Check for updates

Haemophilia

WILEY

Haemophilia WFH EAHAD

ORIGINAL ARTICLE

Beyond the Surface: Bone Marrow Oedema as a Hidden Marker of Pain in Haemophilic Ankles

Sébastien Lobet[1,2,3] | Sylvain Guillaume[4] | Valérie-Anne Chantrain[3,5,6] | Marin Halut[4,7] | Anthe Foubert[5,6] | Lokmane Taihi[4] | Thomas Kirchgesner[4] | Nathalie Roussel[5] | Cedric Hermans[1] | Catherine Lambert[1] | Nicolas Michoux[4] | Frederic E. Lecouvet[4]

[1]Haemostasis and Thrombosis Unit, Division of Haematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium | [2]Service D'ergothérapie Et De Kinésithérapie, Cliniques Universitaires Saint-Luc, Brussels, Belgium | [3]Neuromusculoskeletal Lab (NMSK), Secteur des Sciences de La Santé, Institut de Recherche Expérimentale Et Clinique, Université Catholique de Louvain, Brussels, Belgium | [4]Institut De Recherche Expérimentale & Clinique (IREC) – Department of Radiology, Université Catholique de Louvain (UCLouvain) – Cliniques Universitaires Saint Luc, Brussels, Belgium | [5]Research Group (MOVANT), Department of Rehabilitation Sciences and Physiotherapy (REVAKI), University of Antwerp, Wilrijk, Belgium | [6]Pain in Motion International Research Group, Brussels, Belgium | [7]Department of Radiology, Centre Hospitalier de L'université De Montréal (CHUM), Montréal, Québec, Canada

Correspondence: Sébastien Lobet (sebastien.lobet@uclouvain.be)

Received: 21 March 2025 | **Revised:** 9 December 2025 | **Accepted:** 17 December 2025

Keywords: bone marrow oedema | haemophilia | haemophilic arthropathy | IPSG | magnetic resonance imaging | ultrasonography

ABSTRACT

Introduction:: Magnetic resonance imaging (MRI) is the gold standard for assessing haemophilic arthropathy using the IPSG scale. However, MRI-detected abnormalities often correlate poorly with pain, suggesting that structural damage alone cannot explain symptoms. Assessing additional features such as bone marrow oedema (BME) may better capture disease activity and pain in people with haemophilia (PwH).

Aim: This study aimed to evaluate the presence and extent of bone BME in the ankles of PwH, assess the reproducibility of MRI scoring for BME and IPSG, and examine correlations between MRI findings, clinical parameters, pain, and ultrasound results.

Methods: A prospective study was conducted on 56 PwH, assessing 108 ankle joints via MRI using a 3T scanner. IPSG and BME scores were independently assessed by two blinded radiologists. Statistical analyses assessed inter-reader agreement, correlations between MRI scores, and their associations with ultrasound (HEAD-US), joint health (HJHS), and pain intensity over the past 24 h and 4 weeks.

Results: BME was observed in 45% of left and 34% of right ankles. Both IPSG and BME scores showed high reproducibility. BME scores correlated strongly with pain ($\rho = 0.61$–0.68) and moderately with joint health (HJHS, $\rho = 0.56$), whereas IPSG total scores showed moderate correlations with pain ($\rho = 0.46$–0.51). Resampling analyses confirmed stronger BME-pain associations.

Conclusions: This study shows that BME is common in haemophilic ankles and more strongly associated with pain and joint health than IPSG scores. Integrating BME into MRI assessments may enhance evaluation and monitoring of haemophilic joint disease.

1 | Introduction

Haemophilic arthropathy is an irreversible condition that remains a leading cause of disability and pain in people with haemophilia (PwH), significantly impacting their quality of life [1]. Chronic pain is reported in one out of two individuals with severe haemophilia [2], with the ankle being the most frequently affected joint and the primary source of pain in this population [3].

© 2026 John Wiley & Sons Ltd.

TABLE 1 | Overview of the scoring procedures: IPSG MRI scale, BME quantification score, and HEAD-US protocol.

IPSG MRI scale		TTJ	STJ	Total
Soft tissue changes items				
	Effusion/hemarthrosis	(/3)	(/3)	
	Synovial hyperthrophy	(/3)	(/3)	
	Haemosiderin	(/3)	(/3)	
Soft tissue changes subscore		IPSG TT Soft (/9)	IPSG ST Soft (/9)	
Osteochondral changes items				
	Surface erosions involving subchondral cortex/joint margins	(/2)	(/2)	
	Subchondral cysts	(/2)	(/2)	
	Cartilage degeneration	(/4)	(/4)	
Osteochondral tissue changes subscore		IPSG TT OC (/8)	IPSG ST OC (/8)	
IPSG total score		IPSG TT (/17)	IPSG ST (/17)	IPSG total (/34)
BME quantification score				
		Medial malleolus (/3)	anterior talar surface (/3)	
		Medial tibial surface (/3)	posterior talar surface (/3)	
		Lateral tibial surface (/3)	anterior calcaneal surface (/3)	
		Lateral malleolus (/3)	posterior calcaneal surface (/3)	
		Talar surface facing medial maleolus (/3)	anteromedial talar surface (/3)	
		Talar surface in front of medial medial tibial surface (/3)	anteromedial calcaneal surface (/3)	
		Talar surface in front of medial lateral tibial surface (/3)		
		Talar surface facing lateral maleolus (/3)		
		BME TT (/24)	BME ST (/18)	BME total (/42)
HEAD-US protocol (TTJ only)				
	Hypertrophic synovium (HEAD-US synov.)	(/2)	x	
	Bone changes (HEAD-US bone)	(/2)	x	
	Cartilage changes (HEAD-US cartilage)	(/4)	x	
HEAD-US total		(/8)	x	HEAD-US total (/8)

Abbreviations: BME: bone marrow oedema; GE: gradient echo; HEAD-US: haemophilia early arthropathy detection-ultrasound; HJHS: haemophilia joint health score; IPSG: international prophylaxis study group; MRI: magnetic resonance imaging; PD: proton density; PwH: people with haemophilia; RDC: reproducibility detection coefficient; STJ: subtalar joint; TSE: turbo spin echo; TTJ: tibiotalar joint; US: ultrasound.

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Magnetic resonance imaging (MRI) is the gold standard for evaluating joint damage in PwH. It provides a comprehensive, non-invasive assessment of both osteochondral and soft tissue changes, allowing early detection of haemophilic arthropathy and monitoring of disease progression [4–7]. The International Prophylaxis Study Group (IPSG) scale is currently the reference MRI scoring system for haemophilic joints, evaluating both osteochondral damage (surface erosions, subchondral cysts, and cartilage degradation) and soft tissue changes (effusion, synovial hypertrophy, and hemosiderin deposition) [8]. The IPSG scale is the standard research tool for assessing haemophilic joints, mainly designed for multi-centre studies, but it is not yet validated for routine clinical use. It has demonstrated high intra- and inter-reader reliability for assessing haemophilic arthropathy of the ankle joint, including the tibiotalar (TTJ) and subtalar joints (STJ) [9]. However, while this reliability supports its use for consistent scoring, other aspects such as accuracy and responsiveness remain less well established for detecting and monitoring haemophilic arthropathy.

Recent studies have investigated the relationship between structural joint damage observed through MRI, functional impairment, and pain in individuals with haemophilia [10–13]. Collectively, these investigations suggest a notable discordance between imaging findings and patient-reported pain severity. Several studies, including those by Roussel et al. [12] and Chantrain et al. [13], have shown that patient-reported pain intensity in PwH does not strongly correlate with MRI- or ultrasound-detected joint damage, indicating that factors beyond structural deterioration contribute to pain perception. These findings highlight the complex and multifactorial nature of pain in haemophilia-related joint disease, suggesting that structural damage alone may not fully explain functional limitations and discomfort. However, most available studies are cross-sectional, and longitudinal evidence linking structural changes over time with pain remains limited.

The IPSG score does not incorporate the assessment of bone marrow oedema (BME), although being a key feature observed in various degenerative and inflammatory joint conditions. BME is characterized by an intermediate-to-low signal intensity (SI) on fat-sensitive T1-weighted images and high-to-intermediate SI on fluid-sensitive T2-weighted images, indicating increased water content associated with local inflammation. Its presence has been strongly linked to pain and disease activity in multiple joint disorders [14–19].

