagonistic co-activation changes in response to neurological diseases, following orthopaedic surgeries, in the elderly and in people with haemophilic arthropathy (PWHA).[14–17] However, whether PWHA and an abnormal Walk-DMC also have different levels of pain and joint impairment than those with a normal Walk-DMC and whether the Walk-DMC is associated with the clinical measures of pain and joint impairment are currently unknown.

Assessment of the Walk-DMC index is based on a muscle synergy analysis of gait.[14,15] This analysis assumes that muscles are activated in groups, commonly referred to as synergies or modes.[18,19] Using synergy analysis, we recently found that some synergies were merged in PWHA with a chronic knee constraint.[20] In comparison to complete synergy analysis (i.e. number of synergies, variance accounted for, motor modules and motor primitives), the Walk-DMC index is a metric that can be interpreted rapidly.[14–17,21] Hence, it may be applied clinically, for example to evaluate the effects of orthopaedic interventions.[15] The Walk-DMC has been assessed using the sEMG signals of 5–11 muscles.[14–17,22] However, it is unknown if the number of muscles selected affects this metric.

The primary aim of this study was to apply the Walk-DMC to assess if people diagnosed with haemophilic arthropathy have impaired neural control of gait and investigate the association of the Walk-DMC with pain and joint impairment. The secondary aims were to assess possible clinical predictors of the Walk-DMC and determine the minimal number of muscles required to detect an altered Walk-DMC in PWHA accurately.

2 | MATERIAL AND METHODS

2.1 | Participants

This study was approved by the local ethics committee and conducted in agreement with the Declaration of Helsinki. Part of the data used has been reported in a previous study, which addressed a different research question related to neuromuscular control during gait in PWHA.[16] All participants were informed about the purpose and procedures of the project and gave their written informed consent to participate in the study. Based on non-probability sampling, PWHA were recruited in two hospitals in Santiago (Chile). For the control group (CG), healthy subjects were recruited from the University of Chile (student and employees). The inclusion criteria for PWHA were males, diagnosed with haemophilia A or B, haemophilic arthropathy with a minimum of two points (sum knee and ankle in the evaluated leg) by the Haemophilia Joint Health Score (HJHS),[23,24] over 18 and under 65 years of age, prophylaxis treatment with the deficient factor (i.e. XIII or IX) and body mass index lower than 35 kg/m^2 with the aim of decreasing the potential effect of subcutaneous fat tissue that can reduce the sEMG amplitude by working as a low-pass filter.[25] The exclusion criteria were history of hip, knee or ankle arthroplasty in the evaluated leg; equinus foot; inability to walk without an assistive device; history of muscle or joint bleeding in the lower limbs in the last two months; chronic cardiac and/or respiratory pathology and neurological disease.

For CG, the inclusion criteria were the following: male, over 18 and under 65 years of age and body mass index lower than 35 kg/m^2. The exclusion criteria were the following: acute traumatic injuries or chronic musculoskeletal disorders, signs or symptoms of injury or symptomatic arthritis to the trunk, lower back and lower limb within the past three months, any single positive findings of the Altman's criteria for knee osteoarthritis,[26] history of musculoskeletal surgery in the lower limb and spine, scoliosis; bleeding disorders, cardiac and/or respiratory pathology and neurological disease.

Twenty-two people with severe (n = 19) and moderate (n = 3) haemophilia were recruited (32.3 ± 11.6 years, body mass index 25.6 ± 3.7 kg/m^2, a total HJHS of 41.0 ± 20.4 pts). To calculate the Walk-DMC (see below), 15 healthy control subjects were recruited (31.5 ± 10.1 years, body mass index 24.5 ± 1.9 kg/m^2). Both groups showed similar age and anthropometric characteristics ($P > .05$).

2.2 | Clinical assessment in people with haemophilic arthropathy

The Visual Analog Scale (VAS 0–10 pts) was used to assess pain intensity during barefoot walking. For each participant, the HJHS 2.1 was used to assess joint impairment.[23,24] The HJHS score was applied to the knee and ankle (0–40 pts) of the limb assessed. Gait impairment was evaluated using the global gait score (0–4 pts) of the HJHS. In addition, the total score on the HJHS (0–124 points) was included. At the joint level, the HJHS has a good correlation with X-rays (Pettersson score), and the total HJHS has a moderate correlation with self-reported functions.[27,28] Furthermore, the knee flexion contracture (i.e. loss of joint extension) was assessed to measure knee joint deformity. For setting the knee contracture angle and HJHS, a universal goniometer with a 1° increment (Baseline®, Chattanooga Group Inc) was used.

