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ORIGINAL ARTICLE

Rapid musculoskeletal ultrasound for painful episodes in adult haemophilia patients

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Summary. Little objective information exists about musculoskeletal bleeding patterns in haemophilic arthropathy. Bleeding is assumed to be the cause of painful joints or muscles. Clotting factor treatment is provided empirically, but often does not alleviate pain. We hypothesized that perception of pain aetiology is unreliable, and introduced point-of-care high-resolution musculoskeletal ultrasound (MSKUS) to differentiate intra-articular bleeds vs. joint inflammation, and intra-muscle bleeds vs. other regional pain syndromes. To assess painful musculoskeletal episodes in adult haemophiliacs, we used rapid MSKUS, employing grey scale and power Doppler examination. Forty episodes in 30 adult haemophiliacs were evaluated. Thirty three of the 40 episodes were patient-reported as 'bleeding', five as 'arthritis-type' pain and two as 'undecided'. Of the 33 bleeding reports, only 12 were confirmed by MSKUS; the other episodes revealed other pathology. In contrast, three of five perceived arthritis flares were reclassified as bleeds. Similarly, physician assessment was incorrect in 18 of 40 instances. Swelling and warmth were present in approximately half of confirmed bleeding and non-bleeding episodes, and therefore not useful clinically. Few of the painful episodes were symptom controlled at the time of MSKUS. Management changed based on objective imaging findings in >70% of episodes, which resulted in symptom improvement >60% of the time. Significant discrepancies exist between MSKUS findings and patient/physician-perceived pain classification as bleeding or other musculoskeletal symptoms. Current practice of prescribing clotting factor or conservative measures based on pain perception seems inadequate and suggests that point-of-care imaging should be included into modern haemophilia care.

Keywords: arthritis, haemophilia, hemarthrosis, pain, synovitis, ultrasound

Introduction

Haemarthrosis (intra-articular bleed) and intra-muscular bleeds are the hallmarks of haemophilia and cause considerable morbidity [1]. Recurrent haemarthroses unavoidably lead to disabling haemophilic arthropathy [2], and intra-muscular or cortical bone bleeds may result in pseudotumours [3]. The economic impact of prophylactic and acute management of bleeding episodes with clotting factor is substantial and can exceed $300 000 annually for adult patients with haemophilia (PWH) [4]. Thus, timely and accurate diagnosis, as well as appropriate management with clotting factor preparations to ensure good outcomes of joint or muscle bleeding, is critical.

Currently, painful joint or musculoskeletal episodes in PWH are treated empirically without objective diagnosis. Adult PWH self-administer clotting factor for perceived musculoskeletal bleeds, or use conservative measures for perceived 'arthritis' or musculoskeletal pain based on their own judgement. However, symptoms and findings such as loss of range of motion (ROM), warmth and swelling are non-specific and may occur with bleeding, synovitis/arthritis or other musculoskeletal syndromes. Hence, there is concern that treatment based on perception of pain aetiology alone may be inaccurate. This is especially applicable to adult PWH for whom progressive haemophilic arthropathy makes the discrimination of pain caused

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by recurrent haemarthroses vs. pain caused by haemophilic arthropathy itself, or by other joint pathology, exceptionally challenging.

Rapid, point-of-care imaging, therefore, would be highly desirable to objectively diagnose joint and musculoskeletal pains in haemophilia and is available through musculoskeletal ultrasound (MSKUS). Although magnetic resonance imaging (MRI) is considered the gold standard for musculoskeletal imaging, recent advances in ultrasound technology including high-frequency transducers, spatial compounding sonography and power Doppler capability not only provide high spatial resolution but also yield functional information about musculoskeletal structures [5]. Similar to MRI, MSKUS can visualize anatomy of the musculoskeletal system, including tendons, muscles, ligaments and fluid. With high-frequency transducers, tissue resolution approaches or is higher than with routine MRI [6]. Compared with MRI, MSKUS is rapid, less costly, and does not require contrast administration or sedation for claustrophobia; it is therefore an ideal point-of-care imaging modality [7,8]. In fact, imaging with MSKUS has been validated for a wide spectrum of musculoskeletal pathology in rheumatology, orthopaedics and sports medicine [9]. MSKUS findings have also been shown to correlate with MRI findings in patients with haemophilic arthropathy [10].

Routine MSKUS examination consists of grey-scale (B-mode) ultrasound and power Doppler ultrasound evaluation. Grey-scale ultrasound can visualize various pathologies in tendons, ligaments, cortical bone and synovial space. It can readily distinguish simple and complex (bloody) effusions [11], and has been validated for haemarthrosis detection in haemophilia by joint aspiration [12]. Power Doppler ultrasound examination enables detection of larger Doppler shifts, and therefore low-flow states in the microvasculature, and can visualize vascularization of joint structures, such as synovium [13]. Superimposing grey-scale ultrasound and power Doppler images can be done simultaneously during the same examination which can distinguish hypervascular/hyperaemic synovium from intra- or periarticular fluid without need of contrast administration used in MRI [8].