In the ankle and foot, BME has been identified in multiple conditions, including trauma, stress fractures, complex regional pain syndrome, inflammatory disorders, and in transient or migratory BME syndromes, whose aetiology remains poorly understood [20]. Its presence near ankle joint surfaces has also been associated with pain and with clinical improvement when the signal regresses [21].

Histologically, however, MRI-detected "BME" represents a heterogeneous spectrum of subchondral changes rather than pure interstitial oedema. Studies have shown that areas of BME on MRI may consist of combinations of fibrosis, trabecular microfractures, necrosis, haemorrhage, cystic or pseudocystic change, or fibrovascular marrow replacement [18, 19, 22, 23]. Although terms such as "BME-like signal changes" or "bone marrow lesions" may better reflect this histological heterogeneity, we retain the term BME for clarity and consistency with the haemophilia literature.

In haemophilic ankles, MRI findings often fail to reliably explain joint pain, as current MRI scoring systems do not account for BME [12]. Based on our experience, subchondral BME is frequently observed in haemophilic ankles, yet it remains unaddressed in conventional MRI scoring scales.

We hypothesized that BME contributes to joint pain and may provide complementary information to existing MRI assessments. The aim of this study was therefore to evaluate the presence and extent of BME in haemophilic ankles, assess the reproducibility of MRI scoring for BME and IPSG, and examine correlations between MRI findings, pain, clinical parameters, and ultrasound results.

2 | Materials and Methods

2.1 | Participants and Procedure

Participants were recruited by phone before their annual consultation at the Haemophilia Comprehensive Treatment Centre of the Cliniques universitaires Saint-Luc (Brussels) and the Antwerp University Hospital (Edegem), two of the main Belgian reference centres for haemophilia care. Together, these centres provide follow-up for a large share of the approximately 1,150 PwH registered in Belgium. Eligible candidates were adult males (≥18 years) with moderate or severe haemophilia A or B on a stable treatment regimen for at least six months. Presence of ankle arthropathy or pain was not required for inclusion, as the study aimed to capture the full spectrum of ankle joint involvement in PwH. Exclusion criteria included MRI contraindications, prior ankle arthrodesis or prosthesis, and recent hemarthrosis (within one month) to minimize bias in joint and pain evaluation. Eligibility was first verified through a review of medical records before contacting potential participants, and reconfirmed during the study visit. Participants were then contacted by phone by the study investigators (VAC and AF), who provided study information, confirmed eligibility, and arranged the assessment schedule. Both examiners, VAC and AF, were PhD students not involved in routine clinical care at either haemophilia centre and had no prior relationship with the participants. The study received ethical approval (B300201942304, 2019/28OCT/469), and all participants provided written informed consent.

2.2 | MRI Acquisition

All participants underwent bilateral ankle MRI at Cliniques universitaires Saint-Luc (UCLouvain, Brussels) using the same 3T scanner (Signa Premier, GE Healthcare) and standardized protocol, regardless of their recruitment site. The imaging protocol included sagittal high-resolution 3D T1-weighted turbo spin echo images, along with sagittal, coronal, and axial proton density (PD)-weighted images using the Dixon technique. Sagittal T2*-weighted gradient echo images were also acquired. A 3.0T HD

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

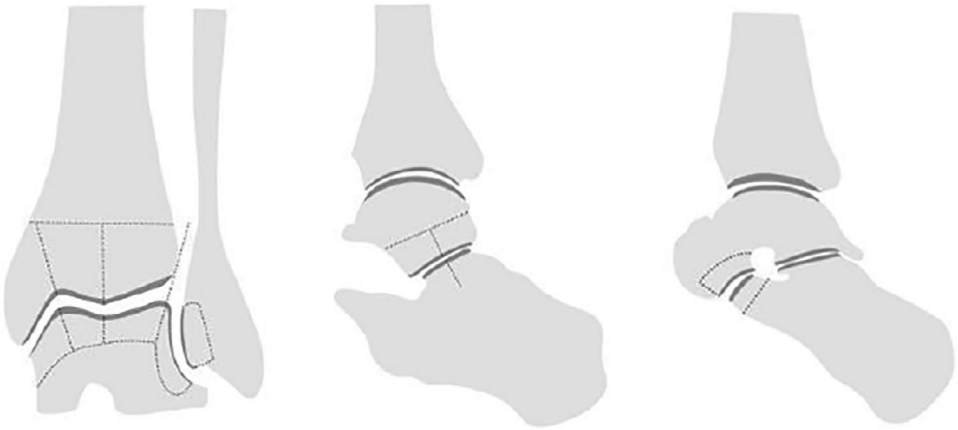


FIGURE 1 | Schematic representations of the ankle compartments used for scoring subchondral bone marrow oedema, inspired by the magnetic resonance imaging score approach (WORMS). The TTJ is analysed in the coronal plane, dividing the talar dome into four sections, the distal tibia into three, and the articular surface of the lateral malleolus into one. The STJ is examined in the sagittal plane, with its postero-lateral portion divided into two compartments and its antero-medial portion into one, corresponding to the talar and calcaneal articular surfaces.

8-channel Foot and Ankle Coil (GE HealthCare) was used for all scans. MRI sequence parameters are presented in Annex 1.

2.3 | MRI Analysis and Scoring Methodology for Joint Assessment

All MRI sequences were analysed on PACS workstations using windowing, scroll, link, and multiplanar reformat tools. For PD-weighted images, only water-only (fat-suppressed) and in-phase (PD-weighted) images were considered. The TTJ and STJ were evaluated using the IPSG-MRI score, with two radiologists (SG and FL) independently scoring all sequences while blinded to other data. SG has 5 years of experience in musculoskeletal MRI, while FL is a senior musculoskeletal radiologist with 30 years of experience in this field. The IPSG-MRI scoring system assigns subscores for soft-tissue (0–9) and osteochondral (0–8) changes (8). Soft-tissue abnormalities—effusion/hemarthrosis, synovial hypertrophy, haemosiderin deposition—are graded 1–3 for small to large involvement; osteochondral damage is scored 1 point per positive finding across erosions, cysts, and cartilage defects (maximum = 17) (Table 1). Joints were classified as "abnormal" if the IPSG-sum score was ≥1/17, unless solely due to effusion.

2.4 | Quantification and Grading of Bone Marrow Oedema

BME was characterized as "an ill-defined area of infiltration within the subchondral bone marrow, exhibiting intermediate to low SI on T1-weighted MR images and intermediate to high SI on water-only PD MR images" [22]. BME quantification was performed using sagittal and coronal water-only PD-weighted MR images. BME quantification followed a compartment-based semi-quantitative approach adapted from the Whole-Organ Magnetic Resonance Imaging Score (WORMS), a validated MRI scoring system extensively used for grading BME in knee osteoarthritis [24] (Figure 1). WORMS was selected for its simplicity, extensive use, and strong validation in large cohorts. Our compartmental schematics were also directly inspired by the regional mapping structure of WORMS, making it an appropriate framework for adaptation to the ankle. Using sagittal and coronal water-only PD-weighted images, the TTJ and STJ were systematically divided into predefined subregions, and BME was graded from 0 to 3 based on its maximal depth beneath the subchondral bone plate, following the principles of WORMS (Table 1). Grade 0 corresponded to no BME, grade 1 corresponded to a depth of 1–5 mm, grade 2 to a depth of 6–10 mm, and grade 3 to a depth > 10 mm. If confluent BME affected both TTJ and STJ surfaces within the talus, a grade of 3 was assigned to both compartments (Figure 2).

2.5 | US Assessment

All ankle joints were assessed using US with a 3.0–13.0 MHz linear probe (Esaote, MyLab Gamma, Genova, Italy). The Haemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) protocol was applied to detect and quantify disease activity, including hypertrophic synovium and osteochondral damage affecting cartilage and bone [25]. This evaluation produced the HEAD-US sum score (0–8), where higher scores indicate more severe joint abnormalities (Table 1). For cartilage and bone assessment, the US examination focused specifically on the talar dome. All US examinations were performed by the same examiner (VAC), trained in the HEAD-US protocol, to ensure consistency and minimize inter-operator variability. The examiner was blinded to MRI results (assessed by radiologists) and pain scores (assessed by AF), but not to the HJHS, which she also performed.

