Received: 18 October 2019 | Revised: 11 December 2019 | Accepted: 13 December 2019

DOI: 10.1111/hae.13925

ORIGINAL ARTICLE

Haemophilia WILEY

Clinical gait features are associated with MRI findings in patients with haemophilic ankle arthropathy

Maarten Eerdekens[1,2,3] | Kathelijne Peerlinck[3,4] | Filip Staes[1] | Jean-Baptiste Pialat[5,6] | Cédric Hermans[7] | Sébastien Lobet[7,8,9] | Kevin Deschamps[2,10]

[1]Department of Rehabilitation Sciences, Musculoskeletal Rehabilitation Research Group, KU Leuven, Heverlee, Belgium

[2]Clinical Motion Analysis Laboratorium (CMAL), UZ Leuven, Pellenberg, Belgium

[3]Haemophilia Center, UZ Leuven, Leuven, Belgium

[4]Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium

[5]Department of Radiology, Centre Hospitalier Lyon-Sud, Hospices Civils de Lyon, Lyon, France

[6]Université Claude Bernard Lyon 1, Université de Lyon, Lyon, France

[7]Service d'hématologie, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[8]Institut de Recherche Expérimentale et Clinique, Neuromusculoskeletal Lab (NMSK), Université Catholique de Louvain, Brussels, Belgium

[9]Service de Médecine Physique et Réadaptation, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[10]Department of Rehabilitation Sciences, Musculoskeletal Rehabilitation Research Group, KU Leuven, Brugge, Belgium

Correspondence
Maarten Eerdekens, Clinical Motion Analysis Laboratorium (CMAL), UZ Leuven, Weligerveld 1, B-3210 Lubbeek (Pellenberg), Belgium.
Email: maarten.eerdekens@uzleuven.be

Funding information
The Pfizer ASPIRE, Grant/Award Number: WI199899; The Novo Nordisk Access to Insight Clinical Research Grant

Abstract

Introduction: Haemophilic ankle arthropathy due to repeated joint bleeds often leads to altered gait in adult patients with haemophilia.

Aim: To investigate the association between clinical gait features and blood-induced ankle joint damage scored using MRI findings in patients with haemophilic ankle arthropathy.

Methods: This observational study investigated 48 ankles of 24 patients with severe haemophilia (median age of 33 years). Blood-induced ankle joint damage was scored by an experienced radiologist using the International Prophylaxis Study Group (IPSG-)MRI score which evaluates the presence or absence of effusion, synovial hypertrophy, haemosiderin, surface erosions, subchondral cysts and cartilage degeneration. Using 3D gait analysis, peak ankle joint power generation and absorption (W/kg) were measured for each ankle since these are surrogate measures for joint loading during walking. Associations between MRI findings and these two clinical gait features were calculated using Spearman's ρ correlation with an α-level correction ($\alpha = 0.01$) for multiple tests.

Results: We found large negative associations between ankle joint peak power generation and IPSG-MRI score ($\rho = -0.631$; $P = <.001$), IPSG-MRI osteochondral subscore ($\rho = -0.701$; $P = <.001$), severity of synovial hypertrophy ($\rho = -0.507$; $P = <.001$) and haemosiderin ($\rho = -0.400$; $P = .005$). Associations were also found for ankle joint peak power absorption and IPSG-MRI score ($\rho = -0.425$; $P = .003$) and IPSG-MRI osteochondral subscore ($\rho = -0.556$; $P = <.001$).

Conclusion: Severe blood-induced ankle joint damage relates to a lowered tolerance towards ankle joint mechanical loading during walking in patients with haemophilia.

KEYWORDS

ankle, arthritis, gait analysis, haemophilia, MRI

1 | INTRODUCTION

In patients with haemophilia (PwH), 80%-90% of bleedings occur at the musculoskeletal system, with the large synovial joints being targeted most often.[1] Repeated joint bleedings induce a complex pathogenesis resulting in synovial hypertrophy, cartilage destruction, muscle arthropathy and ankylosis.[2] This degenerative process is defined as haemophilic arthropathy. Long-term prevention of joint bleeds is therefore currently the main treatment goal in PwH.[3] Yet, the ankle joint seems less receptive to the otherwise good working

treatment strategies,[4] making haemophilic ankle arthropathy currently the most important comorbidity in adult PwH as it affects the ankle joint function.[5] Literature furthermore suggests that already few bleedings cause ankle joint destruction.[6] The latter is a unique manifestation, since primary and secondary arthrosis of the ankle usually develops over years. It is therefore of clinical importance to early on characterize the impact of haemophilic ankle arthropathy on the joint structure and function.