2.3 | Data acquisition

In PWHA, the limb with the highest score on the HJHS was selected for the experiment. In the CG, the dominant limb, which was determined by asking the subjects which leg they would use to kick a ball,

TABLE 1 Muscles configurations used to calculate the Walk-DMC index

Five	Six	Seven	Eight	Nine	Ten	Eleven
MG	MG	MG	MG	MG	MG	MG
TA	TA	TA	TA	TA	TA	TA
RF	RF	RF	RF	RF	RF	RF
BF	BF	BF	BF	BF	BF	BF
ST	ST	ST	ST	ST	ST	ST
	VM	VM	VM	VM	VM	VM
		VL	VL	VL	VL	VL
			LG	LG	LG	LG
				GMAX	GMAX	GMAX
					SOL	SOL
						GMED

Abbreviations: MG, medial gastrocnemius; TA, tibialis anterior; RF, rectus femoris; BF, biceps femoris; ST, semitendinosus; VM, vastus medialis; VL, vastus lateralis; LG, lateral gastrocnemius; GMAX, Gluteus maximus; SOL, soleus, GMED, gluteus medius.

was assessed.[16] After shaving and cleaning the skin with alcohol, surface bipolar electrodes of 2.4 cm diameter (Ag–AgCl, Kendall H124SG) were placed such that the interelectrode spacing was 2 cm on the leg muscles. The localisation of electrodes in the leg muscles (see Table 1) was made according to SENIAM guidelines.[29] Muscle activity patterns were assessed using a wireless sEMG system (MyoSystem DTS; Noraxon USA Inc, Scottsdale, California, USA), with a sampling rate of 1500 Hz. Gait cycle events were detected by a synchronised wireless pressure sensor placed underneath the heel of the foot.

2.4 | Experimental protocol

All PWHA walked barefoot twice for 30 m, with 2 minutes of rest in between tests. PWHA were invited to walk at their preferred velocity. For each participant, the time elapsed in each 30 m walk test was used as a marker of the walking velocity. From 1 to 2 hours before the experiment, PWHA received prophylactic treatment. The CG walked barefoot overground for 30 m twice at a slower velocity to reproduce the mean preferred velocity of PWHA (i.e. 1.0 m/s). To ensure that the walking speed was performed correctly, the time spent travelling 30 m was registered, and immediate feedback on velocity was given to each participant. It is critical to matching the walking velocity between CG and the target population so as not to affect the interpretation of neural control during gait.[21]

2.5 | Walk-DMC calculation

For each group, 20 gait cycles were included in the analysis.[16,21] The Walk-DMC was calculated based on previous studies on neurological diseases and PWHA.[14–16] For the details of sEMG signal processing and Walk-DMC calculation, see the complementary material. Briefly, the Walk-DMC was calculated for each PWHA using the z-score normalisation, including the mean and standard deviation of total variance accounted for one synergy ($TVAF_1$) from the CG at a fixed walking velocity (1 m/s).[14,15] $TVAF_1$ has been shown to be repeatable between days in healthy children and those with cerebral palsy.[21,30] In addition, assessment of Walk-DMC has been reported to be consistent between different motion laboratories for both children and young adults (ages 4–21).[31] Seven selections of muscles (from 5 to 11 leg flexors and extensors) were used to calculate the Walk-DMC. The 11 hip, knee and ankle flexors and extensors were selected based on the four muscle synergies described during walking: acceptance synergy (hip and knee extensors), propulsion synergy (ankle extensors), swig synergy (ankle dorsiflexors and hip flexors) and deceleration synergy (knee flexors).[19] The five muscles used in all selections were based on a previous paper.[14] Subsequently, muscles were added randomly one by one until all included muscles were selected (see Table 1). Note that the configuration with five muscles includes a representation of the four synergies with the representation of at least one muscle (acceptance, rectus femoris; propulsion, medial gastrocnemius; swing, tibialis anterior and rectus femoris; deceleration, semitendinosus and bicep femoris).[19] A Walk-DMC of 100 points is equal to the neural control of CG. An index between 80 and 120 (i.e. + and − two standard deviations from the mean of the CG) was considered within the normal range.[14,15]