2.6 | Joint Health and Pain Assessment

The Haemophilia Joint Health Score, version 2.1 (HJHS 2.1), was applied by the same investigator (VAC) to evaluate ankle joint health [25]. This score assesses swelling, duration of swelling, muscle atrophy, crepitus on motion, loss of flexion, loss of extension, joint pain, and strength, with a maximum of 20 points

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

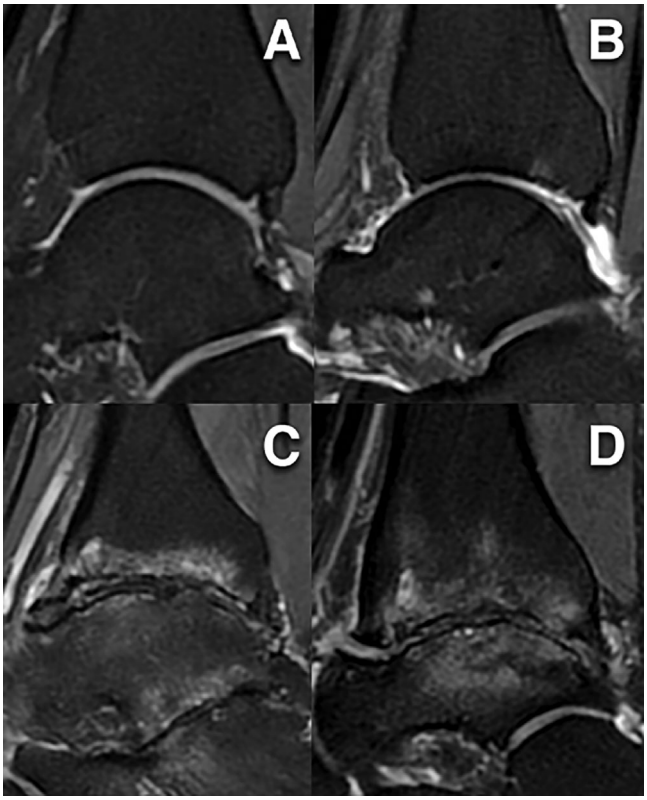


FIGURE 2 | Proton-density weighted MRI images showing various BME scores in the TT joint grade 0: A, grade 1: B, grade 2: C, grade 3: D.

per ankle (the gait score was not included). Higher scores indicate greater severity, and a score of ≥1/20 was considered positive.

Participants rated their ankle pain intensity using a 10-point Numeric Rating Scale (NRS), from 0 ("no pain") to 10 ("worst pain imaginable"), for both the past 24 h (NRS-24H) and the past 4 weeks (NRS-4 W) [26]. The NRS was administered in written form as a subjective self-assessment tool.

US assessments and joint health scores were systematically performed on the same day as the participant's annual haemophilia consultation. MRI examinations were, whenever possible, scheduled on that same day; however, for participants living close to the treatment centre, the MRI could exceptionally be performed within a short interval (maximum of 10 days) from the clinical evaluation. In all cases, pain questionnaires were completed on the same day as the MRI. All study procedures were conducted separately from, and completed before, the clinical consultation to avoid bias and minimize participant burden.

2.7 | Statistical Analysis

Summary statistics were reported as mean [95% CI] for normally distributed data and median [95% CI] for non-normally distributed data (according to Shapiro-Wilk's test). Reproducibility of MRI measurements was evaluated using the Bland–Altman method [27], computing the mean bias, precision (±1.0 × SD), and the reproducibility detection coefficient (RDC = 1.96 × SD), which represents the 95% limits of agreement between readers. A one-sample, two-tailed *t*-test was performed to assess whether the mean bias was significantly different from zero. The grading of BME was performed by the same two radiologists (SG and FL) who independently scored the IPSG-MRI scale, both being blinded to clinical and ultrasound data. Inter-reader agreement was assessed on a subset of 30 patients (pooling left and right ankles), evaluated by the junior (SG) and senior (FL) readers, while the remaining patients were scored by a single reader (SG). Correlations between MRI scores of the left and right ankles were examined using Spearman's rho, treating ankles from the same patient as a cluster. Because significant correlations were found between sides, subsequent analyses were stratified by left and right ankles to avoid violating independence assumptions and to preserve the validity of correlation estimates, including those between MRI scores, US findings, and clinical parameters.

To compare the strength of correlations between MRI measurements and clinical parameters, a resampling procedure without replacement was applied, drawing 300 random samples ($N = 43$ patients) from the full cohort. This resampling approach was used to obtain more robust estimates of the correlation coefficients and to enable a statistical rather than qualitative comparison between them by approximating their sampling distributions through repeated random sampling. A two-sided paired *t*-test (or Wilcoxon test when non-parametric assumptions applied) was performed, and the mean or median difference in Spearman's rho was derived.

A p value < 0.05 was considered statistically significant. Correlation strength was classified as weak (rho < 0.50), moderate ($0.50 \leq$ rho < 0.70), or strong (rho > 0.70) [28]. All statistical analyses were conducted using MATLAB (R2021b Update 2, MathWorks) and MedCalc (v20.211).

3 | Results

3.1 | Study Population and Ankle Joint Characteristics

A total of 104 PwH were initially contacted for participation. Thirty-eight declined the MRI examination, mainly due to time constraints (31/38) or discomfort related to the procedure (4/38), while three did not specify a reason. Additionally, nineteen participants who initially agreed to take part did not complete the NRS pain questionnaires and were therefore excluded. Ultimately, 56 PwH were included in the study, with four ankles excluded due to prior surgical arthrodesis or arthroplasty. The final analysis comprised 55 left and 53 right ankle joints. The distribution of IPSG and BME scores, along with their subscores for the TTJ and STJ, is presented in Table 2.

Among the total IPSG scores, 20% of left ankles and 19% of right ankles showed no structural abnormalities (IPSG total = 0). Soft tissue changes were relatively uncommon, with 69% of left ankles and 62% of right ankles showing no synovial involvement in the TTJ (IPSG subscore for soft tissue changes in the TTJ-IPSG TT Soft = 0), and 67% of left ankles and 70% of right ankles showing no soft tissue changes in the STJ (IPSG subscore for soft tissue changes in the STJ-IPSG ST Soft = 0).

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | Population characteristics and results of scorings.

	Measurements[a] [95%CI] in patient and in left ankle/right ankle	Range given by the 10-90th percentiles left ankle	Range given by the 10-90th percentiles right ankle	Number of score = 0 left ankle	Number of score = 0 right ankle
N participants	56				
N ankles	55 (left)/53 (right)				
Age (years)	34 [32; 42]				
Height (cm)	177 [175; 178]				
Weight (kg)	80 [74; 84]				
BMI	26.0 [24.7; 27.3]				
Haemophilia type					
A	43				
B	13				
Factor deficiency					
Mild	4				
Moderate	13				
Severe	39				
Past/current presence of an inhibitor	5/0				
HJHS					
Ankle score (max. 20 points) (N=108)	3 [1; 7]				
Total joint score (max. 120 points)	14 [6; 33]				
NRS-24H	0.5 [0; 2.75] (left)/1 [0; 2] (right)				
NRS-4W	1.5 [0; 4.75] (left)/2 [0; 4] (right)				
Pain medication					
Pain killer + AINS cox2-inhibitor	20 (35.7%)				
Pain killer—recombinant factor	5 (8.9%)				
Recombinant factor	5 (8.9%)				
Weak opioid	1 (1.8%)				
No treatment	25 (44.6%)				

(Continues)

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | (Continued)