Magnetic resonance imaging (MRI) is the most sensitive medical imaging tool to characterize the ankle joint structure and document the severity of haemophilic ankle arthropathy.[7,8] The International Prophylaxis Study Group (IPSG)-MRI scale was developed to assess both osteochondral and soft-tissue changes in the ankle joint of PwH.[9] The IPSG-MRI scale was later validated and found to be reliable to characterize the ankle joint structure in patients with haemophilic ankle arthropathy.[10]

Three-dimensional gait analysis is found to be an ideal methodological tool to characterize joint function during walking and receives increasing attention in PwH.[11-13] One study to date investigated the relationship between ankle joint structure and ankle joint function in children, adolescents and young adults by associating the IPSG-MRI score with their respective ankle joint kinematics during walking.[10] The findings of this study highlighted a poor correlation between ankle joint structure and function in the aforementioned population. However, these conclusions need to be put in context. For example, of the 73 investigated ankle joints in children, adolescents and young adults, only 14 showed minor MRI or clinical signs of haemophilic ankle arthropathy. This is plausible since haemophilic ankle arthropathy most often affects adult PwH. Furthermore, only kinematic parameters were evaluated, which only reflects a small portion of the complex function of the ankle joint during walking. To further analyse the ankle joint function, recent progresses were achieved by developing multi-segment kinetic foot models, which better grasp the complex function of the ankle and foot joints during walking by analysing kinetic parameters.[14-16] These kinetic parameters are considered to be surrogate measures to evaluate how subjects modify their gait features to cope with the mechanical loading on joints during walking.[17]

The aim of this paper therefore was to investigate the association between blood-induced ankle joint damage and kinetic parameters of the ankle joint in adult PwH. Our hypothesis was to find a negative association between the IPSG-MRI score and kinetic variables in adult patients with haemophilic ankle arthropathy. This might suggest that patients with severe haemophilic ankle arthropathy adopt a different gait strategy to maintain a suitable tolerance towards ankle joint loading.

2 | MATERIALS AND METHODS

The workflow of the data collection and data analysis in this study is displayed in Figure 1.

2.1 | Study participants

The institution's ethical committee approved this multi-centre study (S57147), and a written informed consent was obtained from each study participant. PwH were not eligible to participate in case (a) of an acute lower limb joint bleed at time and maximum 3 weeks prior to the assessments, (b) they were younger than 18 years or older than 55 years of age, (c) they had mild or moderate haemophilia, (d) they underwent orthopaedic surgery to any of the lower limb joints or (e) they were unable to attend the MRI and gait analysis examination on the same day. Participants also had to be able to walk for at least 100 m without rest. A total of 26 PwH were recruited for this study between December 2016 and October 2017 through a Hemophilia Reference Center (n = 18) and a Hemophilia Treatment Center (n = 8). Two patients were excluded; one because of insufficient quality of motion analysis data and another who was not able to attend the gait examination.

2.2 | Clinical gait features

Following clinical gait features were measured using a multi-segment kinetic foot model during quantitative 3D motion analysis: ankle joint peak power generation and ankle joint peak power absorption.[14] These two clinical gait features are considered to be surrogate measures for ankle joint loading during walking.[18] Gait analyses began with the placement of passive retro-reflective markers on anatomical landmarks of both feet according to the Rizzoli Foot Model[19] (Figure 2). All participants performed a walking trial at a self-selected, comfortable speed in a clinical motion analysis laboratory consisting of a 3D motion analysis system (Vicon Motion System Ltd., Oxford Metrics) and a plantar pressure platform (Footscan™ sensors, 2.8 sensors per cm^2, RSscan International) placed on top of a force platform (Advanced Mechanical Technology Inc). The kinetic computation combined the marker position, ground reaction force and plantar pressure data. The centre of pressure and resultant ground reaction force were distributed over three segments of the Rizzoli Foot Model (rearfoot, midfoot and hallux segment) (Figure 2) using the proportionality scheme validated by Saraswat et al.[20]

Inertial parameter calculations of foot segments were based on the mass of the segments and on their geometric solids, whereas the mass of the foot was distributed at 30/60/10 per cent, for the rearfoot/midfoot/hallux, respectively. The inter-segment angle for the ankle joint was defined between the shank and rearfoot segment, with the joint centre definition being between the medial and lateral malleoli. An inverse dynamic analysis program written in Matlab (MathWorks©) computed joint moments and powers starting from the hallux segment and progressing proximally using Newton-Euler equations, similar to a recent methodology published by Deschamps et al.[14] From these calculations, average ankle joint peak power generation and absorption were withheld as discrete outcome variables for each study participant.