2.6 | Statistical analysis

The sample size was calculated considering the negative association reported between plantar flexor strength and tVAF1 in patients with cerebral palsy ($r = -.72$).[32] Twenty-two PWHA were determined to be sufficient to reach a P value of .05 and β of .20. The normality of the data was evaluated through the Shapiro-Wilk test. P values smaller than .05 were considered statistically significant. For the primary aim, the clinical characteristics between PWHA with a normal Walk-DMC and those with an altered one were compared using the 11 hip, knee and ankle flexor and extensor muscles (gold standard). To compare the clinical characteristics between normal and altered Walk-DMC, the independent t-test (if data were normally distributed) or Wilcoxon rank-sum test (if data were not normally distributed) was used. The effect size was calculated based on the t-value (normal distributed) or z-value (not normal distributed). All effect sizes were transformed to *Cohen's d*. *Cohen's d* has been operationally described in the following ranges: < .2 (no effect), .2–.5 (small effect), .5–.8 (moderate effect) and > .8 (large effect). Furthermore, the clinical outcomes (i.e. pain, knee flexion contracture and total HJHS of the limb) were correlated with the Walk-DMC index. The Pearson (normal distributed) and Spearman (not normal distributed) analyses were used. The correlation coefficient (r) was interpreted as < .39 (week association), .4–.60 (moderate association) and .60–1 (strong association).

For the secondary aim, multiple regression was applied to assess the predictor variables of the Walk-DMC index. The different variables (VAS, knee flexion contracture and HJHS of the limb) were entered

TABLE 2 Clinical characteristics of normal and altered Walk-DMC index using 11 muscles

Clinical variables	Normal index	Altered index	p-value	Effect size
Age	26 [20 42]	33 [22 64]	*.047	.9 (large)
Pain (VAS 0–10)	1 [0 4]	4 [0 8]	*.021	2.9 (large)
Chronicity of arthropathy (years)	7 [3 12]	13 [5 35]	*.010	1.3 (large)
Start of prophylaxis (age)	16 [2 38]	26 [12 61]	.181	.6 (moderate)
Knee flexion contracture (degrees)	5 [0 20]	20 [0 35]	*.012	1.2 (large)
HJHS limb (0-40)	12.0 ± 5.8	19.9 ± 6.0	*.006	1.0 (large)
HJHS global gait (0-4)	3 [0 4]	4 [1 4]	*.043	.9 (large)
Total HJHS (0-124)	27.0 ± 17.5	50.8 ± 16.6	*.004	1.4 (large)
Walking velocity (m/s)	1.1 ± .1	1.0 ± .2	.162	.6 (moderate)

Visual analogue scale (VAS).
Haemophilia joint health score (HJHS).
Normal distribution: Mean ± SD.
Not normal distribution: Median [Range].
Normal index (n = 9).
Altered index (n = 13).
*$P < .05$.