	Measurements[a] [95%CI] in patient and in left ankle/right ankle	Range given by the 10-90th percentiles left ankle	Range given by the 10-90th percentiles right ankle	Number of score = 0 left ankle	Number of score = 0 right ankle
MRI assessment					
IPSG TT Soft	0.00 [0.00; 0.00]/0.00 [0.00; 0.00]	[0.00; 4.90]	[0.00; 4.02]	38 (69%)	33 (62%)
IPSG TT OC	2.00 [0.00; 5.00]/3.00 [0.00; 6.00]	[0.00; 8.00]	[0.00; 8.00]	26 (47%)	24 (45%)
IPSG TT	2.00 [0.00; 5.23]/4.00 [1.00; 7.00]	[0.00; 10.8]	[0.00; 10.0]	22 (40%)	16 (30%)
IPSG ST Soft	0.00 [0.00; 0.00]/0.00 [0.00; 0.00]	[0.00; 2.00]	[0.00; 2.02]	37 (67%)	40 (70%)
IPSG ST OC	0.00 [0.00; 0.00]/0.00 [0.00; 2.00]	[0.00; 7.90]	[0.00; 8.00]	39 (70%)	32 (60%)
IPSG ST	1.00 [0.00; 1.00]/1.00 [0.00; 3.00]	[0.00; 8.00]	[0.00; 8.00]	27 (49%)	24 (45%)
BME TT	0.00 [0.00; 6.23]/3.00 [0.00; 9.00]	[0.00; 20.8]	[0.00; 19.0]	32 (58%)	25 (47%)
BME ST	0.00 [0.00; 0.00]/0.00 [0.00; 1.10]	[0.00; 12.0]	[0.00; 13.0]	40 (73%)	32 (60%)
IPSG total	5.00 [2.00; 6.23]/7.00 [4.90; 8.00]	[0.00; 16.0]	[0.00; 16.0]	11 (20%)	10 (19%)
BME total	1.00 [0.00; 7.00]/8.00 [1.00; 10.1]	[0.00; 30.8]	[0.00; 30.0]	25 (45%)	18 (34%)

Abbreviations: BME ST: bone marrow oedema score for the subtalar joint; BME total: bone marrow oedema overall score for both the tibiotalar and subtalar joints; BME TT: bone marrow oedema score for the tibiotalar joint; HJHS: haemophilia joint health score; IPSG ST OC: IPSG subscore for osteochondral changes in the subtalar joint; IPSG ST soft: IPSG subscore for soft tissue changes in the subtalar joint; IPSG ST: IPSG total score for the subtalar joint; IPSG total: IPSG overall score for both the tibiotalar and subtalar joints; IPSG TT OC: IPSG subscore for osteochondral changes in the tibiotalar joint; IPSG TT: IPSG total score for the tibiotalar joint; NRS-24H: numeric rating scale for pain over the past 24 h; NRS-4 W: numeric rating scale for pain over the past 4 weeks; IPSG TT Soft: IPSG subscore for soft tissue changes in the tibiotalar joint; PwH: people with haemophilia.

[a]Median value.

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Osteochondral changes were more frequent, with 53% of left ankles and 55% of right ankles exhibiting some degree of osteochondral damage in the TTJ (IPSG subscore for osteochondral changes in the TTJ-IPSG TT OC > 0). In contrast, 70% of left ankles and 60% of right ankles showed no osteochondral changes in the STJ (IPSG subscore for osteochondral changes in the STJ-IPSG ST OC = 0).

BME was commonly observed, affecting 45% of left ankles and 34% of right ankles (BME overall score for both the TTJ and STJ-BME total > 0). It was absent in 58% of left ankles and 47% of right ankles in the TTJ (BME score for the TTJ-BME TT = 0), and in 73% of left ankles and 60% of right ankles in the STJ (BME score for the STJ-BME ST = 0).

3.2 | Reproducibility

Results from the Bland-Altman analysis are given in Annexes 2 and 3. Small biases were observed across all scores, with absolute differences well below one scoring point. RDC values remained low overall, with all IPSG and BME subscores ≤1 scoring point, while total IPSG and BME scores had RDC values of ≤2 scoring points.

3.3 | Correlation Between MRI, US, Pain and Joint Health Scores

Correlation measures are reported in Table 3, and additional correlations between IPSG scores and BME scores are provided in Annex 4. Only IPSG TT OC, IPSG TT, IPSG total, BME TT, and BME total showed significant correlations with joint health and US scores.

The IPSG TT OC showed a moderate correlation with NRS-24H (rho_left = 0.62, rho_right = 0.59), NRS-4 W (rho_left = 0.59, rho_right = 0.67), and HJHS (rho_left = 0.64, rho_right = 0.71), while also strongly correlating with US-based cartilage (rho_left = 0.82, rho_right = 0.79), bone (rho_left = 0.85, rho_right = 0.78), and total HEAD-US scores (rho_left = 0.81, rho_right = 0.81).

Similarly, BME TT (TTJ alone) and BME total (TTJ and STJ) showed strong correlations with NRS-24H (BME TT: rho_left = 0.76, rho_right = 0.69; BME total: rho_left = 0.74, rho_right = 0.80) and NRS-4 W (BME TT: rho_left = 0.73, rho_right = 0.74; BME total: rho_left = 0.79, rho_right = 0.84), indicating that higher BME scores were associated with greater pain intensity. BME TT also showed a moderate correlation with HJHS (rho_left = 0.64, rho_right = 0.69).

Additionally, strong correlations were observed between BME TT, BME total and the total HEAD-US score (BME TT: rho_left = 0.76, rho_right = 0.75; BME total: rho_left = 0.73, rho_right = 0.73), US-based cartilage (BME TT: rho_left = 0.76, rho_right = 0.70; BME total: rho_left = 0.71, rho_right = 0.71) and bone (BME TT: rho_left = 0.79, rho_right = 0.75; BME total: rho_left = 0.74, rho_right = 0.75) subscores.

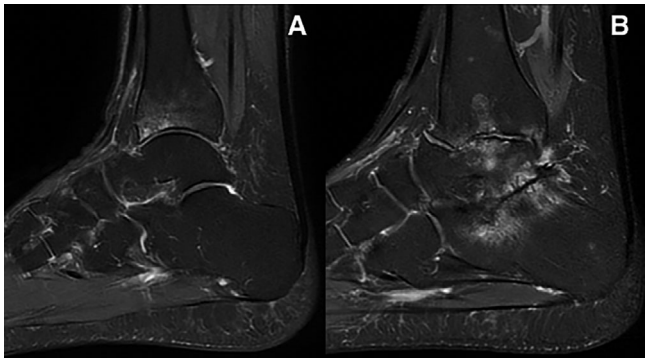


FIGURE 3 | (A) A minimally symptomatic patient with moderate arthropathy (IPSG TT 5/17) presents a low BME score (BME TT 7/24), aligning with mild clinical symptoms (HJHS 4/20, NRS-24 h 3/10, NRS-4w 4/10). (B) A markedly symptomatic patient with severe arthropathy (IPSG TT 7/17, IPSG ST 10/17) displays high BME scores (BME TT 14/24, BME ST 9/18), corresponding to significant clinical symptoms (HJHS 16/20, NRS-24 h 9/10, NRS-4w 9/10).

3.4 | Difference in Correlation Between MRI and Clinical Parameters/US Scores

Results from the resampling study are reported in Table 4. Overall, similar trends were observed in both ankles, except when comparing the correlation between BME TT and US and that between IPSG TT and US.

Correlations between BME TT and respectively NRS-24H, NRS-4 W and HJHS were stronger than those between IPSG TT and these same pain intensity and joint health scores (NRS-24H: difference in rho ranging from +0.09 to +0.12; NRS-4W: difference in rho ranging from +0.10 to +0.12; HJHS: difference in rho ranging from +0.04 to +0.10). Correlations between BME ST and respectively NRS-24H, NRS-4 W and HJHS were stronger than those between IPSG ST and these same pain intensity and joint health scores (NRS-24H: difference in rho ranging from +0.13 to +0.19; NRS-4W: difference in rho ranging from +0.19 to +0.20; HJHS: difference in rho ranging from +0.18 to +0.21). Similarly, stronger correlations between BME ST and US scores compared to those between IPSG ST and US scores were observed (total HEAD-US: difference in rho ranging from +0.08 to +0.13; cartilage: difference in rho ranging from +0.08 to +0.13; bone: difference in rho ranging from +0.06 to +0.17; synovium: difference in rho ranging from +0.07 to +0.18). Correlations between BME total and respectively NRS-24H, NRS-4 W and HJHS were also stronger than those between IPSG total and the same pain intensity and joint health scores (NRS-24H: difference in rho ranging from +0.07 to +0.18; NRS-4W: difference in rho ranging from +0.12 to +0.16; HJHS: difference in rho ranging from +0.03 to +0.12) (Figure 3). However, no clear difference in correlation with HEAD-US parameters was observed (small positive differences in favor of BME total being observed for the right ankle, while small negative differences in favor of IPSG total being observed for the left ankle).

