Muskuloskeletal

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

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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.14-7 Clinical examination of joints and muscles, besides examining posture and gait, are the most often used assessments by physiotherapists for haemophilia care.9 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).7-13

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/m2 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/m2. 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/m², 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/m²). 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,
For each group, 20 gait cycles were included in the analysis.16,21 The 2.5 m control during gait.21 and the target population so as not to affect the interpretation of neu-

participant. It is critical to matching the walking velocity between CG was registered, and immediate feedback on velocity was given to each experiment, PWHA received prophylactic treatment. The CG walked used as a marker of the walking velocity. From 1 to 2 hours before the experiment, PWHA were invited to walk at their preferred veloc-

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

was assessed.16 After shaving and cleaning the skin with alcohol, sur-
face 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

### 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 (TVAF₁) from the CG at a fixed walking velocity (1 m/s).14,15 TVAF₁ 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), swing 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 biceps 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>
<thead>
<tr>
<th>Clinical variables</th>
<th>Normal index</th>
<th>Altered index</th>
<th>p-value</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26 [20 42]</td>
<td>33 [22 64]</td>
<td>.047</td>
<td>.9 (large)</td>
</tr>
<tr>
<td>Pain (VAS 0–10)</td>
<td>1 [0 4]</td>
<td>4 [0 8]</td>
<td>.021</td>
<td>2.9 (large)</td>
</tr>
<tr>
<td>Chronicity of arthropathy (years)</td>
<td>7 [3 12]</td>
<td>13 [5 35]</td>
<td>.010</td>
<td>1.3 (large)</td>
</tr>
<tr>
<td>Start of prophylaxis (age)</td>
<td>16 [2 38]</td>
<td>26 [12 61]</td>
<td>.181</td>
<td>.6 (moderate)</td>
</tr>
<tr>
<td>Knee flexion contracture (degrees)</td>
<td>5 [0 20]</td>
<td>20 [0 35]</td>
<td>.012</td>
<td>1.2 (large)</td>
</tr>
<tr>
<td>HJHS limb (0-40)</td>
<td>12.0 ± 5.8</td>
<td>19.9 ± 6.0</td>
<td>.006</td>
<td>1.0 (large)</td>
</tr>
<tr>
<td>HJHS global gait (0-4)</td>
<td>3 [0 4]</td>
<td>4 [1 4]</td>
<td>.043</td>
<td>.9 (large)</td>
</tr>
<tr>
<td>Total HJHS (0-124)</td>
<td>27.0 ± 17.5</td>
<td>50.8 ± 16.6</td>
<td>.004</td>
<td>1.4 (large)</td>
</tr>
<tr>
<td>Walking velocity (m/s)</td>
<td>1.1 ± .1</td>
<td>1.0 ± .2</td>
<td>.162</td>
<td>.6 (moderate)</td>
</tr>
</tbody>
</table>

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).
TABLE 3  Regression models

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model A</td>
<td>.28</td>
<td>14.7</td>
<td>.011</td>
</tr>
</tbody>
</table>

Independent variable Coefficients SD P-value

| Constant | 88.3  | 4.7 | < .001 |
| Pain (VAS) | −3.8  | 1.4 | .011   |

Model B

<table>
<thead>
<tr>
<th>$R^2$</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>.44</td>
<td>13.3</td>
<td>.004</td>
</tr>
</tbody>
</table>

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).

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
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. The small sample size and lower joint damage amongst the recruited PHWA are potential reasons for the absence of a significant association. In children with cerebral palsy and Duchenne muscular dystrophy, a moderate-to-high association between limb muscle weakness and TVAF has been reported. In people with knee osteoarthritis, increased co-activation between antagonists during gait has been associated with disease severity, 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. Second, joint deterioration can be accompanied by altered proprioception affecting joint and gait stability, which may be compensated by increased co-activation of antagonists.

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. 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. 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. Long-term exposure to arthropathy, pain and a joint constraint may cause secondary adaptations of the central nervous system. 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.

4.2 | 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. 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. 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 and consistent between motion laboratories, 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.

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

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