2.3 | MRI protocol

Both ankles were imaged consecutively in a single examination using a 3.0-T MRI scan equipped with a dedicated 16-channel foot-ankle coil (Signa PET/MR, GE Heatlthcare). MRI examinations consisted of a sagittal T1-weighted fast spin echo sequence (repetition time msec/echo time msec, 430/11; flip angle, 148°; acquisition matrix: 448 × 320; field of view, 200 mm), a sagittal T2*-weighted gradient-echo sequence (700/18; flip angle, 15°; acquisition matrix: 320 × 320; field of view, 200 mm) and a sagittal (4926/42; flip angle, 133°; acquisition matrix: 448 × 448; field of view, 200 mm) and coronal (4370/46; flip angle, 133°; acquisition matrix: 448 × 448; field of view, 160 mm) T2*-weighted fast spin echo with fat saturation sequence. All sequences were performed with a 3 mm slice thickness, 0.3 mm slice spacing, 31.25-111.11 kHz bandwidth, one signal acquired and an echo train length of two to 8. The MRI examination time was approximately 30 minutes per ankle.

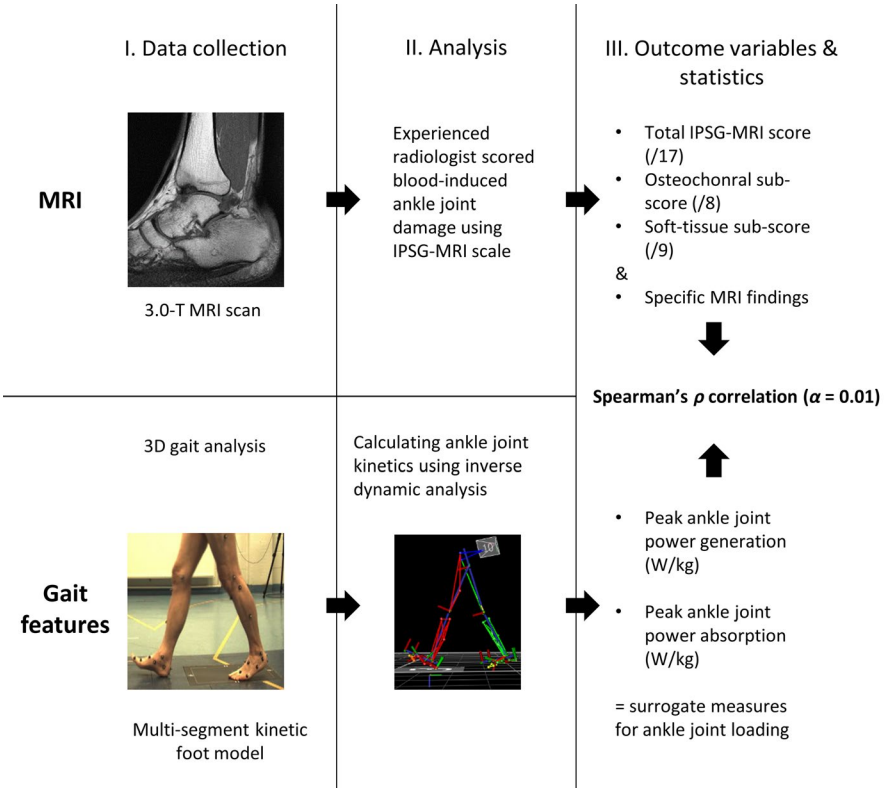

FIGURE 1 Workflow used to investigate the association between MRI findings and clinical gait features in patients with haemophilic ankle arthropathy

