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Advanced Hemophilic Arthropathy: Sensitivity of Soft Tissue Discrimination With Musculoskeletal Ultrasound

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Objectives—Point-of-care musculoskeletal ultrasound (US) is increasingly used by hemophilia providers to guide management; however, pathologic tissue differentiation with US is uncertain. We sought to determine the extent to which point-of-care musculoskeletal US can identify and discriminate pathologic soft tissue changes in hemophilic arthropathy.

Methods—Thirty-six adult patients with hemophilia A/B were prospectively enrolled. Point-of-care musculoskeletal US examinations were performed on arthropathic joints (16 knees, 10 ankles, and 10 elbows) using standard views by a musculoskeletal US–trained and certified hematologist, who recorded abnormal intra-articular soft tissue accumulation. Within 3 days, magnetic resonance imaging was performed using conventional and multiecho ultrashort echo time sequences. Soft tissue identification (synovial proliferation with or without hemosiderin, fat, and/or blood products) was performed by a musculoskeletal radiologist. Findings obtained with both imaging modalities were compared and correlated in a blinded fashion.

Results—There was perfect agreement between the modalities on the presence of abnormal soft tissue (34 of 36 cases). However, musculoskeletal US was unable to discriminate between coagulated blood, synovium, intrasynovial or extrasynovial fat tissue, or hemosiderin deposits because of wide variations in echogenicity.

Conclusions—Musculoskeletal US is valuable for point-of-care imaging to determine the presence of soft tissue accumulation in discrete areas. However, because of limitations of musculoskeletal US in discriminating the nature of pathologic soft tissues and detecting hemosiderin, magnetic resonance imaging will be required if such discrimination is clinically important.

Key Words—arthropathy; hemophilia; magnetic resonance imaging; musculoskeletal (diagnostic); point-of-care; ultrasound

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Abbreviations

MRI, magnetic resonance imaging; TE, echo time; TR, repetition time; US, ultrasound

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Joint arthropathy is a common clinical manifestation of hemophilia.[1–3] Contributing factors to hemophilic joint damage are thought to include recurrent hemarthroses, synovial inflammation, and soft tissue hypertrophy, ultimately leading to osteochondral deformities and destruction.[4–7] Use of imaging in hemophilia continues to progress. Although magnetic resonance imaging (MRI) has long been considered the reference standard, recent advances in technology, accessibility, and training have made ultrasound (US) an attractive alternative. In fact, it is now evident that musculoskeletal US has a number of benefits compared with MRI in that musculoskeletal

US is faster, more economical, and without the need of sedation for claustrophobic patients or children. Musculoskeletal US does not require intravenous contrast to distinguish synovial proliferation from fluid[8–10] and can be used to assess synovial vascularity in arthritic conditions,[11] including hemophilic arthropathy.[3,5,12,13]

One of the most important aspects of musculoskeletal US is that point-of-care imaging is now possible. Musculoskeletal US has been shown to be effective and helpful for management of a wide spectrum of musculoskeletal disorders spanning multiple disciplines[14–16] and has been introduced into hemophilia clinics to assist providers with in-office management of hemophilic arthropathy.[3,12,17,18] In particular, musculoskeletal US has been found to be critical for identifying tissue abnormalities contributing to pain in patients with hemophilia[12] and to rapidly and accurately determine whether hemarthrosis is present.[3,17,18] Musculoskeletal US has also been proposed to quantify tissue abnormalities in semiquantitative scoring algorithms.[2,13,19,20]

Musculoskeletal US use is growing rapidly in routine management of hemophilia, and it is evident that validation of pathologic tissue annotation is necessary, particularly for the development of scaling systems to assess the overall joint health status, either by semiquantitative algorithms or quantitatively by applying direct tissue measurements. Toward this goal, standardization must occur, and a consensus regarding US definitions of pathologic conditions must be reached. Although it is accepted that US can readily distinguish between fluid and soft tissue,[3,13,21] the correct assignment and differentiation between individual tissue types such as synovium (with and without hemosiderin deposits) and fat remain less certain. For instance, synovial hypertrophy is typically hypoechoic relative to subdermal fat but at times also can be isoechoic or hyperechoic.[22] In addition, whether and to what extent altered echogenicity in synovium of hemophilic joints can be ascribed to hemosiderin deposition are unclear and currently debated.[23,24] Altogether, these factors may confound the distinction of different pathologic tissues and their discrimination from other surrounding structures. The purpose of this study was to elucidate the role and limitations of musculoskeletal US for the detection and discrimination of soft tissue findings in hemophilic arthropathy and to inform the development of US joint assessment tools as well as diagnostic and therapeutic management decisions. A comparison was made with MRI as a reference standard.