As many patients at our centre reported inadequate pain relief or no response to sometimes prolonged (up to 10 days) intense clotting factor replacement, we hypothesized that routine clinical assessment is unreliable for diagnosis and management of musculoskeletal pain in adult haemophiliacs, and that MSKUS evaluation could determine objectively whether acute joint and musculoskeletal pain are associated with bleeding, synovitis or other regional musculoskeletal pain syndromes. Here, we report our findings, demonstrating a remarkable discrepancy between patient-perceived aetiology of musculoskeletal pain and objective MSKUS findings. The results of this study suggest a paradigm shift in the approach to diagnosis and management of painful episodes in PWH.

Materials and methods

Patient population and data extracted

Between 06/2012 and 10/2012, 30 consecutive patients with haemophilia A or B (all severities), age 21 years and older, reported painful spontaneous or traumatic episodes of joint or musculoskeletal pain to our Hemophilia Treatment Center (HTC). All were evaluated by physical examination and MSKUS within 48 h of onset of symptoms while following their usual treatment algorithm based on perceived pain aetiology. Upon presentation, patients were consented for prospective and retrospective utilization of imaging studies, laboratory studies, data related to age, race, type and severity of haemophilia, inhibitor status (neutralizing antibodies against FVIII or FIX), plasma clotting factor activity levels, clinical history and findings. Treatment was adjusted according to MSKUS findings. Patients were contacted by telephone 1–3 days later and asked if symptoms were improved, unchanged or worse. Two additional patients, who were asymptomatic, were also consented for evaluation. All patients were males. No patient declined the clinic visit, study inclusion, or was excluded from analysis. The study protocol, data acquisition and patient confidentiality safeguards were approved by the Institutional Review Board.

Clinical evaluation and MSKUS

Physical examination for all patients was performed by the haemophilia physician (AvD). Physical examination included inspection, palpation for warmth, swelling and recording of patient-perceived ROM deficit. Ultrasound studies were performed by the rheumatologist (AC) formally trained in MSKUS. No additional analgesics had to be administered at the time of MSKUS examination. The rheumatologist was blinded to the clinical diagnosis of the haemophilia physician, but was aware of patient perception. Previously recorded baseline exam of the same joint or musculoskeletal area was used as reference. GE Logiq e BT11 US-module with real-time spatial compound imaging and speckle reduction capability, equipped with high frequency 8–13 MHz linear transducer, was used for MSKUS. Grey scale (B-mode) and power Doppler examination was performed using standardized imaging protocols for each joint area as previously described [14–16]. Sonopalpation was used to evaluate compressibility and displacement of intra-articular material. Dynamic joint evaluations were performed when appropriate. MSKUS-guided arthrocentesis was performed for

effusions. Informed consent was obtained for each procedure.

Statistical analysis

Student's *t*-test was used to assess statistical significance. *P*-values of ≤ 0.05 were considered significant.

Results

Patient- or physician-perceived pain aetiology in relation to bleeding or non-bleeding as determined by MSKUS

Thirty patients experiencing 40 consecutive painful joint or musculoskeletal episodes were evaluated for pain aetiology (bleeding into joints or muscle vs. 'arthritic-type' or other musculoskeletal pain). In one of these patients joint baseline status was studied in the absence of symptoms. In another patient treatment efficacy was assessed after start of clotting factor prophylaxis for confirmed haemarthrosis (by aspiration). Patient characteristics and types of episodes are reported in Table 1. Median time to evaluation after the patient had contacted the HTC was 10 h (range 2–48 h), with 70% of episodes evaluated within 24 h of reported pain.

Patient-perceived pain aetiology was correct in only approximately 1/3rd of episodes. Only 12 of 33 patient-perceived bleeding episodes and two of five perceived 'arthritic-type' joint pains were confirmed as such by MSKUS. Three of the five 'arthritic-type' episodes were reclassified as haemarthroses (Fig. 1a). In two instances, patients were unsure as to the aetiology of their pain, and MSKUS detected bleeding in one and synovitis in the other. Physician judgment, based on patient interview and physical examination, was similarly inaccurate. MSKUS confirmed only 18 of 40 physician-diagnosed episodes, and established diagnoses in six additional episodes where physician judgment was uncertain. Of those, two were associated with bleeding and four were not. As assessed by MSKUS, the physician classified haemarthrosis and/or muscle bleeding correctly in six of 16 confirmed bleeding, and in 11 of 19 confirmed non-bleeding episodes. (Fig. 1b). Taken together, patients and/or physicians misclassified bleeding and non-bleeding events in the majority of instances. An agreement between patient- and physician-perceived bleeding was present in only nine instances, of which four were confirmed by MSKUS. Of note, one patient- and physician-perceived muscle bleed was reclassified by MSKUS as meralgia paresthetica without bleeding.