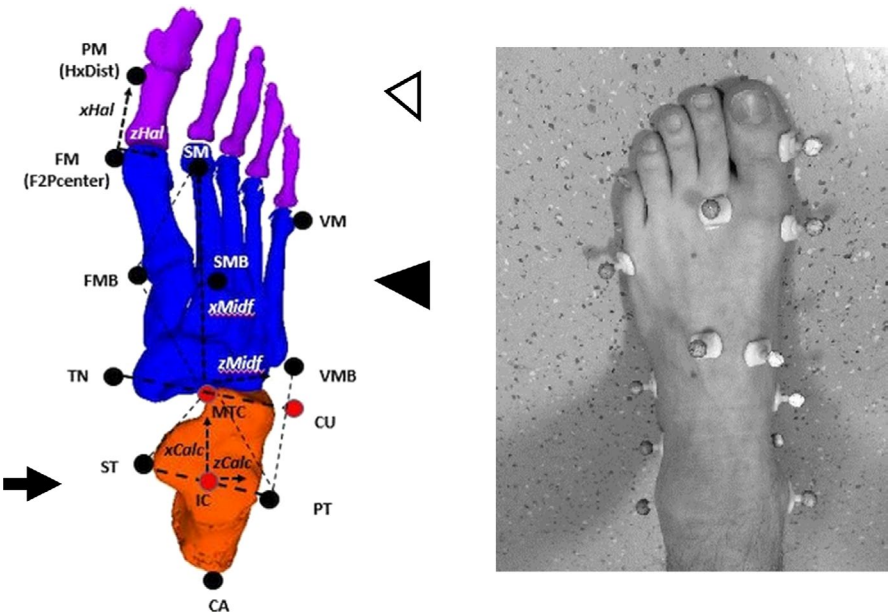

FIGURE 2 Left: Marker placement Rizzoli Foot Model; Right: Segment definition Rizzoli Foot Model: rearfoot (black arrow), midfoot (black arrowhead), hallux (white arrowhead). Ankle joint defined between shank and rearfoot segment

2.4 | MRI interpretation

All 48 MRI ankle images were interpreted and scored using the IPSG-MRI scale by a reader with 17 years of experience in the field of haemophilic joint imaging (J-B. P.), to depict blood-induced ankle joint damage. The reader was blinded to demographic, clinical and gait analysis data of each study participant. IPSG-MRI scale was scored out of 17 points, with 0/17 meaning no blood-induced ankle joint damage and 17/17 most severely damaged. A soft-tissue subscale (maximum 9 points), consisting of following MRI findings: joint effusions/haemarthrosis, synovial hypertrophy and haemosiderin and an osteochondral subscale (maximum 8 points), consisting of following MRI findings: surface erosions, subchondral cysts and cartilage degeneration were also scored.

2.5 | Statistical analysis

All statistical analyses were performed in SPSS 20.0 (IBM). Associations between clinical gait features and MRI findings were analysed using Spearman's rank correlation test and were considered to be small (ρ = 0.1-0.3), medium (ρ = 0.3-0.5) or large (ρ = 0.5-1.0).[21] We considered an α-value of 0.01 to correct for multiple testing.

3 | RESULTS

We performed gait analyses and MRI scans on 48 ankle joints of 24 adult patients with severe haemophilia. Median peak power generation in all ankle joints was 1.55 W/kg, median peak power absorption 0.35 W/kg. Median IPSG-MRI score was 8/17 and median scores for the soft-tissue subscale and osteochondral subscale were 2/9 and 7/8, respectively (Table 1).

The frequency distribution of specific MRI findings in adult patients with severe haemophilia showed no, small, moderate and large joint effusions/haemarthrosis in, respectively, 22, 20, 5 and 1 ankles. Concerning synovial hypertrophy, none was found in 20 ankle joints. Twenty-five ankle joints showed a small synovial hypertrophy, and three ankle joints were scored with moderate synovial hypertrophy. No, small, moderate and large haemosiderin was scored in, respectively, 16, 19, 10 and 3 ankle joints. MRI findings for the osteochondral subscale showed that 16 ankle joints had no surface erosions, 6 ankle joints showed a minimal degree of surface erosions and 26 ankle joints had at least half of their articular surface eroded in at least one bone. Nine ankle joints showed no subchondral cysts, 4 had at least one subchondral cyst and 25 ankle joints showed subchondral cysts in at least two bones. No cartilage degeneration was seen in 16 ankle joints. Three ankle joints had some loss of cartilage height (score: 1/4). Two ankle joints showed loss of more than or equal to half of the total volume cartilage in at least one bone. Seven ankle joints had a full-thickness loss of joint cartilage in at least a small area and 20 ankle joints possessed a full-thickness loss of joint cartilage including at least one half of the joint surface (Table 2 and Figure 3).

TABLE 1 Demographics, IPSG-MRI scores and clinical gait features of participants with haemophilic ankle arthropathy (median (range))

Characteristic	Value
Number of participants	24
Number of ankles investigated	48
Sex (M/F)	24/0
Age (years)	33 (20; 48)
Body Mass (kg)	76.4 (64.4; 114.6)
Height (cm)	177.3 (166.0; 192.0)
BMI (kg/m^2)	24.8 (31.2; 19.8)
Side (L/R)	24/24
Severe/moderate/mild[a]	24/0/0
IPSG-MRI score TTJ (/17)[b]	8 (0; 14)
IPSG-MRI soft-tissue subscore TTJ (/9)	2 (0; 6)
IPSG-MRI Osteochondral subscore TTJ (/8)	7 (0; 8)
Ankle joint peak power generation (W/kg)	1.55 (0.59; 3.12)
Ankle joint peak power absorption (W/kg)	0.35 (0.09; 1.41)

Abbreviations: BMI, body mass index; F, female; IPSG, International Prophylaxis Study Group; L, left; M, male; R, right; TTJ, tibiotalar joint.