Materials and Methods

Patient Population and Data Extracted

Adult patients with hemophilia A or B of all severities, age 21 years and older (n = 36), seen consecutively during routine clinic visits over a 4-month period, undergoing US examinations of arthropathic joints to monitor clinical progression, and willing to undergo consecutive MRI of the same joint within 3 days provided written informed consent for the study. In total, 16 knees, 10 ankles, and 10 elbow joints were imaged, which together represent the 3 most commonly affected joints in hemophilic arthropathy. Joints were defined as arthropathic by the responsible hematologist before imaging, when patients identified them as previous target joints (frequent bleeding) and/or when notable deformities and function deficits were present on the physical examination. Additionally, hemophilia joint health scores[25] and radiographic Pettersson scores[26] were collected at the time of inclusion to provide objective proof of arthropathy. The degree of arthropathy was also determined by MRI scoring as recommended by the International Prophylaxis Study Group.[27] The study protocol, data acquisition, and patient confidentiality safeguards were approved by the Human Research Protection Program at the University of California San Diego.

Imaging

All US studies were performed by a hematologist (with 5 years of musculoskeletal US experience) who was formally trained and certified in musculoskeletal US through the American Registry for Diagnostic Medical Sonography. A 6–15-MHz linear transducer was used for imaging (LOGIQ S8; GE Healthcare Technologies, Milwaukee, WI). Musculoskeletal US examinations were performed by using standard imaging planes for each joint area.[19] Sonopalpation was used as appropriate.

Magnetic resonance imaging was performed on a clinical 3T scanner (Signa HDx; GE Healthcare Technologies) and either an 8-channel knee coil, 4-channel ankle coil, or 8-channel flexible surface coil (for knees, ankles, and elbows, respectively) using the following 2-dimensional sequences: sagittal fast spin echo T1-weighted (repetition time [TR]/echo time [TE], 650/10 milliseconds; echo train length of 4; 4-mm slice thickness; 0.5-mm interslice gap; 384 × 320 matrix; 14-cm field of view; and 1 signal average), sagittal fast spin echo T2-weighted with fat suppression (TR/TE, 4000/65

milliseconds; echo train length of 12; 4-mm slice thickness; 0.3-mm interslice gap; 384 × 288 matrix; 14-cm field of view; and 2 signal averages), coronal fast spin echo T1-weighted (TR/TE, 650/10 milliseconds; echo train length of 4; 4-mm slice thickness, 0.5-mm interslice gap, 384 × 320 matrix, 14-cm field of view, and 2 signal averages), coronal fast spin echo T2-weighted with fat suppression (TR/TE, 5000/65 milliseconds, echo train length of 16, 4-mm slice thickness, 0.5-mm interslice gap, 384 × 320 matrix, 14-cm field of view, and 1 signal average), axial fast spin echo T1-weighted (TR/TE, 650/10 milliseconds; echo train length of 4; 4-mm slice thickness; 0.5-mm interslice gap; 320 × 288 matrix; 14-cm field of view; and 1 signal averages), and axial fast spin echo intermediate-weighted with fat suppression (TR/TE, 3200/40 milliseconds; echo train length of 9; 4-mm slice thickness; 0.5-mm interslice gap; 320 × 288 matrix; 14-cm field of view; and 1 signal averages). In addition, sagittal 3-dimensional ultrashort TE images were acquired with a cone readout trajectory at 4 different TEs (TR/TEs, 15/0.03, 2.8–3, 5.6–6, and 8.4-9 milliseconds; flip angle, 11°; 4-mm slice thickness; 256 × 256 matrix; 14-cm field of view; and time ≈6 minutes).[28] An intravenous contrast agent was administered for select cases when clinically indicated.

Joint Assessment, Image Interpretation, and Data Analysis

On musculoskeletal US images, the presence of soft tissue was recorded when noncompressible abnormal intra-articular material was detected.[22] The echogenicity of the noncompressible material was compared relative to the adjacent soft tissue and was noted as hypoechoic, hyperechoic, or mixed. Intra-articular fluid was also noted when the material was entirely compressible.