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 | Spearman's rho correlation coefficients assess the association between MRI scores and US/clinical parameters. Each MRI score includes measures from the left ankle (white line) and the right ankle (grey line). When both ankles showed the same trend, a color-coded scheme highlighted the correlation strength: Yellow for weak, light green for moderate, and dark green for strong correlations. Only statistically significant correlations are reported. For example, IPSG TT OC demonstrated at least a moderate correlation with NRS-24H, NRS-4 W, and HJHS, consistently observed in both ankles.

	NRS-24H		NRS-4W		HJHS ankle joint score		HEAD US total		HEAD US synovium		HEAD US cartilage		HEAD US bone	
Scores	Rho	*p* value	Rho	*p* value	Rho	*p* value	Rho	*p* value	Rho	*p* value	Rho	*p* value	Rho	*p* value
IPSG TT SOFT	0.41 [0.16; 0.61]	0.0019[a]	0.33 [0.06; 0.55]	0.0162[a]	–	0.1462	–	0.1297	–	0.1784	–	0.1686	–	0.1029
	–	0.5529	–	0.8102	–	0.4658	–	0.4889	–	0.5466	–	0.85	–	0.3073
IPSG TT OC	0.62 [0.42; 0.76]	<0.0001[a]	0.59 [0.39; 0.74]	<0.0001[a]	0.64 [0.46; 0.78]	<0.0001[a]	0.81 [0.70; 0.89]	<0.0001[a]	0.67 [0.49; 0.79]	<0.0001[a]	0.81 [0.70; 0.89]	<0.0001[a]	0.85 [0.76; 0.91]	<0.0001[a]
	0.59 [0.38; 0.74]	<0.0001[a]	0.67 [0.49; 0.80]	<0.0001[a]	0.71 [0.55; 0.82]	<0.0001[a]	0.81 [0.69; 0.89]	<0.0001[a]	0.57 [0.35; 0.73]	<0.0001[a]	0.79 [0.65; 0.87]	<0.0001[a]	0.78 [0.65; 0.87]	<0.0001[a]
IPSG ST SOFT	–	0.7758	–	0.8726	–	0.9378	–	0.9199	–	0.5082	–	0.9687	–	0.8869
	–	0.2671	–	0.2285	–	0.2201	–	0.3916	–	0.3348	–	0.3384	–	0.4846
IPSG ST OC	–	0.0536	0.40 [0.15; 0.61]	0.0025[a]	0.38 [0.12; 0.59]	0.0049[a]	0.32 [0.05; 0.54]	0.0202[a]	0.34 [0.09; 0.56]	0.0117[a]	0.28 [0.01; 0.51]	0.0403[a]	–	0.0605
	0.41 [0.15; 0.61]	0.0028[a]	0.46 [0.21; 0.65]	0.0007[a]	0.30 [0.03; 0.53]	0.0298[a]	–	0.1059	–	0.8838	–	0.0776	0.29 [0.01; 0.52]	0.0373[a]
IPSG TT	0.67 [0.49; 0.80]	<0.0001[a]	0.61 [0.41; 0.76]	<0.0001[a]	0.60 [0.40; 0.75]	<0.0001[a]	0.76 [0.62; 0.85]	<0.0001[a]	0.64 [0.44; 0.77]	<0.0001[a]	0.75 [0.61; 0.85]	<0.0001[a]	0.80 [0.67; 0.88]	<0.0001[a]
	0.62 [0.41; 0.76]	<0.0001[a]	0.62 [0.41; 0.76]	<0.0001[a]	0.58 [0.37; 0.74]	<0.0001[a]	0.78 [0.64; 0.86]	<0.0001[a]	0.55 [0.33; 0.72]	<0.0001[a]	0.73 [0.58; 0.84]	<0.0001[a]	0.77 [0.63; 0.86]	<0.0001[a]
IPSG ST	–	0.1409	0.31 [0.04; 0.53]	0.0244[a]	–	0.0693	–	0.1054	–	0.1658	–	0.1717	–	0.1507
	0.33 [0.06; 0.55]	0.0180[a]	0.37 [0.11; 0.58]	0.0068[a]	–	0.0937	–	0.1965	–	0.8418	–	0.1493	–	0.0843
IPSG total	0.68 [0.50; 0.80]	<0.0001[a]	0.67 [0.49; 0.79]	<0.0001[a]	0.66 [0.48; 0.79]	<0.0001[a]	0.77 [0.64; 0.86]	<0.0001[a]	0.68 [0.51; 0.80]	<0.0001[a]	0.76 [0.61; 0.85]	<0.0001[a]	0.79 [0.66; 0.87]	<0.0001[a]
	0.62 [0.41; 0.76]	<0.0001[a]	0.69 [0.51; 0.81]	<0.0001[a]	0.62 [0.41; 0.76]	<0.0001[a]	0.69 [0.52; 0.81]	<0.0001[a]	0.42 [0.17; 0.62]	0.0017[a]	0.68 [0.50; 0.80]	<0.0001[a]	0.70 [0.53; 0.82]	<0.0001[a]
BME TT	0.76 [0.62; 0.86]	<0.0001[a]	0.73 [0.57; 0.83]	<0.0001[a]	0.64 [0.45; 0.77]	<0.0001[a]	0.76 [0.61; 0.85]	<0.0001[a]	0.64 [0.44; 0.77]	<0.0001[a]	0.75 [0.61; 0.85]	<0.0001[a]	0.79 [0.67; 0.88]	<0.0001[a]
	0.69 [0.51; 0.81]	<0.0001[a]	0.74 [0.58; 0.84]	<0.0001[a]	0.69 [0.51; 0.81]	<0.0001[a]	0.74 [0.59; 0.85]	<0.0001[a]	0.53 [0.30; 0.70]	0.0001[a]	0.70 [0.53; 0.82]	<0.0001[a]	0.75 [0.59; 0.85]	<0.0001[a]
BME ST	0.33 [0.07; 0.55]	0.0141[a]	0.50 [0.27; 0.68]	0.0001[a]	0.46 [0.21; 0.65]	0.0005[a]	0.31 [0.04; 0.53]	0.0231[a]	0.37 [0.12; 0.58]	0.0057[a]	0.27 [0.00; 0.50]	0.0497[a]	–	0.0564
	0.52 [0.28; 0.69]	0.0001[a]	0.56 [0.34; 0.72]	<0.0001[a]	0.41 [0.16; 0.62]	0.0023[a]	0.31 [0.04; 0.54]	0.0240[a]	–	0.7822	0.34 [0.07; 0.56]	0.0140[a]	0.41 [0.15; 0.61]	0.0025
BME total	0.74 [0.58; 0.84]	<0.0001[a]	0.79 [0.66; 0.87]	<0.0001[a]	0.69 [0.51; 0.81]	<0.0001[a]	0.72 [0.57; 0.83]	<0.0001[a]	0.68 [0.50; 0.80]	<0.0001[a]	0.70 [0.54; 0.82]	<0.0001[a]	0.74 [0.58; 0.84]	<0.0001[a]
	0.80 [0.67; 0.88]	<0.0001[a]	0.84 [0.74; 0.91]	<0.0001[a]	0.73 [0.57; 0.83]	<0.0001[a]	0.73 [0.56; 0.83]	<0.0001[a]	0.45 [0.20; 0.64]	0.0009[a]	0.71 [0.54; 0.82]	<0.0001[a]	0.75 [0.60; 0.85]	<0.0001[a]

Abbreviations: HEAD-US bone: HEAD-US subscore for bone changes; HEAD-US cartilage: HEAD-US subscore for cartilage changes; HEAD-US synovium: HEAD-US subscore for synovial changes; HEAD-US total: HEAD-US total score for the tibiotalar joint; HJHS: Haemophilia joint health score; IPSG TT OC: IPSG subscore for osteochondral changes in the tibiotalar joint; NRS-24H: Numeric rating scale for pain over the past 24 h; NRS-4 W: Numeric rating scale for pain over the past 4 weeks.