[a]severe haemophilia: <1% of clotting factor; moderate haemophilia: 1%-5% clotting factor; mild haemophilia: >5% clotting factor.

[b]IPSG-MRI TTJ score of 0/17 means no blood-induced joint damage rated using MRI. 17/17 means most severely blood-induced joint damage possible rated using MRI.

3.1 | Clinical gait features and IPSG-MRI scores

We found a large, negative association for both the ankle joint peak power generation and the total IPSG-MRI score (ρ = −0.631, P = <.001) and ankle joint peak power generation and the IPSG-MRI osteochondral subscale (ρ = −0.706, P = <.001). A trend towards a moderate negative association between ankle joint peak power and the soft-tissue subscale was observed (ρ = −0.364, P = .011) (Table 3).

There was a medium, negative association between ankle joint peak power absorption and the total IPSG-MRI score (ρ = −0.425, P = .003) and a large, negative association between ankle joint peak power absorption and the IPSG-MRI osteochondral subscale (ρ = −0.556, P < .001). No association was found between ankle joint peak power absorption and the IPSG-MRI soft-tissue subscale (ρ = −0.139, P = .347) (Table 3).

3.2 | Clinical gait features and specific MRI findings

A larger ankle joint effusion/haemarthrosis was not associated with a lowered ankle joint peak power generation (ρ = 0.142, P = .335). A moderate negative association between ankle joint peak power generation and haemosiderin was observed (ρ = −0.400, P = .005). We also found a large, negative association between synovial

TABLE 2 Frequency distribution of abnormalities scored using IPSG-MRI scale and mean (±SD) of two clinical gait features in 48 ankles with haemophilic arthropathy

	Score				
IPSG-MRI item	**0**	**1**	**2**	**3**	**4**
Soft-tissue subscore (/9)[a]					
Effusion/haemarthrosis	20	22	5	1	n.a.
Synovial hypertrophy	20	25	3	0	n.a.
Haemosiderin	16	19	10	3	n.a.
Osteochondral subscore (/8)					
Surface erosions[b]	16	6	26	n.a.	n.a.
Subchondral cysts[c]	19	4	25	n.a.	n.a.
Cartilage degradation[d]	16	3	2	7	20

Abbreviation: N.a., not applicable.

[a]Scoring of effusion/haemarthrosis, synovial hypertrophy and haemosiderin: none (0), small (1), moderate (2) and large (3).

[b]Scoring of surface erosions: none (0), any bony surface erosion (1) and ≥half of articular surface eroded in at least one bone (2).

[c]Scoring of subchondral cysts: none (0), at least one subchondral cyst (1) and subchondral cysts in at least two bones (2).

[d]Scoring of cartilage degradation: none (0), any loss of cartilage height (1), loss of ≥half of total volume cartilage in at least one bone (2), full-thickness loss of joint cartilage in at least one area (3) and full-thickness loss of joint cartilage including at least one half of the joint surface (4).

hypertrophy and ankle joint peak power generation (ρ = −0.507, P < .001), meaning that a greater synovial hypertrophy results in a lowered ankle joint peak power generation (table 3). No associations were found between ankle joint peak power generation/absorption and any other specific MRI findings (table 3).

4 | DISCUSSION

Haemophilic ankle arthropathy originates from a combination of repetitive bleeding episodes and chronic biomechanical loading.[6] The purpose of our study was therefore to investigate the association between biomechanical gait features and MRI findings in patients with haemophilic ankle arthropathy. We did so by calculating the ankle joint peak powers, measured using 3D quantitative motion analysis. These biomechanical parameters were then correlated to the IPSG-MRI scores, which represented the severity of blood-induced ankle joint damage in patients with haemophilic ankle arthropathy.[9]

The main findings of this study seem to substantiate our initial hypothesis as PwH with severely damaged ankle joints generate and absorb less ankle joint power, which is correlated with a lowered tolerance towards ankle joint stress during walking. Potential reasons for the found correlations might arise from ankle pain during walking, limited mobility and stiffness[10] and calf muscle atrophy and/or weakness due to muscle bleedings or disuse in patients with severe haemophilia. These functional consequences in the ankle joint often lead to antalgic walking patterns. This way, patients adopt a hip strategy with less push off (ankle joint power generation) and more pull off at the end of stance phase. A new hypothesis therefore may be that these patients need to compensate by generating and absorbing more joint power in other lower limb joints and therefore induce more stress in these joints during walking.