A fellowship-trained musculoskeletal radiologist (with 6 years of experience) was blinded to the musculoskeletal US results and independently recorded the presence or absence of intra-articular joint fluid, soft tissue, or blood products after evaluation of all images in the MRI protocol. Prior MR imaging examinations were also evaluated, when available. Fluid and tissue discrimination was performed in a standard manner as follows: fluid shows an increased signal on all fluid-sensitive sequences and a comparable signal on T1-weighted images relative to muscle, most typically hypointense when the fluid is bland; fat shows a hyperintense signal on T1-weighted images relative to muscle with a hypointense signal on all sequences after a spectral fat suppression preparatory pulse; and hemosiderin shows progressive loss of the signal with increasing TEs on the multiecho ultrashort TE sequence (with special consideration of chemical shift artifacts of the second kind for voxels containing both fat and water on out-of-phase TEs[29]. It is recognized that conventional MRI sequences cannot effectively distinguish between fluids of various degrees of complexity (such as saline versus blood).[30] However, when blood is coagulated or a blood-fluid level is appreciated, hemarthrosis can be diagnosed, and blood clots are distinguished on the basis of retraction and degradation products, as previously described.[31–34] Regarding synovial proliferation, it is recognized that synovium without hemosiderin may show a variety of signal intensities depending on the precise composition, at times approaching that of fluid on conventional fluid-sensitive clinical sequences.[35–37] However, synovial proliferation in hemophilia[38,39] often contains fibroblasts and fibrotic tissue and in these cases should be less intense than fluid on fluid-sensitive sequences.

Statistical Analyses

We assessed the agreement between US and MRI for the detection of soft tissue of any type. The Fisher exact test was performed to compare MRI-based synovial proliferation with and without hemosiderin versus US echogenicity. Descriptive statistics were applied to joint scoring using radiographic, clinical, and MRI scales.

Results

Patient and Joint Characteristics

In total, 36 patients (mean age, 44 years; SD, 15.7 years; range, 21–70 years) were recruited (10 ankles, 16 knees, and 10 elbows) and imaged with both MRI and musculoskeletal US. All 36 joints were affected by hemophilic arthropathy, evidenced by either a positive radiographic Pettersson score (mean, 8.0; SD, 4.5; range, 0–12), a clinical hemophilia joint health score (mean, 4.7; SD, 3.7; range, 0–11), and/or an International Prophylaxis Study Group MRI score (mean, 10.9; SD, 4.6; range, 0–22).

Soft Tissue Assessment With Musculoskeletal US Compared With MRI

Both musculoskeletal US and MRI showed the presence and absence of abnormal soft tissue expansion in 34 and 2 of the 36 patients, respectively, with complete

Table 1. Predominant Echogenicity of Synovial Proliferation on US Imaging in the Presence or Absence of Hemosiderin Documented by MRI

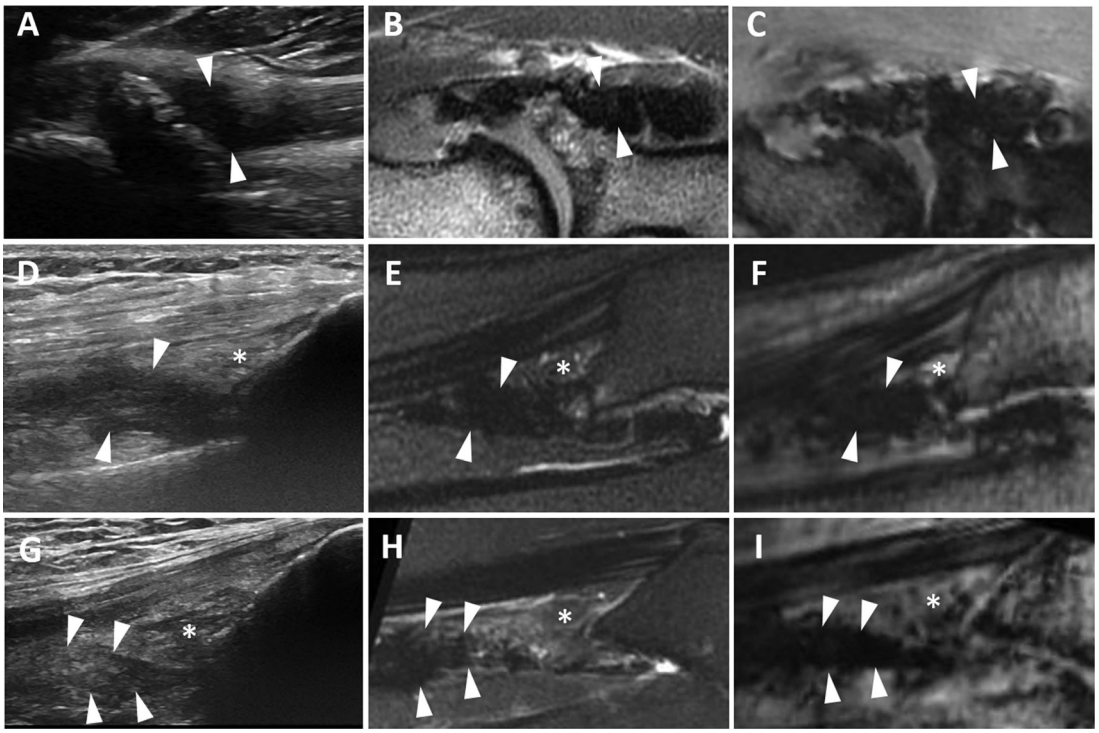
	Predominant Echogenicity on US			
MRI Appearance	**Hyper**	**Hypo**	**Mixed**	**Total**
Hemosiderin absent	3	2	1	6
Hemosiderin present	3	18	5	26
Total	6	20	6	32