Two MSKUS evaluations were performed unrelated to acute pain assessment. One evaluation assessed baseline target joint status of the right ankle in a 23-year-old patient with severe haemophilia B. This patient later presented for repeat MSKUS of the same joint during a patient-perceived 'arthritic-type' painful episode; MSKUS examination revealed haemarthrosis. The second evaluation assessed the therapeutic efficacy of clotting factor prophylaxis started in a 65-year-old patient with severe haemophilia B. This patient had presented 6 months earlier with chronic intermittent knee pain, warmth, swelling and bloody effusion by joint aspiration. MSKUS was helpful to objectively confirm absence of bleeding and/or synovitis associated with resolution of symptoms.

Table 1. (a) Patient characteristics (b) Musculoskeletal ultrasound studies performed.

(a)	
Haemophilia A/B	25/5
Inhibitor pos/Inhibitor hx known	2/2
Haemophilia Severity	
Severe	19
Moderate	3
Mild	8
(b)	
Total # of ultrasound studies	42
Painful episodes	40
Spontaneous	
Ankle	10
Knee	15
Elbow	6
Hip	2
Muscle	2
Traumatic	
Muscle	3
Ankle	1
Shoulder	1
Baseline joint status	
Ankle	1
Treatment efficacy	
Knee	1

Symptoms during painful episodes and plasma factor activity levels at the time of MSKUS

All painful joint or musculoskeletal episodes were associated with patient-perceived loss of ROM irrespective of bleeding or non-bleeding. By physical examination, swelling and warmth were present in approximately half of the confirmed bleeding and non-bleeding episodes (Fig. 2a). Plasma clotting factor activity levels at the time of MSKUS were available for 34 painful episodes. Factor activity levels of <1% were charted as 0.9% FVIII- or FIX activity. There was no difference between mean factor activity levels ($n = 17$ FVIII; $n = 3$ FIX) during painful episodes with or without bleeding. Mean factor activity levels were 32.5% (Interquartiles (0.9; 64) for painful episodes with bleeding, and 24.4% (Interquartiles 4; 26) for painful episodes without bleeding (Fig. 2b). Overall, 25 of the 33 measured clotting factor levels were above known intrinsic clotting factor activity (9/13 for bleeding episodes; 16/21 for non-bleeding episodes).

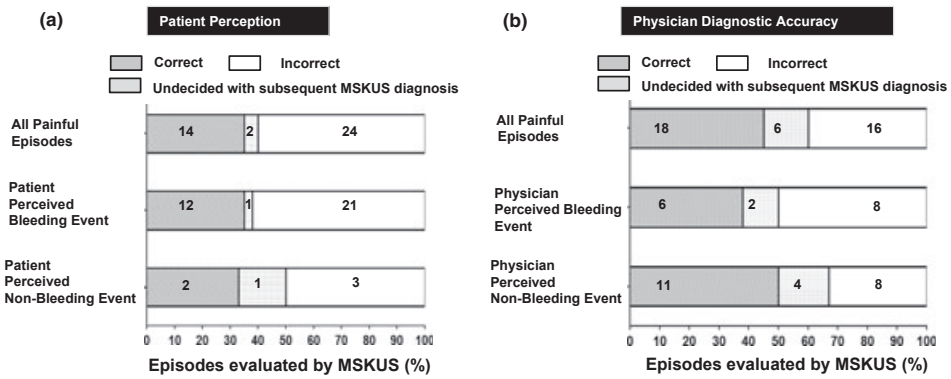

Fig. 1. Musculoskeletal ultrasound (MSKUS) revealed that patient- or physician-perceived pain aetiology was correct in only ~1/3rd of painful musculoskeletal episodes. Haemophilia patients experiencing painful musculoskeletal episodes reported their perceived pain aetiology (bleeding into joints or muscle vs. "arthritic-type" or other musculoskeletal pain) and were evaluated by physical exam within 48 h after reporting pain, followed by imaging diagnosis with MSKUS. (a) Patient-perceived pain aetiology in relation to imaging results by MSKUS. (b) Accuracy of physician diagnoses in relation to imaging results by MSKUS.