An association between total IPSG-MRI scores and both clinical gait features was found. Brunel et al[10] previously reported weak associations between this IPSG-MRI score and kinematic gait features in haemophilic children with no to moderate ankle joint damage. These authors did however not find any associations between synovial hypertrophy findings and gait features as synovial hypertrophy lesions were not common in their study population,[10] contrarily to the current study. Our findings did show that synovial hypertrophy on MRI might serve as a good parameter to predict functional outcome, probably through the manifestation of impingement-induced pain during the inflammatory stage of haemarthroses.[22] In addition, effusion-derived haemosiderin deposit has been considered as a critical biomarker in the early phase of haemophilic arthropathy causing chronic synovitis, which then extends to the articular surface, explaining the observed association here (Figure 3).

Since the total IPSG-MRI score and osteochondral subscore are associated with the investigated clinical gait features in contrast to

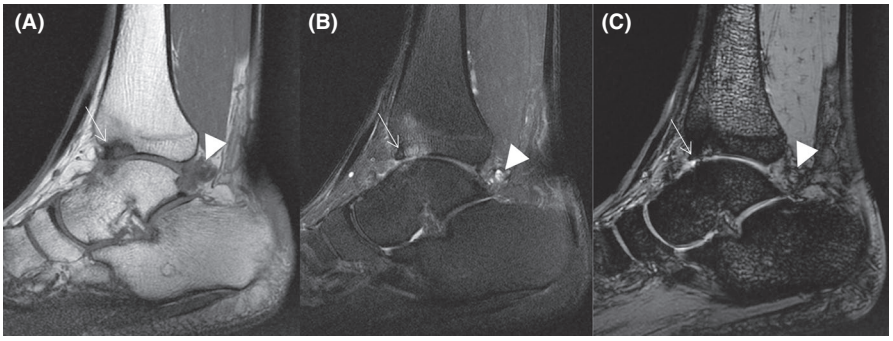

FIGURE 3 MRI spin echo T1 (A), spin echo fat-suppressed-T2 (B) and gradient-echo T2 (C)-weighted images acquired in the sagittal plane on the ankle in a patient with haemophilia. Presence of osteochondral changes with focal cartilage loss and subchondral cyst predominant at the anterior aspect of the tibia (arrows). The posterior articular recess shows limited synovial hypertrophy and haemosiderin deposit (arrow heads)

TABLE 3 Association between two clinical gait features and MRI findings

	Ankle peak power generation		Ankle peak power absorption	
	Spearman's ρ	*P*-value	Spearman's ρ	*P*-value
IPSG-MRI score	**−0.631**	**<.001**	**−0.425**	**.003**
IPSG-MRI soft-tissue subscore	−0.364	.011	−0.139	.347
IPSG-MRI osteochondral subscore	**−0.706**	**<.001**	**−0.556**	**<.001**
Effusion/haemarthrosis	0.142	.335	0.123	.405
Synovial hypertrophy	**−0.507**	**<.001**	−0.305	.035
Haemosiderin	−0.400	.005	−0.187	.204
Joint surface erosions	−0.194	.187	−0.194	.186
Subchondral cysts	−0.058	.693	−0.172	.242
Cartilage degeneration	−0.160	.278	−0.194	.186

Note: Bold *P*-values are significant ($P \leq .003$). Interpretation Spearman's ρ: 0.1-0.3 (small); 0.3-0.5 (medium); 0.5-1.0 (large).

Abbreviation: IPSG, International Prophylaxis Study Group.

each specific MRI finding, except for synovial hypertrophy and haemosiderin, it may imply that the IPSG-MRI score is a clinically valuable scale in adult patients with haemophilic ankle arthropathy and rates high according to 'diagnostic accuracy efficacy'.[23]

Foppen et al[24] suggested that joint effusion is not specific for haemophilic ankle arthropathy and we indeed did not find an association between joint effusion on MRI and clinical gait features.

One study in a similar patient population described that more than 4 bleeding episodes cause substantial joint damage.[25] Other research found that an annual joint bleeding rate of <3 bleeds, dependent on the size and duration of the bleeds, is required to maintain a healthy joint status.[26] Linking these statements to our current findings may suggest that whenever PwH have <3 ankle joint bleeds per year, dependent on the size and duration of the bleeds, their clinical gait features would remain unaffected.