$P = .126$, Fisher exact test.

agreement between the imaging modalities in all cases. Magnetic resonance imaging was used for tissue delineation and showed that synovial proliferation with or without hemosiderin was present in 26 and 6 cases, whereas fat tissue expansion was present in 6 cases. Blood clots were seen in 3 cases. With the use of MRI as a comparator, musculoskeletal US was unable to discriminate soft tissue types (synovial proliferation with or without hemosiderin, fatty tissue expansion, and blood clots) based on echogenicity. None of the abnormal soft tissue types was found to have specific features on musculoskeletal US imaging. The echogenicity of fatty tissue expansion was deemed predominantly hypoechoic in 4 cases and hyperechoic in 2 cases. Of the 3 blood clots, 2 were predominantly hypoechoic, and 1 was of mixed echogenicity. Hemosiderin-laden synovium could be predominantly hypoechoic or hyperechoic or could appear with mixed echogenicity, similar to non–hemosiderin-laden synovial proliferation (Table 1). Although there was a propensity of hypoechoic synovium in the presence of hemosiderin (18 of 26 cases [69%]) compared with synovial proliferation without hemosiderin (2 of 6 [33%]), this difference was not significant ($P = .126$; Table 1).

Key findings are illustrated by the figures. Hemosiderin-laden synovial proliferation had no unifying US characteristics. The echogenicity of hemosiderin varied widely from predominantly hypoechoic to hyperechoic patterns. Figure 1 shows 3 distinct US appearances

Figure 1. Various echo textures of hemosiderin-laden synovial proliferation: annular recess in the elbow of a 39-year-old patient (**A–C**) and suprapatellar recesses in the knees of a 23-year-old patient (**D–F**) and a 38-year-old patient (**G–I**). **A, D**, and **G**, Longitudinal US images show thick, noncompressible tissue with increasing coarseness and a heterogeneous echo texture (arrowheads), which differs between patients. **B, C, E, F, H**, and **I**, Sagittal T2-weighted and ultrashort TE gradient MR images (TE, 6.0 milliseconds) show hypointense tissue with blooming, consistent with hemosiderin-laden synovium. Asterisks indicate suprapatellar fat pad.



of MRI-proven hemosiderin-laden synovial proliferation, including a nearly anechoic pattern (Figure 1A), a mixed but predominantly hypoechoic pattern (Figure 1D), and a hyperechoic pattern (Figure 1G). Moreover, synovial proliferation, even without confounding hemosiderin depositions, also had no unifying echogenic features and could present either with a nearly anechoic pattern (Figure 2A) or a hypoechoic pattern (Figure 2D), again resembling certain echogenicity patterns of hemosiderin-laden synovial proliferation (Figures 1, A and D, and 2, A and D). Moreover, it appeared that hemosiderin was not always distributed equally in proliferating synovium, sometimes with zones of highly focal depositions abutted by enhancing less hemosiderin-laden synovitis, as shown by MRI in Figure 3, B, C, E, and F. The example shown in Figure 3 shows that joints with advanced hemophilic arthropathy and abundant synovial proliferation can have complex patterns of hemosiderin distribution and synovial inflammation which, although discernable on MRI, cannot be discriminated by US. The corresponding US images were highly heterogeneous, not permitting a distinction of the different synovial properties shown on MRI based on echogenicity. Ultrasound images included regions that were predominantly anechoic or hypoechoic and coarsely granular in some areas (Figure 3, A and D). The various US patterns were not associated with distinct MRI appearances of hemosiderin-laden synovium or areas of enhancing synovitis.