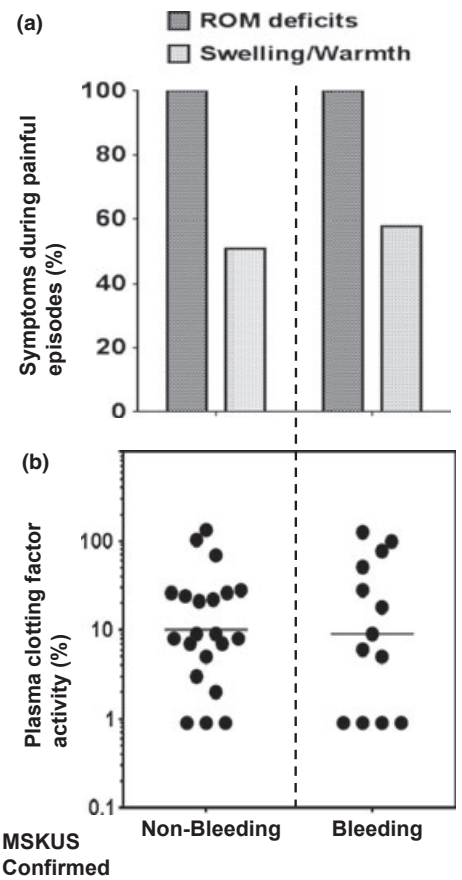

Fig. 2. Symptoms during painful episodes and plasma factor activity levels at the time of musculoskeletal ultrasound (MSKUS) were similar for bleeding and non-bleeding episodes. (a) Patient-perceived loss of active range of motion (ROM) was associated with all painful episodes. Among MSKUS-diagnosed episodes of bleeding or arthritis-type/musculoskeletal pain, swelling and warmth on physical exam were present in a similar number of episodes in each diagnostic category ($P = 0.7$). (b) Plasma factor activities drawn at the time of MSKUS were available for 34 episodes and were plotted by geometric mean. Factor activity levels were similar for bleeding and non-bleeding episodes ($P = 0.6$), suggesting over- or undertreatment with clotting factor for the majority of episodes.

MSKUS findings

Of the 35 painful joint episodes, 13 (37%) were associated with a complex effusion consistent with intra-articular blood, 11 (31.5%) were associated with a simple effusion without sonographic evidence of intra-articular blood and 11 (31.5%) did not have sonographic effusion. The majority of effusions were aspirated (11 complex effusions and six simple effusions). Visual inspection (straw colour vs. frankly bloody appearance of synovial fluid) confirmed presence or absence of haemarthrosis. Various degrees of synovial thickening and osteophytes consistent with various degrees of haemophilic arthropathy were found in almost all joints. The degree of synovial thickening varied from mild to a 'rheumatoid-like' synovial villous proliferation with 'cauliflower' appearance. Synovial power Doppler signal consistent with synovial hypervascularity and/or active synovitis was found to be associated with and without intra-articular bleeding; however, it was significantly more common in bleeding joints (11 of 13; 85%) vs. non-bleeding joints (9 of 22; 41%; $P < 0.05$) (Table 2). Signs of degenerative joint disease, flat feet, tendon and ligament pathology including Achilles tendinitis, plantar fasciitis, tibialis tendinosis and posttraumatic ankle ligament derangement were common findings, suggesting that haemophilic arthropathy may predispose to their development, and therefore initiate or aggravate pain in the absence of acute intra-articular bleeding.

Impact of MSKUS findings on management decisions

MSKUS findings directly changed treatment for 29 of 40 painful episodes (Fig. 3a). MSKUS also guided continuation of clotting factor prophylaxis in one asymptomatic patient who previously presented with haemarthrosis; this case was classified as no change in

Table 2. Musculoskeletal ultrasound findings in symptomatic haemophilia patients.