A limitation to our study is the amount of participants in our study group. However, some considerations need to be addressed to put this in perspective. First, epidemiological data by the Belgian Hemophilia Association show that about 440 people suffer from severe haemophilia in Belgium.[27] Based on this, we managed to investigate roughly 10% of all Belgian patients with severe haemophilia between 18 and 55 years of age with our sample group. Second, the observed frequency distributions of blood-induced ankle joint lesions found on MRI in this study closely resemble the actual clinical situation, since PwH either have no damage due to good preventive treatment strategies, or they have severely damaged ankle joints due to multiple bleeding episodes.[25,26,28] We did not, from a statistical viewpoint, account for differences in walking speed. Participants were asked to walk at a self-selected and comfortable speed to not influence their natural gait pattern, and it would therefore be unnatural to account for walking speed in the statistical measurements. On top, the effect of increased walking speed on joint kinetics only plays a significant role when the walking speed supersedes 6 km/h,[29] which was never the case in any of the participants. Also, due to the absence of sufficient medical background information on the other lower limb joints, we were not able to quantify the amount of arthropathy in all of the lower limb joints of the patients. We were therefore unable to account for this in the results. However, these two latter limitations do need to be taken into account when interpreting the results.

The findings in this study demonstrated a relationship between structural and functional findings in patients with haemophilic ankle arthropathy. It may therefore be clinically interpreted that musculoskeletal management in these patients could be improved by shifting our focus on preserving the correct amount of ankle joint stress. This could be perceived by using specific exercise therapies, adapted footwear or surgical interventions, amongst other therapeutic interventions. These results may also furthermore support the use of 3D gait analysis in PwH to monitor the functional consequences of blood-induced ankle joint damage. Future longitudinal studies are needed to confirm the clinical relevance of these findings.

5 | CONCLUSION

We found five associations between two clinical gait features and several MRI findings in adults with haemophilia. Both the IPSG-MRI score and the osteochondral subscale were significantly associated with ankle joint peak power generation and absorption. Synovial hypertrophy and haemosiderin were the only MRI findings associated with ankle joint peak power generation. Specific MRI findings, including joint effusion, joint surface erosion(s), subchondral cysts and cartilage degeneration were not directly associated with clinical gait features. PwH with severe blood-induced ankle joint damage showed a lower tolerance towards joint stress, whereas patients with no MRI-scored ankle joint damage were found to have a preserved tolerance towards joint stress during walking.

ACKNOWLEDGEMENTS

The authors would like to sincerely commend the medical staff of the Hemophilia Reference Center of the University Hospitals Leuven and the Hemophilia Treatment Center of Cliniques Universitaires Saint-Luc for their aid in recruiting participants. We furthermore like to thank Steffen Fieuws for his insights and consultancy on the statistical approach of these data. The study was supported by The Pfizer ASPIRE research grant (WI199899) and The Novo Nordisk Access to Insight Clinical Research Grant (KD). Sponsors had no involvement in this article.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

ME wrote the paper. ME, FS and KD designed the research study. ME and J-BP collected data. KP and CH managed the recruitment of participants. ME, KP, CH, J-BP and KD analysed the data. FS, SL and KD critically revised the paper. FS, SL and KD revised the statistical analysis. ME, KP and CH clinically interpreted the results. J-BP analysed MRI findings. All authors read and approved the final version of the manuscript before submission.

ORCID

Maarten Eerdekens https://orcid.org/0000-0003-0809-4809
Cédric Hermans https://orcid.org/0000-0001-5429-8437
Sébastien Lobet https://orcid.org/0000-0002-3829-6850