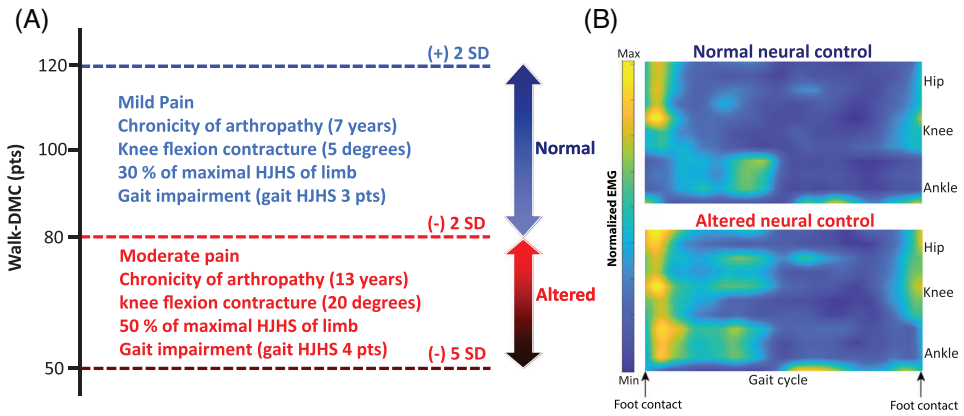

FIGURE 1 (A) Clinical interpretation of those people with haemophilic arthropathy with and without altered Walk-DMC. Haemophilia health joint score (HJHS). Gait impairment was defined as the maximum score of the gait score of the HJHS (i.e. 4 points). (B) Colour map of the average muscle activation pattern of PWHA with normal and altered neural control of gait. The gait cycle starts with the stance phase. Muscle activity of each muscle in each participant was normalized to the maximum value of all included cycles (20 cycles). The yellow colour represents the maximum value (1) of the normalized muscle activity. Electromyography (EMG)

conditionally using the forward method. Furthermore, the agreement between the 5–10 selected muscles and the gold standard (11 muscles) to detect the altered Walk-DMC was calculated using the Kappa statistic. The kappa was interpreted as none (≤ 0), no or weak agreement (.01–.20), fair (.21–.40), moderate (.41–.60), substantial (.61–.80) and almost perfect (.81–1.00).

3 | RESULTS

3.1 | Differences in clinical characteristics between normal and altered neural control

Neural control was found to be altered (i.e. Walk-DMC < 80) in 13 out of 22 PWHA. PWHA with an altered Walk-DMC showed more years with arthropathy, more pain, higher knee flexion contracture and a higher HJHS score (Table 2, Figure 1A) than those with a normal Walk-DMC index. We also found that PHWA with an altered Walk-DMC index showed a tendency to start prophylactic treatment later than those with a normal Walk-DMC index ($P = .181$, moderate effect) (Table 2). The colour map of muscle activation during gait indicates that PWHA with altered neural control have greater co-activation of hip, knee and ankle joint muscles, particularly at the beginning of the stance phase (Figure 1B).

3.2 | Association between altered Walk-DMC and clinical outcome measures

Significant, negative, moderate associations between Walk-DMC and pain ($r = -.59$, $P = .004$), knee flexion contracture ($r = -.58$, $P = .004$) and HJHS of the limb ($r = -.52$, $P = .013$) were found (Figure 2).

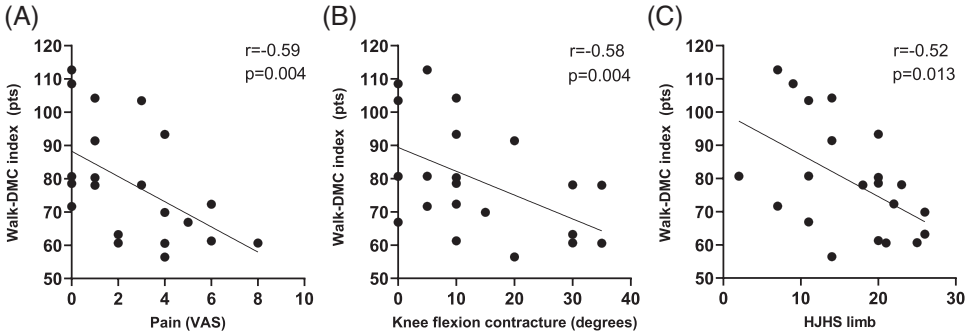

FIGURE 2 Correlations between Walk-DMC and clinical outcomes. Haemophilia health joint score (HJHS). Visual analogue scale (VAS)

TABLE 3 Regression models

	R^2	SE	*P*-value
Model A	.28	14.7	*.011
Independent variable	**Coefficients**	**SD**	***P*-value**
Constant	88.3	4.7	* < .001
Pain (VAS)	−3.8	1.4	*.011
	R^2	SE	*P*-value
Model B	.44	13.3	*.004
Independent variable	**Coefficients**	**SD**	***P*-value**
Constant	94.7	5.0	* < .001
Pain (VAS)	−3.0	1.3	*.029
Knee flexion contracture (degrees)	−.6	.2	*.029

Visual analogue scale (VAS).
The standard error (SE).
Standard deviation (SD).
*$P < .05$.