		Ultrasound findings					
Patient No	Examined site	Bleed	Simple effusion	Synovial thickening	Hyperaemia synovium/Fat pad	Osteophytes	Radiographic findings
1	R ankle	–	–	+	+/+	+	7/13
1*	L ankle	+	NA	+	+/+	+	7/13
2	R ankle	–	–	–	–/–	+	0/13
2†	R ankle	+	NA	–	–	+	0/13
3‡	R ankle	+	NA	+	+/+	+	ND
3	L knee	–	+	+	+/+	+	Severe DJD
4	R knee	+	NA	+	+/–	+	Severe DJD
5	R ankle	–	–	–	–/–	+	1/13
6§	L thigh	–	NA	NA	NA	NA	NA
7	L knee	–	+	+	+/+	+	Severe HA
7†	L knee	–	+	+	+/+	+	Severe HA
8	R knee	+	NA	+	+/+	+	Hx/o TKR¶
8†	R knee	+	NA	+	+/+	+	Hx/o TKR¶
9	R ankle	–	-	+	–/–	+	0/13
9†	R ankle	–	–	+	–/–	+	0/13
10	R thigh	+	NA	NA	NA	NA	NA
11	R knee	–	–	–	–	+	11/13
12	L knee	–	–	+	+/+	+	8/13
13	R elbow	+	NA	+	+/+	+	Erosions
14	L ankle	–	–	+‖	+/–‖	+	2/13
7	L knee	–	+	+	–/+	+	S/p TKR
1	B/l elbows	+Rt>Lt	NA	+	–/+	+	4/13>5/13
9	R calf	–	NA	NA	NA	NA	NA
15	R buttock	+	NA	NA	NA	NA	NA
16	L ankle	–	+	+	–/–	+	3/13
17	L hip/ thigh**	–	–	NA	NA	NA	NA
17	L knee	–	+	-	–/–	+	2/13
18	L knee	+	NA	+	+/+	+	11/13
18†	L knee	+	NA	+	+/+	+	11/13
19	R ankle	–	–	+	+/–	+	6/13
20	L hip	–	–	–	–/–	+	Moderate DJD
21	R knee	+	NA	+	–/+	+	10/13
22††	R shoulder	–	+	–	–	–	NA
23	R elbow	–	+	+	–/–	+	6/13
24	R knee	–	+	+	+/–	+	1/13
25	L elbow	+	NA	+	+/+	+	11/13
25†	L elbow	–	–	+	+/+	+	11/13
26	R knee	–	+	–	–/–	–	Not available
27	R ankle	–	–	–	–/–	–	0/13
28	L knee	+	N/A	+	+/–	–	Tricompartment OA
29	L elbow	–	+	+	–/–	+	11/13
30	R calf	+	N/A	N/A	N/A	N/A	N/A

R, right; L, left; NA, not applicable; ND, not done; DJD, degenerative joint disease; HA, haemophilic arthropathy; OA, Osteoarthritis; Hx/o TKR, history of total knee replacement; S/p TKR, status post total knee replacement; B/l, bilateral. Ankle examination included tibiotalar, subtalar (limited sonographic window) and midfoot joint examination; simple effusion, presence of intra-articular fluid without sonographic characteristics of haemorrhage; hyperaemia, presence of power Doppler signal. Radiological findings are shown as Pettersson score or short overall impression.

*Case 1 – bleeding into subtalar and tibiotalar joints.

†Interval examination of the same joint.

‡Case 3 – bleeding into talonavicular joint.

§Case 6 – Dx of meralgia paresthetica.

¶No radiographic evidence of prosthetic loosening.

‖Case 14 – tibiotalar and talonavicular joints.

**Dx of trochanteric bursitis.

††Dx of rotator cuff tear.

treatment. For 9 of the 16 confirmed bleeding episodes there was initiation (n = 3), or intensification (n = 6) of acute clotting factor administration. For the remaining seven episodes no changes were made.

Conversely, acute treatment with clotting factor for confirmed non-bleeding episodes was either discontinued (n = 10) or not initiated (n = 12) in 22 of 23 episodes. In one case, strong patient fixation on his bleeding disorder did not allow immediate cessation of clotting factor. Alternative conservative treatment measures were pursued for 21 of 23 painful non-bleeding episodes, either by physical therapy, initiation of oral anti-inflammatory agents (Cyclo-oxygenase-2 inhibitors) (n = 12), or intra-articular steroid injection (n = 9).

MSKUS-directed treatment decisions resulted in patient-reported symptom improvement, no change or worsening in 25/40 (63.5%), 15/40 (36%) or 0/40