An abnormal intraarticular soft tissue composition can be highly complex, change in character over time, and represent ectopic tissue other than synovial proliferation, as shown in an elbow studied with sequential MRI 6 years apart. Figure 4, A and D, shows 2 adjacent images from the US examination that was performed concurrently with the latest elbow MRI. The US images show noncompressible soft tissue in the annular recess of a severely arthropathic elbow, where usually synovial hypertrophy would be suspected. However, US revealed a multistructured tissue mass with areas of distinctly different echogenicities that were not consistent with the usually more uniform appearance of synovium. This soft tissue mass was shown to be predominantly hypointense on MRI (Figure 4, B and E), consistent with hemosiderin-laden synovial proliferation. However, there were internal regions that were hyperintense, suspected to be areas of active bleeding. Of note, the soft tissue mass had no distinctive features compared with previously shown synovial US appearances mentioned above. On review of a comparison MRI examination 6 years previously, it was noted that the hemosiderin-laden synovial proliferation was previously homogeneously hypointense (Figure 4, C and F), without regions of different intensities. This case illustrates that hemosiderin-laden synovium remains biologically active and can occasionally show frank intrasynovial bleeding, thus creating a complicated appearance on both US and MR images

Figure 2. Various echo textures of synovial proliferation without hemosiderin: anterior recess of the tibiotalar joint in a 57-year-old man (**A–C**) and anterior recess of the elbow in a 42-year-old man (**D–F**). **A**, Longitudinal US image shows hypoechoic, noncompressible tissue (arrowhead). **B**, Sagittal T2-weighted, fat-suppressed MR image shows hyperintense synovial proliferation (arrowhead). **C**, Ultrashort TE gradient MR image (TE, 10.8 milliseconds) shows lack of blooming, indicative of lack of hemosiderin (arrowhead). **D**, Axial US image shows isoechoic, noncompressible tissue (arrowhead). **E**, Axial T2-weighted, fat-suppressed MR image shows predominantly hyperintense synovial proliferation without a blooming artifact (arrowhead). **F**, Axial T1-weighted, fat-suppressed, post–intravenous contrast MR image confirms thick, enhancing synovium without hemosiderin.