3.3 | Predictors of the Walk-DMC index

The regression analysis with the forwarding method includes two models (model A: pain and model B: pain with knee flexion contracture) (Table 3). The model that best predicted the Walk-DMC index was the pain with knee flexion contracture, which explained 44% of the variance of the Walk-DMC with a standard error of 13 points (Table 3). The association between pain and knee flexion contracture was not significant ($r = .35$, $P = .107$). The variance inflation factor was 1.07 for both variables, indicating an absence of multicollinearity. The residuals were normally distributed.

3.4 | The number of muscles to detect the altered Walk-DMC

The number of muscles included affected the value of the Walk-DMC index and thereby the number of subjects with an abnormal value (Figure 3A and 3B). For a substantial agreement (kappa > .6) with the gold standard (i.e. 11 muscles), a minimum of eight knee and ankle flexors and extensors were needed (Figure 3C).

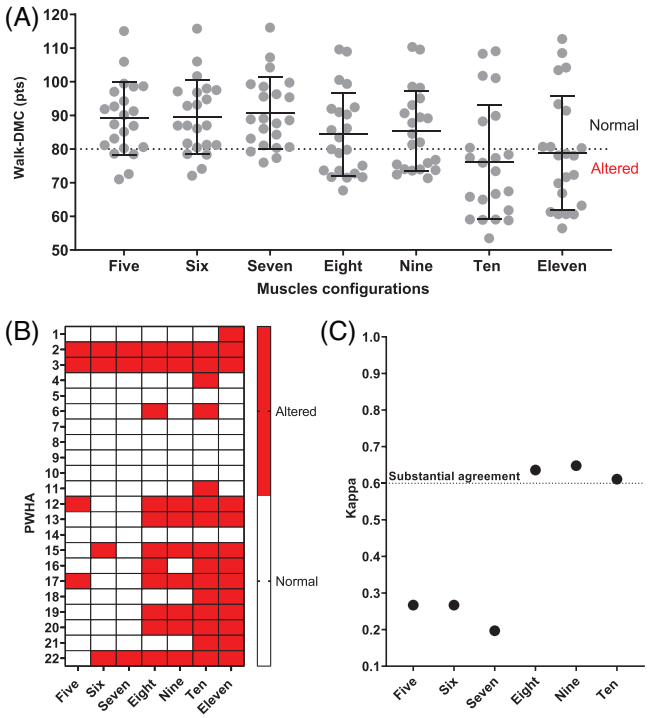

FIGURE 3 (A) The Walk-DMC index in people with haemophilic arthropathy for the different muscle configurations. (B) Detection of altered Walk-DMC index in people with haemophilic arthropathy for the different muscle configurations. (C) The agreement between the different configurations (5–10 muscles) and the gold standard configuration (11 muscles), as assessed with the kappa statistical test

4 | DISCUSSION

The main results of this study are: (i) The neural control of gait was not altered in all PWHA; (ii) PWHA with an altered Walk-DMC showed more years with arthropathy, experienced more pain and had a higher knee flexion contracture and greater joint and gait impairment; (iii) The Walk-DMC was moderately associated with pain, knee flexion contracture and HJHS; (iv) Pain level and knee flexion contracture explained 44% of the variance of the Walk-DMC index; (v) A minimum of eight knee and ankle flexor and extensor muscles need to be included in the assessment of Walk-DMC. To the authors' current knowledge, this is

the first study that reports the association of pain and joint impairment with altered neural control of gait in PWHA.

4.1 | Clinical interpretation of altered neural control of gait in PWHA

PWHA with altered neural control of gait experienced more pain and 50% of the maximal score of HJHS of the limb. The association between neural control and pain in PWHA has not been reported before. Previously, our research group reported that neural control is affected in some PWHA, but no significant association with joint damage was found.[16] The small sample size and lower joint damage amongst the recruited PHWA are potential reasons for the absence of a significant association.[16] In children with cerebral palsy and Duchenne muscular dystrophy, a moderate-to-high association between limb muscle weakness and $TVAF_1$ has been reported.[32] In people with knee osteoarthritis, increased co-activation between antagonists during gait has been associated with disease severity,[33] but this was not based on the Walk-DMC. Pain and joint impairment may affect neural control of gait by different mechanisms. First, pain may cause increased co-activation between antagonists as a strategy to protect tissues from further injury.[33,34] Second, joint deterioration can be accompanied by altered proprioception affecting joint and gait stability, which may be compensated by increased co-activation of antagonists.[33,35,36]