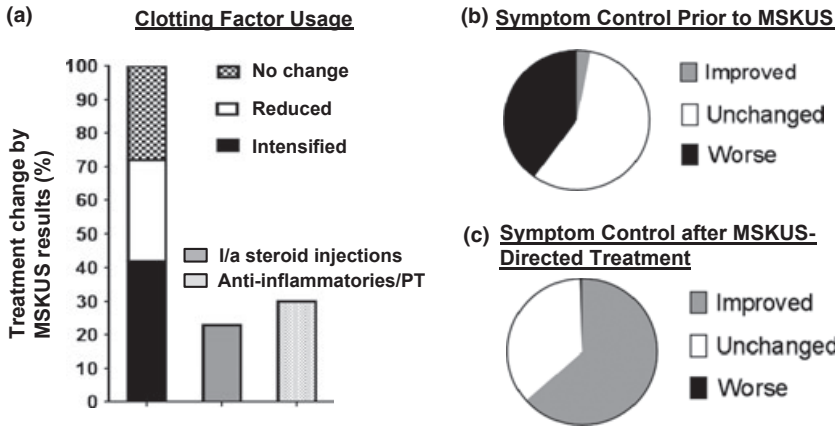

Fig. 3. Diagnostic musculoskeletal ultrasound (MSKUS) changed therapy and improved symptoms for the majority of episodes. (a) Diagnostic MSKUS changed the treatment algorithm for 30 of 41 episodes (spontaneous or traumatic pain episodes; $n = 40$; evaluation of treatment efficacy after start of prophylaxis; $n = 1$). Several patients received intra-articular (i/a) joint injections with steroids, or oral anti-inflammatories with or without physical therapy (PT). (b) Patient-perceived subjective symptom control prior to MSKUS. (c) MSKUS directed treatment resulted in symptom improvement for the majority of painful episodes.

(0%) instances respectively. Of note, at the time of MSKUS, only 7/40 episodes were symptom controlled, suggesting that treatment based on pain perception alone had been ineffective (Fig. 3b).

Case studies

Examples of painful episodes evaluated by MSKUS, demonstrating haemarthrosis vs. synovitis, and the clinical context in which they occurred are shown in Figs 4a/b.

Discussion and conclusions

Here, we demonstrate for the first time that rapid, high-resolution MSKUS is a valuable point-of-care imaging tool to distinguish whether acute joint and/or musculoskeletal pain episodes in adult PWH are associated with bleeding or not. We found a large discrepancy between patient- or physician-perceived pain aetiology compared with MSKUS findings in the majority of pain episodes. Because presenting clinical symptoms and physical findings such as loss of ROM, warmth or swelling did not discriminate non-bleeding from bleeding events, only approximately 1/3rd of the painful musculoskeletal episodes were judged correctly either by the patient or physician. Average plasma clotting factor activity levels at the time of MSKUS were comparable for confirmed bleeding or non-bleeding episodes, suggesting under- or overutilization of clotting factor preparations relative to the underlying pain aetiology. For example, plasma factor activities <1% for episodes associated with bleeding at the time of MSKUS indicate undertreatment, whereas plasma clotting factor activity levels >100% in episodes not associated with bleeding indicate overtreatment. In this context, it is notable that symptoms were poorly controlled for all painful episodes at the time patients presented to clinic. MSKUS findings prompted a change in management strategies in the majority of instances. The imaging-guided treatment correction, whereby clotting factor administration was adjusted according to bleeding or non-bleeding and conservative measures (physical therapy, anti-inflammatory agents or intra-articular steroid injections) were prescribed, resulted in symptom improvement for the majority of episodes. Although the heterogeneity and complexity of patients and the observational nature of this study do not permit firm conclusions as to the benefits of MSKUS-guided treatment interventions, the effectiveness of interventions in the majority of patients strongly suggests that MSKUS deserves future investigation for integration into clinical decision making and the management of painful episodes.

A much higher number of patients with perceived bleeding episodes as opposed to 'arthritic episodes' reported their symptoms to our HTC, most likely triggered by their belief that they needed additional clotting factor prescriptions. Further study is needed to establish how many 'arthritic-type' episodes, which might have been reclassified as bleeding by MSKUS, were not reported and were therefore missed and treated inadequately.

In addition to practical considerations for acute haemophilia care, our findings reveal our limited understanding of the mechanisms of initiation and perpetuation of joint bleeds in haemophilic arthropathy. At the molecular level, iron deposition, free radical generation, cytokine production, neoangiogenesis and synovial hypertrophy are all implicated in synovial and cartilage injury, resulting in changes and inflammation thought to be a nidus for intra-articular bleeding [2]. Our MSKUS findings demonstrated that hyperaemic synovium was significantly more often