[a]Significant p value < 0.05.

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 | Differences in correlation strength (rho values) were evaluated using a resampling procedure. Each comparison includes measures from the left ankle (white line) and the right ankle (grey line). Only statistically significant differences are reported. For example, the correlation between BME TT and NRS-24H is stronger than that between IPSG TT and NRS-24H, showing a correlation gain of at least +0.091 across both ankles, a trend consistently observed in both.

		NRS-24H	NRS-4W	HJHS	HEAD-US cartilage	HEAD-US bone	HEAD-US synovium	HEAD-US total
BME TT—IPSG TT	*p* value	<0.0001[b]	<0.0001[b]	<0.0001[a]	0.18	0.20	0.49	0.13
	Differences	+0.091 [+0.088; +0.094]	+0.104 [+0.101; +0.108]	+0.038 [+0.034; +0.041]	–	–	–	–
	p value	<0.0001[b]	<0.0001[b]	<0.0001[a]	<0.0001[b]	< 0.0001[a]	< 0.0001[b]	< 0.0001[a]
	Differences	+0.123 [+0.119; +0.127]	+0.122 [+0.118; +0.125]	+0.104 [+0.100; +0.108]	−0.031 [−0.035; −0.028]	−0.019 [−0.021; −0.016]	−0.024 [−0.028; −0.020]	−0.028 [−0.031; −0.026]
BME ST—IPSG ST	*p* value	<0.0001[b]	<0.0001[a]	<0.0001[b]	<0.0001[b]	<0.0001[b]	<0.0001[a]	<0.0001[b]
	Differences	+0.130 [+0.125; +0.136]	+0.201 [+0.196; +0.206]	+0.210 [+0.204; +0.216]	+0.079 [+0.074; +0.085]	+0.064 [+0.058; +0.069]	+0.181 [+0.175; +0.186]	+0.084 [+0.079; +0.090]
	p value	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]
	Differences	+0.187 [+0.183; +0.191]	+0.188 [+0.184; +0.192]	+0.178 [+0.173; +0.183]	+0.134 [+0.129; +0.140]	+0.169 [+0.164; +0.175]	+0.067 [+0.061; +0.072]	+0.129 [+0.124; +0.134]
BME total—IPSG total	*p* value	<0.0001[b]	<0.0001[b]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[b]	<0.0001[b]
	Differences	+0.065 [+0.062; +0.068]	+0.115 [+0.112; +0.119]	+0.025 [+0.021; +0.028]	−0.049 [−0.052; −0.045]	−0.052 [−0.055; −0.049]	−0.009 [−0.012; −0.004]	−0.049 [−0.053; −0.049]
	p value	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[a]	<0.0001[b]	<0.0001[a]
	Differences	+0.179 [+0.175; +0.183]	+0.155 [+0.152; +0.158]	+0.115 [+0.111; +0.118]	+0.033 [+0.029; +0.037]	+0.050 [+0.047; +0.053]	+0.026 [+0.022; +0.029]	+0.034 [+0.031; +0.038]

Abbreviations: BME TT: bone marrow oedema score for the tibiotalar joint; HEAD-US bone: HEAD-US subscore for bone changes; HEAD-US cartilage: HEAD-US subscore for cartilage changes; HEAD-US synovium: HEAD-US subscore for synovial changes; HEAD-US total: HEAD-US total score for the tibiotalar joint; HJHS: Haemophilia joint health score; IPSG TT: IPSG total score for the tibiotalar joint; NRS-24H: numeric rating scale for pain over the past 24 h; NRS-4 W: numeric rating scale for pain over the past 4 weeks.

[a]Significant paired *t*-test.

[b]Significant Wilcoxon test.

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

4 | Discussion

Our study indicates that BME is a common feature in haemophilic ankles, even in patients with no or mild arthropathy, and that it is strongly associated with pain intensity and joint health. While MRI scoring systems like IPSG primarily assess structural damage, they do not account for BME, which may play a key role in pain perception, disease activity, and potentially in disease progression. Integrating BME assessment into routine imaging could therefore enhance joint health evaluation in PwH. However, as this cross-sectional design does not allow causal inference, further longitudinal studies, including patients with more advanced arthropathy, are needed to clarify the prognostic value of BME in haemophilic joint disease. BME was present in 45% of left ankles and 34% of right ankles, with its scores showing stronger correlations with pain intensity (NRS-24H, NRS-4 W) and joint function (HJHS) than IPSG scores. This suggests that BME captures unique disease characteristics, providing clinicians with a valuable tool for assessing pain perception and disease activity beyond chronic joint damage measured by IPSG. Resampling analyses further confirmed that BME scores were more consistently linked to pain. While the IPSG total score had a moderate correlation with pain, its osteochondral and soft tissue subscores showed weaker associations. The reproducibility analysis demonstrated strong inter-reader agreement for both IPSG and BME scoring, reinforcing their reliability in clinical and research settings. As high reproducibility was demonstrated, further analyses used data from the junior expert reader (SG) only.

Our study builds on Chantrain et al.'s findings of a weak correlation between NRS pain scores and MRI or ultrasound, based on 100 patients for MRI and 163 patients for US [13]. Uniquely, we assessed and scored BME in a subset of our sample, which was not examined in their study. In our study, BME was analyzed in 56 PwH, providing additional insight into the relationship between structural joint changes and pain perception. BME and IPSG total scores correlated strongly with HEAD-US total and osteochondral scores but had weak or no correlation with HEAD-US synovial scores. Notably, BME total and BME TT exhibited moderate to strong correlations with NRS-24H, NRS-4 W, and HJHS, further supporting the clinical relevance of BME in haemophilic joint health (Table 3).

These findings align with previous studies in musculoskeletal conditions, where subchondral BME has been linked to joint pain [21]. BME is a dynamic and transient phenomenon, extensively studied in osteoarthritis, inflammatory arthritis, and stress-related bone injuries. It is often associated with pain flare-ups and joint deterioration, making it a valuable biomarker for disease monitoring [22, 23, 29]. Unlike irreversible joint damage, BME may reflect an active response to mechanical stress, inflammation, or microtrauma and can sometimes resolve spontaneously with appropriate management, such as activity modification, load reduction, and targeted rehabilitation [30].

Histologically, the MRI-detected BME pattern corresponds to various underlying changes. Initially thought to result from extracellular fluid accumulation due to its fluid-like signal characteristics on MRI [31], BME is now recognized as a non-specific marker appearing in diverse conditions. In trauma, it may indicate haemorrhage near fractures [32], while in inflammatory arthritis, it reflects cellular infiltrates and increased vascularity [33, 34]. In osteoarthritis, pathological analyses suggest that oedema is a minor component, whereas bone marrow fibrosis, fibrovascular tissue, trabecular microfractures, or cellular necrosis are commonly observed [22, 23, 29]. Given its heterogeneous nature, some authors propose the term "oedema-like marrow signal intensity (ELMSI)" to better describe this phenomenon [35].

Growing evidence shows that BME is a dynamic and potentially reversible process. Longitudinal knee MRI studies have demonstrated that subchondral BME lesions may decrease or fully resolve over time. In the MOST cohort, Roemer et al. reported that many BME lesions regressed or disappeared over 30 months, confirming their non-permanent nature [36]. Similarly, Zhang et al. showed that reductions in BME are associated with parallel improvements in knee pain, reinforcing its transient character [37]. Reversibility has also been documented in the spine, where Modic type 1 endplate changes often evolve into fatty marrow (type 2) or return to normal signal. Together, these findings indicate that "edema-like" marrow abnormalities reflect active lesions with well-documented potential for regression.

Mechanical overload and repetitive stress are key contributors to BME, as observed in osteoarthritis and stress fractures [38]. In PwH, where joint integrity is already compromised, excessive mechanical stress may exacerbate BME and pain. This underscores the importance of patient education on joint load management, personalized exercise adaptation, and injury prevention strategies.