We also observed that PWHA with altered neural control of gait had more significant knee flexion contracture, more years with arthropathy, and a tendency to start prophylaxis treatment later than those with a normal Walk-DMC (see Table 2). The mechanical constraints on the knee may explain the altered neural control in PWHA. However, in healthy individuals, a simulated severe knee flexion contracture (20°) did not change the neural control of gait.[20] Only long-term exposure to a knee joint constraint of a substantial amplitude (≈ 20°) seems to cause structural changes in the neural control of gait.[20] Mechanically, a knee flexion contracture may result in higher loads on a smaller joint surface area, which may increase the level of pain, alter the neural control of gait and increase joint stiffness.[20,37] Long-term exposure to arthropathy, pain and a joint constraint may cause secondary adaptations of the central nervous system.[20] Once such adaptations have occurred, it may be challenging to return neural control to normal (e.g. after total knee arthroplasty).

It is important to note that some individuals with abnormal Walk-DMC index values showed low pain and knee flexion contracture (Figure 2), indicating the variability of neural control of gait in response to arthropathy. To understand the potential inter-relationship between clinical outcomes, we performed a multiple regression analysis to predict the Walk-DMC index using the clinical outcomes (pain, knee flexion contracture and HJHS of the limb). We observed that pain with knee flexion contracture was the model that best predicted the Walk-DMC index (Table 3). However, other non-mechanical factors such altered pain processing, kinesiophobia and catastrophism may also affect neural control and should be addressed in future studies.[4,38,39]

4.2 | Minimal number of muscles for valid assessment of the Walk-DMC

It has been suggested that the number of muscles recorded appears to influence the outcomes of synergy calculations.[22,40] We found that the Walk-DMC based on the sEMG signal from five to eight muscles was different from that based on 11 muscles. Our results agree with the study by Steele et al. (2013), which reported that a small number of muscle configurations might underestimate the complexity of neuromuscular control.[40] We propose that the sEMG of a minimum of eight leg muscles needs to be included in assessment of the Walk-DMC.

4.3 | Limitations

To determine the minimal number of muscles required for a valid assessment of the Walk-DMC in PWHA, we tested only a random selection of 5–11 muscles. Another approach, such as muscle selection by size (i.e. volume and cross-sectional area), may help to understand motor impairment related to altered Walk-DMC index. Moreover, proprioception was not assessed. Therefore, it was not possible to associate the changes in somatosensory processing and the alteration of neural control of gait. Finally, although the Walk-DMC is repeatable between days[21,30] and consistent between motion laboratories,[31] reproducibility data are not available for PWHA.

5 | CONCLUSION

PWHA with abnormal neural control of gait also have more years with arthropathy, more pain and more impaired joints. Our results indicate an association between the Walk-DMC index and joint damage, specifically with pain in combination with knee flexion contracture. However, the assessment of the Walk-DMC index is sensitive to the number of muscles used for sEMG measurements. The Walk-DMC index may be used as an additional assessment tool to monitor disease progression in PWHA.

ACKNOWLEDGEMENTS

The authors thank all participants in this study, the Chilean Society of Haemophilia, Inherited Bleeding Disorder Treatment Centre of the Roberto del Río Hospital and Traumatology unit of San José Hospital, particularly Verónica Soto and Andrés Oyarzún, for facilitating the recruitment of people with haemophilia.

CONFLICT OF INTEREST

There are no financial or personal conflicts of interest with respect to the research, authorship and/or publication of this article.