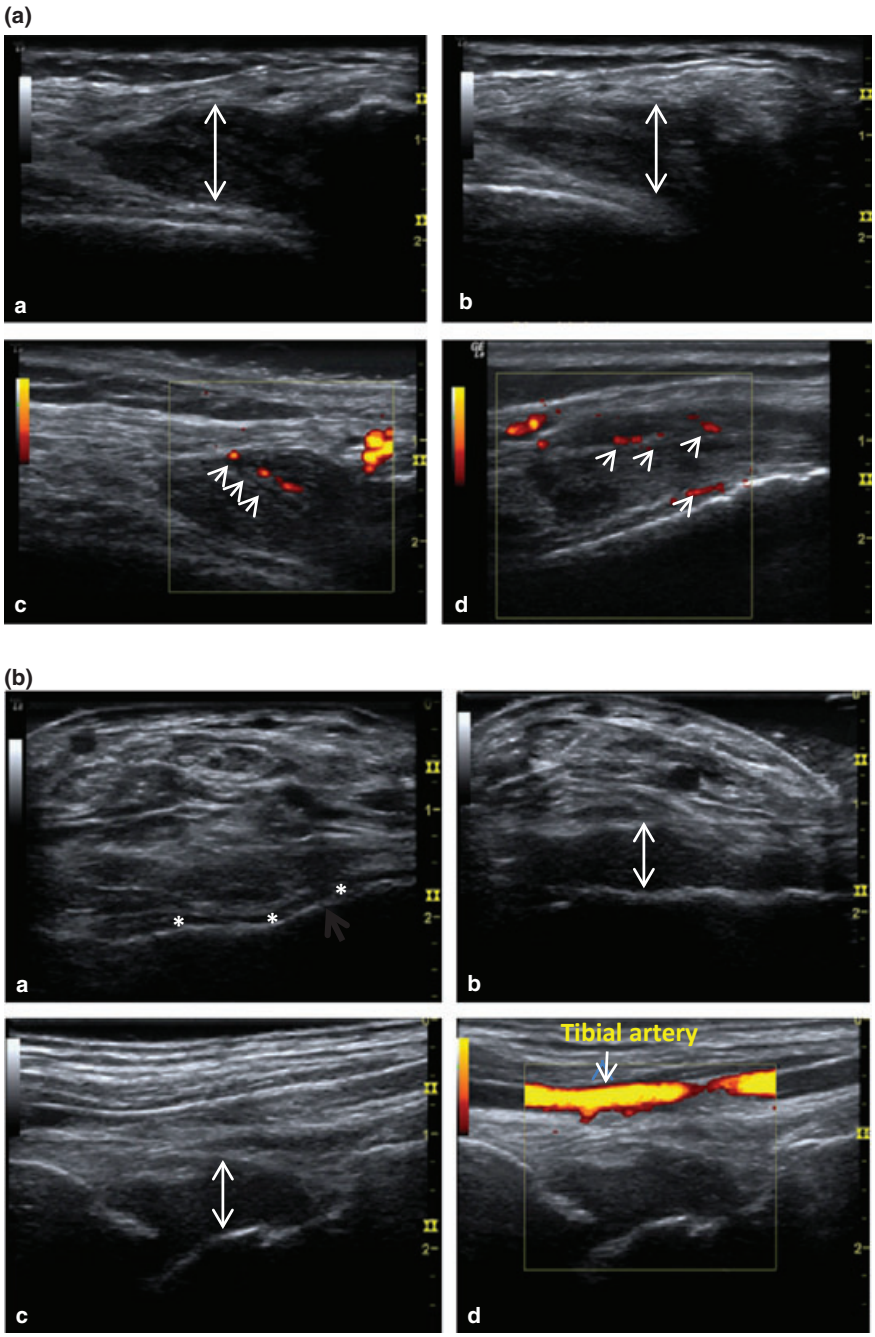

Fig. 4. Two case studies illustrating musculoskeletal ultrasound (MSKUS) in the diagnosis of bleeding and non-bleeding episodes. (a) 37-year-old man with severe *haemophilia A*, undergoing immune tolerance induction for inhibitor, presented with knee pain, warmth and swelling, perceived to be joint bleeding. a: Axial view of the lateral gutter of the left knee showed heterogeneous hypoechoic-to-anechoic intra-articular material (arrow). b: The intra-articular (i/a) material was hardly compressible and not displaceable (arrow) suggestive of thickened synovial tissue. c: Consistent with grey-scale ultrasound findings, power Doppler (PD) ultrasound revealed multiple vascularized/hyperaemic areas within the intra-articular space confirming the presence of vascularized synovial tissue (arrows). d: Orthogonal view of the area shown in c – confirmed presence of PD signal in multiple areas suggestive of thickened hypervascular synovial tissue without evidence of sonographic effusion. This episode was reclassified as synovitis. The patient received a dose of bypassing agent in conjunction with i/a steroid, which provided prompt, long-lasting (~2 months) relief of the joint symptoms. (b) 23-year-old man with severe *haemophilia B* presented with ankle pain. He had stopped prophylaxis in favour of on-demand FIX treatment and rarely treated himself due to his perception that "most painful episodes are due to arthritis". He had undergone baseline ankle MSKUS previously and presented several weeks later with a typical perceived "arthritic episode". a: Baseline axial view of the ankle showed normal thin anechoic synovial space in the tibiotalar joint (*). b: Interval examination during pain episode showed marked volume increased tibiotalar synovial space (arrow). Complex homogenous echogenic pattern and compressibility of the synovial space were consistent with complex effusion//intra-articular bleed. c: Orthogonal view of the d: Orthogonal view with power Doppler examination demonstrated absence of tissue vascularization in the area of interest consistent with effusion. This episode was reclassified as acute haemarthrosis, which was confirmed by ultrasound-guided joint aspiration. The patient received daily FIX infusion for 3 days with symptomatic relief. Prophylaxis was reinstituted with patient adherence since.