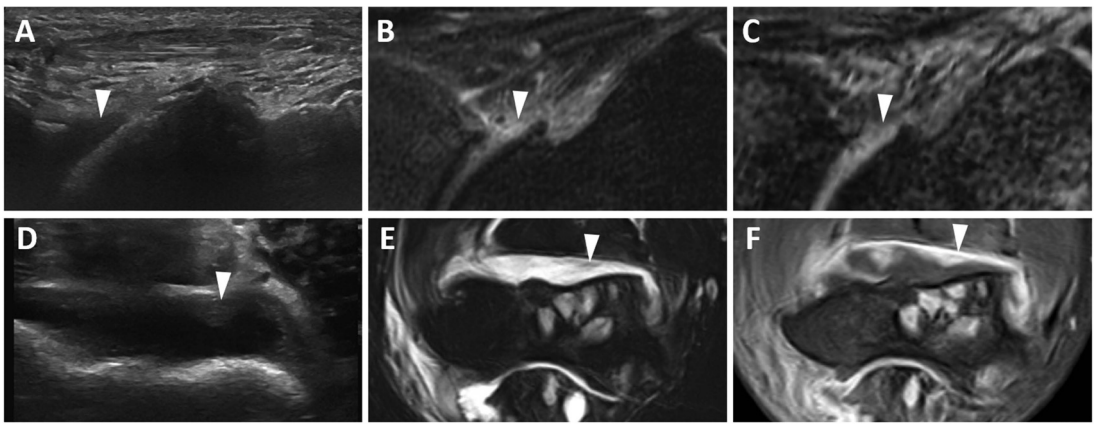


Figure 3. Various echo textures of synovial proliferation containing hemosiderin: axial posterior views (**A–C**) and long-axis anterior views (**D–F**) of the elbow joint in a 44-year-old man (distal humerus labeled with asterisks). **A**, Axial US image shows noncompressible tissue in the posterolateral recess (arrowhead) with a granular, hypoechoic pattern and the posterior recess (thick arrow) with a hyperechoic pattern. **B**, Axial intermediate-weighted (TR/TE, 1712/23 milliseconds), fat-suppressed image shows hemosiderin-laden synovial proliferation in the posterolateral recess (arrowhead). **C**, Axial T1-weighted, fat-suppressed, post–intravenous contrast MR image shows enhancing synovium in the posterolateral (thin arrow) and posterior (thick arrow) recesses. **D**, Longitudinal US image shows mixed, predominantly hyperechoic, noncompressible tissue directly at the level of the joint line (arrowhead). **E**, Sagittal T1-weighted MR image shows hypointense, hemosiderin-laden synovium (arrowhead). **F**, Sagittal T1-weighted, fat-suppressed, post–intravenous contrast MR image shows areas of avid enhancement (thin arrow) adjacent to hypointense areas (arrowhead), consistent with synovium containing various amounts of hemosiderin.

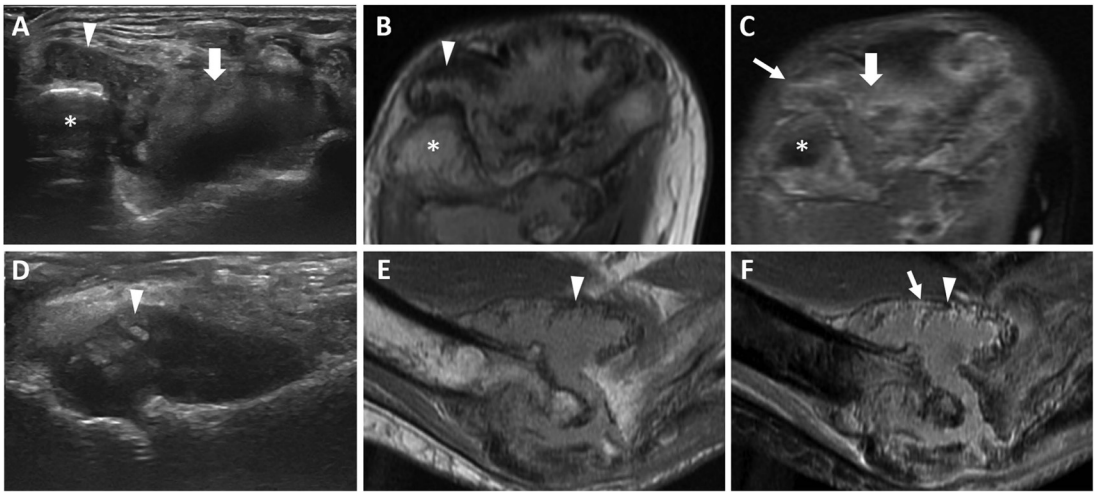
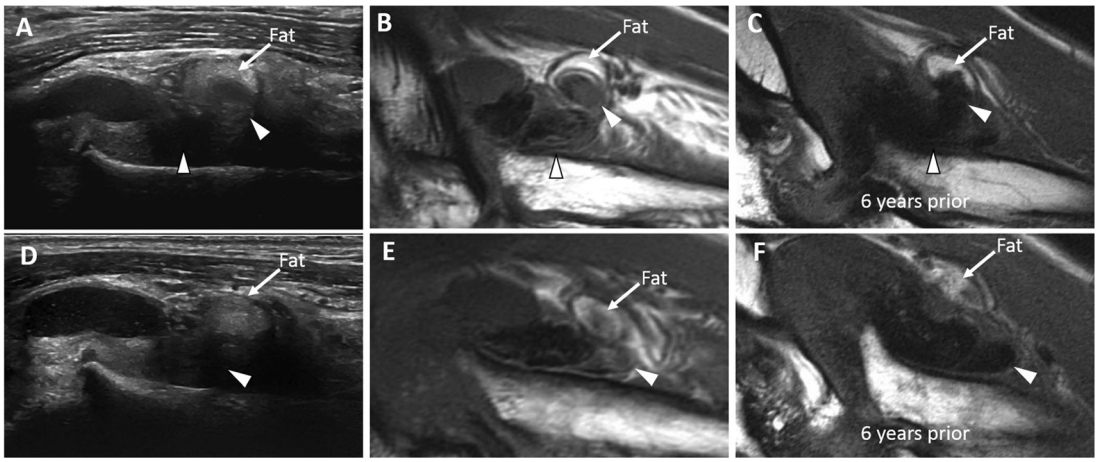