AUTHOR CONTRIBUTIONS

CCM performed the research, designed the research study, contributed essential reagents or tools, analysed the data and wrote the

paper. SPA and HM designed the research study, contributed essential reagents or tools, analysed the data and wrote the paper. MC analysed the data and wrote the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Carlos Cruz-Montecinos https://orcid.org/0000-0002-3835-3368
Huub Maas https://orcid.org/0000-0002-2304-2735
Mauricio Cerda https://orcid.org/0000-0003-3447-1815
Sofía Pérez-Alenda https://orcid.org/0000-0002-0841-5767

REFERENCES

1. Van Vulpen L, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018;24:44-49.
2. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020;26:1-158.
3. Boadas A, Ozelo MC, Solano M, et al. Haemophilia care in Latin America: assessment and perspectives. *Haemophilia*. 2018;24(6):e395-e401.
4. Kruger S, Hilberg T. Understanding the pain profile in patients with haemophilia: impaired descending pain inhibition as measured by conditioned pain modulation. *Haemophilia*. 2020;26(2):236-242.
5. Lobet S, Detrembleur C, Francq B, Hermans C. Natural progression of blood-induced joint damage in patients with haemophilia: clinical relevance and reproducibility of three-dimensional gait analysis. *Haemophilia*. 2010;16(5):813-821.
6. McLaughlin JM, Munn JE, Anderson TL, Lambing A, Tortella B, Witkop ML. Predictors of quality of life among adolescents and young adults with a bleeding disorder. *Health Qual Life Outcomes*. 2017;15(1):67.
7. Stephensen D, Drechsler WI, Scott OM. Biomechanics of lower limb haemophilic arthropathy. *Blood Rev*. 2012;26(5):213-221.
8. Stephensen D, de Kleijn P, Matlary RED, et al. Scope of practice of haemophilia physiotherapists: a European survey. *Haemophilia*. 2019;25(3):514-520.
9. Stephensen D, Taylor S, Bladen M, Drechsler WI. Relationship between physical function and biomechanical gait patterns in boys with haemophilia. *Haemophilia*. 2016;22(6):e512-e518.
10. Seuser A, Navarrete-Duran M, Auerswald G, Mancuso ME. Muscle function deterioration in patients with haemophilia: prospective experience from Costa Rica. *Haemophilia*. 2018;24(4):e230-e241.
11. Lobet S, Peerlinck K, Hermans C, Van Damme A, Staes F, Deschamps K. Acquired multi-segment foot kinematics in haemophilic children, adolescents and young adults with or without haemophilic ankle arthropathy. *Haemophilia*. 2020;26(4):701-710.
12. Pasta G, Annunziata S, Polizzi A, et al. The progression of hemophilic arthropathy: the role of biomarkers. *Int J Mol Sci*. 2020;21(19):7292.
13. Putz P, Durstberger S, Kaufmann C, et al. 3D gait analysis, haemophilia joint health score, leg muscle laterality and biomarkers of joint damage: a cross-sectional comparative assessment of haemophilic arthropathy. *Haemophilia*. 2020;26(6):e323-e333.
14. Steele KM, Rozumalski A, Schwartz MH. Muscle synergies and complexity of neuromuscular control during gait in cerebral palsy. *Dev Med Child Neurol*. 2015;57(12):1176-1182.
15. Schwartz MH, Rozumalski A, Steele KM. Dynamic motor control is associated with treatment outcomes for children with cerebral palsy. *Dev Med Child Neurol*. 2016;58(11):1139-1145.
16. Cruz-Montecinos C, Pérez-Alenda S, Cerda M, Maas H. Neuromuscular control during gait in people with haemophilic arthropathy. *Haemophilia*. 2019;25(2):e69.
17. Collimore AN, Aiello AJ, Pohlig RT, Awad LN. The dynamic motor control index as a marker of age-related neuromuscular impairment. *Front Aging Neurosci*. 2021;13:387.
18. Tresch MC, Saltiel P, Bizzi E. The construction of movement by the spinal cord. *Nat Neurosci*. 1999;2(2):162-167.
19. Ivanenko YP, Poppele RE, Lacquaniti F. Five basic muscle activation patterns account for muscle activity during human locomotion. *J Physiol*. 2004;556(1):267-282.
20. Cruz-Montecinos C, Perez-Alenda S, Cerda M, Maas H. Modular reorganization of gait in chronic but not in artificial knee joint constraint. *J Neurophysiol*. 2021;126(2):516-531.
21. Shuman B, Goudriaan M, Bar-On L, Schwartz MH, Desloovere K, Steele KM. Repeatability of muscle synergies within and between days for typically developing children and children with cerebral palsy. *Gait Posture*. 2016;45:127-132.
22. Bekius A, Bach MM, van der Krogt MM, de Vries R, Buizer AI, Dominici N. Muscle synergies during walking in children with cerebral palsy: a systematic review. *Front Physiol*. 2020;11:632.
23. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12(5):518-525.
24. Sun J, Hilliard P, Feldman B, et al. Chinese hemophilia joint health score 2.1 reliability study. *Haemophilia*. 2014;20(3):435-440.
25. Cooper MA, Herda TJ, Vardiman JP, Gallagher PM, Fry AC. Relationships between skinfold thickness and electromyographic and mechanomyographic amplitude recorded during voluntary and non-voluntary muscle actions. *J Electromyogr Kinesiol*. 2014;24(2):207-213.
26. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum*. 1986;29(8):1039-1049.
27. Poonnoose P, Hilliard P, Doria A, et al. Correlating clinical and radiological assessment of joints in haemophilia: results of a cross sectional study. *Haemophilia*. 2016;22(6):925-933.
28. Ribeiro AJT, Amorim FF, Soares BMD, Santana LA, Imoto AM. Functional and joint evaluation in a prospective cohort of patients with severe haemophilia. *Haemophilia*. 2021;27(2):314-320.
29. Hermens HJ, Freriks B, Merletti R, et al. European recommendations for surface electromyography. *Roessingh Res Dev*. 1999;8(2):13-54.
30. Steele KM, Munger ME, Peters KM, Shuman BR, Schwartz MH. Repeatability of electromyography recordings and muscle synergies during gait among children with cerebral palsy. *Gait Posture*. 2019;67:290-295.
31. MacWilliams BA, McMulkin ML, Rozumalski A, Schwartz MH. Synergies analysis produces consistent results between motion analysis laboratories. *Gait Posture*. 2021;86:139-143.
32. Goudriaan M, Shuman BR, Steele KM, et al. Non-neural muscle weakness has limited influence on complexity of motor control during gait. *Front Human Neurosci*. 2018;12:5.
33. Mills K, Hunt MA, Leigh R, Ferber R. A systematic review and meta-analysis of lower limb neuromuscular alterations associated with knee osteoarthritis during level walking. *Clin Biomech*. 2013;28(7):713-724.
34. Hodges PW. Pain and motor control: from the laboratory to rehabilitation. *J Electromyogr Kinesiol*. 2011;21(2):220-228.
35. Deschamps K, Staes F, Eerdekens M, et al. Postural control during a transition task in haemophilic children, adolescents and young adults with haemophilic ankle arthropathy. *Haemophilia*. 2018;24(4):667-674.
36. Hilberg T, Herbsleb M, Gabriel H, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. *Haemophilia*. 2001;7(6):582-588.