At the molecular level, histological studies of patients with MRI-detected BME have identified the local secretion of proinflammatory cytokines and angiogenesis factors, which may contribute to nerve fibre irritation and pain development [39, 40]. These mechanisms, commonly associated with inflammatory and degenerative joint diseases, could similarly affect haemophilic joints, where recurrent microbleeds, synovial inflammation, and mechanical stress are prevalent. BME may serve as a marker of ongoing joint stress and an early indicator of disease activity. Given its potential reversibility, imaging-based BME monitoring could provide valuable insights into treatment effectiveness and the impact of lifestyle modifications. BME should not replace existing recommended outcomes but may provide complementary information, acting as an objective imaging correlate of pain and joint stress. Its dynamic and potentially reversible nature could make it valuable for explaining pain–structure discordance and monitoring responses to targeted interventions.

This study has limitations, including its cross-sectional design and focus on TTJ and STJ. Ongoing longitudinal MRI studies aim to track disease progression, assess the prognostic value of MRI features, and evaluate BME's role in treatment response. Future research should investigate BME in other commonly affected joints in PwH and develop new scoring models incorporating BME as an MRI parameter. Additionally, longitudinal studies should explore BME's evolution, its link to pain and functional impairment, and the impact of targeted interventions such as

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

rehabilitation and load redistribution strategies to improve joint management in PwH.

5 | Conclusion

This study emphasizes the frequent presence of BME in the subchondral bone marrow of the TTJ and STJ in PwH, showing a strong correlation with imaging scores like IPSG and HEAD-US. BME severity on MRI is more strongly associated with pain and joint health scores than existing MRI scoring methods. Given the multifactorial nature of pain, further research is needed to clarify BME's role in pain assessment. Integrating BME evaluation into research and refining scoring systems could enhance joint disease assessment in haemophilia. Clinically, proactive joint management through activity monitoring, physiotherapy, and neuromuscular training may help reduce mechanical stress and potentially mitigate progression.

Acknowledgements

The authors would like to thank all the patients who participated in the cited studies, as well as all the healthcare professionals who contributed to the research programs and helped report and publish the findings.

Funding

The authors have nothing to report.

Disclosure

The authors declare that they have no interests that could be perceived as posing any issue. SL, SG, VAC, AF, NM and FL designed the research study, analysed the data, and wrote the paper. MH, LT, TK, NR, CH and CL critically reviewed the manuscript and provided valuable insights that contributed to the refinement of the final version.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol received approval from the Institutional Review Board (approval numbers: B300201942304 and 2019/28OCT/469). All participants provided written informed consent prior to participation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article are available from the corresponding author upon reasonable request. Due to patient privacy and ethical restrictions related to haemophilia care, datasets cannot be made publicly available.

References

1. V. A. Chantrain, C. Lambert, P. De Smet, et al., "Pain Interferes with Daily Activities, Emotions and Sleep in Adults With Severe, Moderate and Mild Haemophilia: A National Cross-sectional Survey," *Haemophilia [Internet]* 29, no. 2 (2023): 521–529, https://pubmed.ncbi.nlm.nih.gov/36657103/.

2. A. C. Paredes, P. Teixeira, A. Almeida, and P. R. Pinto, "Prevalence and Interference of Chronic Pain among People with Hemophilia: A Systematic Review and Meta-Analysis," *Journal of Pain [Internet]* 22, no. 10 (2021): 1134–1145, https://pubmed.ncbi.nlm.nih.gov/33945849/.

3. J. Hmida, T. Hilberg, P. Ransmann, et al., "Most Subjectively Affected Joints in Patients With Haemophilia—What Has Changed After 20 Years in Germany?," *Haemophilia [Internet]* 28, no. 4 (2022): 663–670, https://pubmed.ncbi.nlm.nih.gov/35420240/.

4. R. Nuss, R. F. Kilcoyne, S. Geraghty, et al., "MRI Findings in Haemophilic Joints Treated With Radiosynoviorthesis With Development of an MRI Scale of Joint Damage," *Haemophilia [Internet]* 6, no. 3 (2000): 162–169, https://pubmed.ncbi.nlm.nih.gov/10792474/.

5. M. Dobón, J. F. Lucía, C. Aguilar, et al., "Value of Magnetic Resonance Imaging for the Diagnosis and Follow-up of Haemophilic Arthropathy," *Haemophilia [Internet]* 9, no. 1 (2003): 76–85, https://pubmed.ncbi.nlm.nih.gov/12558783/.

6. R. Soler, F. López-Fernández, E. Rodríguez, and M. M. H. arthropathy, "A Scoring System for Magnetic Resonance Imaging," *European Radiology [Internet]* 12, no. 4 (2002): 836–843, https://pubmed.ncbi.nlm.nih.gov/11960235/.

7. M. B. Funk, H. Schmidt, S. Becker, et al., "Modified Magnetic Resonance Imaging Score Compared With Orthopaedic and Radiological Scores for the Evaluation of Haemophilic Arthropathy," *Haemophilia [Internet]* 8, no. 2 (2002): 98–103, https://pubmed.ncbi.nlm.nih.gov/11952844/.

8. B. Lundin, M. L. Manco-Johnson, D. M. Ignas, et al., "An MRI Scale for Assessment of Haemophilic Arthropathy From the International Prophylaxis Study Group," *Haemophilia [Internet]* 18, no. 6 (2012): 962–970, https://pubmed.ncbi.nlm.nih.gov/22765835/.

9. T. Brunel, S. Lobet, K. Deschamps, 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 [Internet]* 24, no. 1 (2018): 141–148, https://pubmed.ncbi.nlm.nih.gov/29168597/.

10. A. S. Doria, N. Zhang, B. Lundin, et al., "Quantitative versus Semiquantitative MR Imaging of Cartilage in Blood-induced Arthritic Ankles: Preliminary Findings," *Pediatric Radiology [Internet]* 44, no. 5 (2014): 576–586, https://pubmed.ncbi.nlm.nih.gov/24522564/.

11. W. Foppen, D. Sluiter, T. D. Witkamp, W. Mali, and K. Fischer, "Haemophilic Magnetic Resonance Imaging Score in Healthy Controls Playing Sports," *Haemophilia [Internet]* 19, no. 6 (2013): 939–943, https://pubmed.ncbi.nlm.nih.gov/23710616/.

12. N. A. Roussel, V. A. Chantrain, A. Foubert, et al., "Gaining More Insight Into Ankle Pain in Haemophilia: A Study Exploring Pain, Structural and Functional Evaluation of the Ankle Joint," *Haemophilia [Internet]* 28, no. 3 (2022): 480–490, https://pubmed.ncbi.nlm.nih.gov/35294993/.

13. V. A. Chantrain, S. Guillaume, A. Foubert, et al., "Discordance Between Joint Pain and Imagery Severity in the Ankle Joint and Contributors of Lower Limb Activity Limitations in Adults With Haemophilia: A Cross-sectional Study," *Haemophilia [Internet]* 29, no. 2 (2023): 648–657, https://pubmed.ncbi.nlm.nih.gov/36696283/.

14. D. T. Felson, C. E. Chaisson, C. L. Hill, et al., "The Association of Bone Marrow Lesions With Pain in Knee Osteoarthritis," *Annals of Internal Medicine [Internet]* 134, no. 7 (2001): 541–549, https://pubmed.ncbi.nlm.nih.gov/11281736/.

15. K. H. Koo, I. O. Ahn, R. Kim, et al., "Bone Marrow Edema and Associated Pain in Early Stage Osteonecrosis of the Femoral Head: Prospective Study With Serial MR Images," *Radiology [Internet]* 213, no. 3 (1999): 715–722, https://pubmed.ncbi.nlm.nih.gov/10580944/.

16. T. M. Link and X. Li, "Bone Marrow Changes in Osteoarthritis," *Seminars in Musculoskeletal Radiology [Internet]* 15, no. 3 (2011): 238–246, https://pubmed.ncbi.nlm.nih.gov/21644197/.