REFERENCES

1. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. *Blood*. 2015;125:2038-2044.
2. Lafeber FPJG, Miossec P, Valentino LA. Physiopathology of haemophilic arthropathy. *Haemophilia*. 2008;14(s4):3-9.
3. Gringeri A, Lundin B, Von Mackensen S, et al. A randomized clinical trial of prophylaxis in children with hemophilia A (the ESPRIT study). *J Thromb Haemost*. 2011;9:700-710.
4. Mccarthy A, Moore A, Redhead L, Mclaughlin P, Iorio A, Chowdary P. Development of haemophilic arthropathy of the ankle: Results of a Delphi consensus survey on potential contributory factors. *Haemophilia*. 2015;21:116-123.
5. Ling M, Heysen JPH, Duncan EM, Rodgers SE, Lloyd JV. High incidence of ankle arthropathy in mild and moderate haemophilia A. *Thromb Haemost*. 2011;105(02):261-268.
6. Hooiveld M, Roosendaal G, Vianen M, Van den Berg M, Bijlsma J, Lafeber F. Blood-induced joint-damage: longterm effects in vitro and in vivo. *J Rheumatol*. 2003;30:339-344.
7. Rodriguez-Merchan EC, Jimenez-Yuste V, Aznar JA, et al. Joint protection in haemophilia. *Haemophilia*. 2011;17:1-23.
8. Keshava SN, Gibikote SV, Mohanta A, et al. Ultrasound and magnetic resonance imaging of healthy paediatric ankles and knees: A baseline for comparison with haemophilic joints. *Haemophilia*. 2015;21(3):e210-e222.
9. Lundin B, Manco-Johnson ML, Ignas DM, et al. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. *Haemophilia*. 2012;18:962-970.
10. Brunel T, Lobet S, Deschamps K, et al. Reliability and clinical features associated with the IPSG MRI tibiotalar and subtalar joint scores in children, adolescents and young adults with haemophilia. *Haemophilia*. 2018;24:141-148.
11. Stephensen D, Drechsler WI, Scott OM. Biomechanics of lower limb haemophilic arthropathy. *Blood Rev*. 2012;26:213-221.
12. 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;16:813-821.
13. Lobet S, Hermans C, Bastien GJ, Massaad F, Detrembleur C. Impact of ankle osteoarthritis on the energetics and mechanics of gait: The case of hemophilic arthropathy. *Clin Biomech*. 2012;27:625-631.
14. Deschamps K, Eerdekens M, Desmet D, Matricali GA, Wuite S, Staes F. Estimation of foot joint kinetics in three and four segment foot models using an existing proportionality scheme: application in paediatric barefoot walking. *J Biomech Elsevier Ltd*. 2017;61:168-175.
15. MacWilliams BA, Cowley M, Nicholson DE. Foot kinematics and kinetics during adolescent gait. *Gait Posture*. 2003;17:214-224.
16. Dixon PC, Böhm H, Döderlein L. Ankle and midfoot kinetics during normal gait: a multi-segment approach. *J Biomech*. 2012;45:1011-1016.
17. Fouasson-Chailloux A, Maugars Y, Vinatier C, et al. Clinical relevance of 3D gait analysis in patients with haemophilia. *Haemophilia*. 2018;24:703-710.
18. Eerdekens M, Staes F, Matricali GA, Wuite S, Peerlinck K, Deschamps K. Quantifying clinical misinterpretations associated to one-segment kinetic foot modelling in both a healthy and patient population. *Clin Biomech Elsevier*. 2019;67:160-165.
19. Leardini A, Benedetti MG, Berti L, Bettinelli D, Nativo R, Giannini S. Rear-foot, mid-foot and fore-foot motion during the stance phase of gait. *Gait Posture*. 2007;25:453-462.
20. Saraswat P, MacWilliams BA, Davis RB, D'Astous JL. Kinematics and kinetics of normal and planovalgus feet during walking. *Gait Posture* Elsevier B.V. 2014;39:339-345.
21. Corder GW, Foreman DI. *Nonparametric Statistics for Non-Statisticians: A Step-by-Step Approach*. Hoboken, NJ: Wiley. 2011.
22. Melchiorre D, Manetti M, Matucci-cerinic M. Pathophysiology of Hemophilic Arthropathy. *J Clin Med*. 2017;63:1-8.
23. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Mak*. 1991;11(2):88-94.
24. Foppen W, van der Schaaf IC, Witkamp TD, Fischer K. Is joint effusion on MRI specific for haemophilia? *Haemophilia*. 2014;20:582-586.
25. Funk MB, Schmidt H, Becker S, et al. Modified magnetic resonance imaging score compared with orthopaedic and radiological scores for the evaluation of haemophilic arthropathy. *Haemophilia*. 2002;8:98-103.
26. Gringeri A, Ewenstein B, Reininger A. The burden of bleeding in haemophilia: is one bleed too many? *Haemophilia*. 2014;20:459-463.
27. Henrard S, Devleesschauwer B, Beutels P, et al. The health and economic burden of haemophilia in Belgium: a rare, expensive and challenging disease. *Orphanet J Rare Dis*. 2014;9:39.
28. Groen W, Van Der Net J, Bos K, et al. Joint health and functional ability in children with haemophilia who receive intensive replacement therapy. *Haemophilia*. 2011;17:783-790.
29. Eerdekens M, Deschamps K, Staes F. The impact of walking speed on the kinetic behaviour of different foot joints. *Gait Posture Elsevier*. 2019;68:375-381.

How to cite this article: Eerdekens M, Peerlinck K, Staes F, et al. Clinical gait features are associated with MRI findings in patients with haemophilic ankle arthropathy. *Haemophilia*. 2020;00:1–7. https://doi.org/10.1111/hae.13925