associated with overt joint bleeding than sonographic synovial hypertrophy alone, but it remains unknown if 'microbleeding' may have contributed to pain during episodes without overt bleeding. It is noteworthy that 'microbleeding' into haemophilic joints has long been believed by the haemophilia community [17,18], but has never been conclusively detected by high-sensitivity imaging techniques such as MRI or MSKUS. To the best of our knowledge, it also has never been described by histology of synovial tissue. Therefore, while 'microbleeding' is an important concept it currently lacks definition. We observed that joint fluid, aspirated under ultrasound guidance during episodes associated with effusions (aspirated in the majority of cases), confirmed the absence or presence of bleeding by imaging. Simple effusions were always straw coloured, whereas complex effusions were frankly bloody or serosanginous. However, even in the absence of overt bleeding, 'microbleeding' into synovial tissue pockets that is undetectable by current conventional imaging is conceivable, but the contribution to pain and the benefit of clotting factor replacement in that setting remain unknown. These findings underscore the need for prospective studies that could establish the relationships between synovial swelling, inflammation, hypervascularity/hyperaemia and bleeding during painful episodes and pain-free intervals. Such knowledge will ultimately lead to improved treatment algorithms for the prevention and management of haemophilic arthropathy.

Our findings question appropriate goals for plasma clotting factor activity levels for bleed prevention in adult PWH. In general, factor activity levels of 1% are largely considered protective against spontaneous joint bleeding [19], but individual thresholds for bleed prevention remain unknown. The current consensus was derived from a paediatric population with pristine joints (29 of 35 individuals with Pettersson joint scores of zero). Therefore, these data may not be applicable to the ageing PWH with progressive arthropathy and various degrees of synovial hypertrophy and hypervascularization. These synovial changes potentially can increase synovial vulnerability for injury and bleeding. Of note, for four MSKUS-confirmed spontaneous joint bleeding episodes in our series where patients had not administered clotting factor for at least 48 h prior to symptoms and MSKUS, plasma factor activities at the time of MSKUS were 5%, 8%, 9% and 28%. As evidenced by these cases, it is conceivable that the threshold of clotting factor activity levels required to prevent bleeding in adults with established haemophilic arthropathy may be higher than previously thought. Prospective studies with precise knowledge of timing and dosing of clotting factor preparations in relation to bleeding episodes and pharmacokinetic modelling will be necessary to determine appropriate clotting factor activity thresholds for bleed prevention in this population.

In summary, within the limitations of an observational study for complications in an orphan disease with complex heterogeneous joint pathology, we demonstrated that point-of-care MSKUS could be a valuable tool to assist with diagnosis of acute joint or muscle pain in PWH. If the technology is incorporated into haemophilia clinics, it is important to ensure that the operator is appropriately trained in MSKUS, as well as proficient in musculoskeletal medicine to interpret normal and pathological joint findings. Since MSKUS has at least equal if not greater sensitivity to detect soft tissue changes and the presence of effusions compared with MRI [6,8], introduction of MSKUS could provide a significant advance towards individualized care as acute overt bleeding requires clotting factor replacement, whereas painful episodes without bleeding may not. Musculoskeletal pain without bleeding may benefit from treatments established for musculoskeletal diseases encountered in sports medicine, podiatry, and including rheumatoid arthritis and osteoarthritis.

The current practice of prescribing clotting factor or conservative measures based on patient or physician perception of pain alone, without use of objective imaging evaluation, appears to be inadequate for modern haemophilia care and may ultimately compromise outcomes. Notably, the American College of Rheumatology has recommended MSKUS for diagnosis of synovitis in rheumatoid arthritis as it has been found superior to physical exam [9]. Findings from our study generated many questions that remain unresolved including the role of 'microbleeding' during painful episodes, the possibility of subclinical bleeding contributing to arthropathy, the contribution of hyperaemic synovitis flares to pain during bleeding episodes, short-term and long-term benefits of imaging-based treatment decisions, bleeding propensity in relation to synovial pathology and protective plasma clotting factor thresholds. Clearly, prospective studies addressing these questions are essential to further advance our understanding of haemophilic arthropathy and to further improve outcomes in adults with haemophilia.

Author contribution

AC carried out the ultrasound examinations and interpretations, assisted with data analysis and the manuscript draft. IWS contributed to data analysis and drafted the manuscript. CSG assisted with data collection and study execution. AvD designed the study, analysed and interpreted the data and drafted of the manuscript.

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Disclosures

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