17. T. Nakamae, K. Yamada, T. Shimbo, et al., "Bone Marrow Edema and Low Back Pain in Elderly Degenerative Lumbar Scoliosis: A Cross-Sectional Study," *Spine (Phila Pa 1976) [Internet]*

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

41, no. 10 (2016): 885–892, https://pubmed.ncbi.nlm.nih.gov/26641841/.

18. M. S. Taljanovic, A. R. Graham, J. B. Benjamin, et al., "Bone Marrow Edema Pattern in Advanced Hip Osteoarthritis: Quantitative Assessment With Magnetic Resonance Imaging and Correlation With Clinical Examination, Radiographic Findings, and Histopathology," *Skeletal Radiology [Internet]* 37, no. 5 (2008): 423–431, https://pubmed.ncbi.nlm.nih.gov/18274742/.

19. L. Xu, D. Hayashi, F. W. Roemer, D. T. Felson, and A. Guermazi, "Magnetic Resonance Imaging of Subchondral Bone Marrow Lesions in Association With Osteoarthritis," *Seminars in Arthritis and Rheumatism [Internet]* 42, no. 2 (2012): 105–118, https://pubmed.ncbi.nlm.nih.gov/22542276/.

20. P. Szaro, M. Geijer, and N. Solidakis, "Traumatic and Non-traumatic Bone Marrow Edema in Ankle MRI: A Pictorial Essay," *Insights Imaging [Internet]* 11, no. 1 (2020): 97, https://pubmed.ncbi.nlm.nih.gov/32804284/.

21. Y. Nakamura, S. Uchiyama, M. Kamimura, M. Komatsu, S. Ikegami, and H. Kato, "Bone Alterations Are Associated With Ankle Osteoarthritis Joint Pain," *Scientific Reports [Internet]* 6 (2016): 18717, https://pubmed.ncbi.nlm.nih.gov/26776564/.

22. M. Zanetti, E. Bruder, J. Romero, and J. Hodler, "Bone Marrow Edema Pattern in Osteoarthritic Knees: Correlation Between MR Imaging and Histologic Findings," *Radiology [Internet]* 215, no. 3 (2000): 835–840, https://pubmed.ncbi.nlm.nih.gov/10831707/.

23. H. Leydet-Quilici, T. Le Corroller, C. Bouvier, et al., "Advanced Hip Osteoarthritis: Magnetic Resonance Imaging Aspects and Histopathology Correlations," *Osteoarthritis Cartilage [Internet]* 18, no. 11 (2010): 1429–1435, https://pubmed.ncbi.nlm.nih.gov/20727415/.

24. C. G. Peterfy, A. Guermazi, S. Zaim, et al., "Whole-organ Magnetic Resonance Imaging Score (WORMS) of the Knee in Osteoarthritis," *Osteoarthritis Cartilage [Internet]* 12, no. 3 (2004): 177–190, https://pubmed.ncbi.nlm.nih.gov/14972335/.

25. C. Martinoli, O. Casa Alberighi Della, G. Di Minno, et al., "Development and Definition of a Simplified Scanning Procedure and Scoring Method for Haemophilia Early Arthropathy Detection With Ultrasound (HEAD-US)," *Thrombosis and Haemostasis [Internet]* 109, no. 6 (2013): 1170–1179, https://pubmed.ncbi.nlm.nih.gov/23571706/.

26. A. Williamson and B. Hoggart, "Pain: A Review of Three Commonly Used Pain Rating Scales," *Journal of Clinical Nursing [Internet]* 14, no. 7 (2005): 798–804, https://pubmed.ncbi.nlm.nih.gov/16000093/.

27. J. W. Bartlett and C. Frost, "Reliability, Repeatability and Reproducibility: Analysis of Measurement Errors in Continuous Variables," *Ultrasound in Obstetrics & Gynecology [Internet]* 31, no. 4 (2008): 466–475, https://pubmed.ncbi.nlm.nih.gov/18306169/.

28. G. R. Norman and D. L. Streiner, *Biostatistics: The Bare Essentials* (PMPH USA (BC Decker), 2008). editor.

29. E. Saadat, B. Jobke, B. Chu, et al., "Diagnostic Performance of in Vivo 3-T MRI for Articular Cartilage Abnormalities in human Osteoarthritic Knees Using Histology as Standard of Reference," *European Radiology [Internet]* 18, no. 10 (2008): 2292–2302, https://pubmed.ncbi.nlm.nih.gov/18491096/.

30. U. Tarantino, C. Greggi, I. Cariati, et al., "Reviewing Bone Marrow Edema in Athletes: A Difficult Diagnostic and Clinical Approach," *Medicina (Kaunas) [Internet]* 57, no. 11 (2021): 1215, https://pubmed.ncbi.nlm.nih.gov/34833361/.

31. G. Schett, "Bone Marrow Edema," *Annals of the New York Academy of Sciences [Internet]* 1154 (2009): 35–40, https://pubmed.ncbi.nlm.nih.gov/19250229/.

32. E. Kon, M. Ronga, G. Filardo, et al., "Bone Marrow Lesions and Subchondral Bone Pathology of the Knee," *Knee Surgery, Sports Traumatology, Arthroscopy [Internet]* 24, no. 6 (2016): 1797–1814, https://pubmed.ncbi.nlm.nih.gov/27075892/.

33. E. Jimenez-Boj, I. Nöbauer-Huhmann, B. Hanslik-Schnabel, et al., "Bone Erosions and Bone Marrow Edema as Defined by Magnetic Resonance Imaging Reflect True Bone Marrow Inflammation in Rheumatoid Arthritis," *Arthritis & Rheumatology [Internet]* 56, no. 4 (2007): 1118–1124, https://pubmed.ncbi.nlm.nih.gov/17393390/.

34. F. M. McQueen and B. Ostendorf, "What Is MRI Bone Oedema in Rheumatoid Arthritis and Why Does It Matter?," *Arthritis Research & Therapy [Internet]* 8, no. 6 (2006): 222, https://pubmed.ncbi.nlm.nih.gov/17169137/.

35. D. Maraghelli, M. L. Brandi, M. Matucci Cerinic, A. J. Peired, and S. Colagrande, "Edema-Like Marrow Signal Intensity: A Narrative Review With a Pictorial Essay," *Skeletal Radiology [Internet]* 50, no. 4 (2021): 645–663, https://pubmed.ncbi.nlm.nih.gov/33029648/.

36. F. W. Roemer, A. Guermazi, M. K. Javaid, et al., "Change in MRI-detected Subchondral Bone Marrow Lesions Is Associated With Cartilage Loss: The MOST Study. A Longitudinal Multicentre Study of Knee Osteoarthritis," *Annals of the Rheumatic Diseases [Internet]* 68, no. 9 (2009): 1461–1465, https://pubmed.ncbi.nlm.nih.gov/18829615/.

37. Y. Zhang, M. Nevitt, J. Niu, et al., "Fluctuation of Knee Pain and Changes in Bone Marrow Lesions, Effusions, and Synovitis on Magnetic Resonance Imaging," *Arthritis & Rheumatology [Internet]* 63, no. 3 (2011): 691–699, https://pubmed.ncbi.nlm.nih.gov/21360498/.

38. A. M. Starr, M. A. Wessely, U. Albastaki, C. Pierre-Jerome, and N. W. Kettner, "Bone Marrow Edema: Pathophysiology, Differential Diagnosis, and Imaging," *Acta Radiologica [Internet]* 49, no. 7 (2008): 771–786, https://pubmed.ncbi.nlm.nih.gov/18608031/.

39. E. F. Eriksen, "Treatment of Bone Marrow Lesions (bone marrow edema)," *BoneKEy Reports [Internet]* 4 (2015): 755, https://pubmed.ncbi.nlm.nih.gov/26644910/.

40. K. Livia, F. Thomas, and J. Raphael, "Pain Control With Ibandronate for Bone Marrow Oedema of the Knee," *Swiss Medical Weekly [Internet]* 150, no. 47 (2020): w20365, https://pubmed.ncbi.nlm.nih.gov/33246342/.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Information file 1: hae70221-sup-0001-SuppMat.zip

13652516, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/hae.70221 by Universite Catholique De Louvain, Wiley Online Library on [10/02/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License