37. Campbell TM, McGonagle D. Flexion contracture is a risk factor for knee osteoarthritis incidence, progression and earlier arthroplasty: data from the osteoarthritis initiative. *Ann Phys Rehabil Med*. 2021;64(2):101439.
38. De Oliveira Silva D, Willy RW, Barton CJ, Christensen K, Pazzinatto MF, Azevedo FM. Pain and disability in women with patellofemoral pain relate to kinesiophobia, but not to patellofemoral joint loading variables. *Scand J Med Sci Sports*. 2020;30(11):2215-2221.
39. Ucero-Lozano R, López-Pina JA, Ortiz-Pérez A, Cuesta-Barriuso R. The relationship between chronic pain and psychosocial aspects in patients with haemophilic arthropathy. A cross-sectional study. *Haemophilia*. 2022;28(1):176-182.
40. Steele KM, Tresch MC, Perreault EJ. The number and choice of muscles impact the results of muscle synergy analyses. *Front Comput Neurosci*. 2013;7:105.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Cruz-Montecinos C, Maas H, Cerda M, Pérez-Alenda S. Altered neural control of gait and its association with pain and joint impairment in adults with haemophilic arthropathy: Clinical and methodological implications. *Haemophilia*. 2022;28:497–504. https://doi.org/10.1111/hae.14517