Figure 4. Various echo textures of hemosiderin-laden synovial proliferation: anterior aspect of the radiocapitellar compartment of the elbow in a 48-year-old man (**A, B, D**, and **E**) and 6 years previously (**C** and **F**). **A** and **D**, Long-axis US images show mixed echogenicity in the annular recess, with predominantly noncompressible tissue (arrowheads). **B** and **E**, Sagittal T1-weighted MR images obtained on the same day as the US images show hemosiderin-laden synovial proliferation with mixed internal signal intensity, suggestive of more recent blood products (arrowheads). **C** and **F**, Sagittal T1-weighted MR images 6 years before presentation show homogeneously hypointense hemosiderin-laden synovium (arrowheads). To facilitate comparison between all images, a curvilinear region of intra-articular fat is present anteriorly and labeled, acting as an internal anatomic landmark.



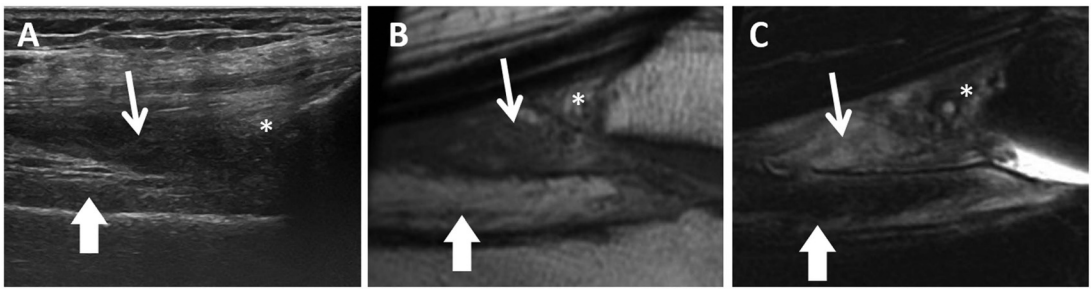
and further highlighting the limitations of pathologic tissue discrimination with US.

Moreover, coagulating blood or a blood clot was indistinguishable from synovial proliferation with or without hemosiderin. Figure 5 shows suprapatellar expansion in an asymptomatic patient. The area was mildly compressible, with a predominantly hypoechoic US appearance, whereas the soft tissue echogenicity was found to be nearly identical to previously shown US patterns of synovial proliferation with (Figure 1D) or without (Figure 2D) hemosiderin. However, MRI showed the presence of a blood clot rather than synovial proliferation. Moreover, findings in this patient also demonstrate that fat pad echogenicity can be heterogeneous in hemophilic joints. The prefemoral fat pad, usually visualized as a hyperechoic area abutting the suprapatellar recess in normal joints, showed heterogeneous echogenicity (Figure 5A), blending into the area of coagulating blood. The T2-weighted, fat-suppressed MR images showed an increased signal at the periphery of the inferior aspect, which may represent edema (Figure 5C). This observation highlights the idea that pathologic fat pads or blood clots can be easily confused with synovial hypertrophy, which is usually assumed to be the cause of suprapatellar soft tissue expansion. Figure 6 further illustrates various appearances of intraarticular fatty tissue, bearing the potential to be mistaken for synovial hypertrophy. Figure 6, A and B, shows small floating fronds of hyperechoic tissue in fluid, which was displaced on sonopalpation, only to return to the same position after release of pressure. Magnetic resonance imaging confirmed these fronds to represent fat and not synovial tissue, consistent with secondary lipoma arborescens (intrasynovial fat metaplasia). In another patient, a tonguelike, hyperechoic soft tissue structure was surrounded by fluid (Figure 6I), which extended in and out of plane on repeated compression with the US transducer. Magnetic resonance imaging showed this tissue to represent a thickened projection of an expanded extrasynovial prefemoral fat pad (Figure 6, K and L), whereas on US imaging, this finding may have been recorded as synovial proliferation because of its typical location.

Discussion

Nonradiologists across medical specialties increasingly use US in clinics and at the bedside for rapid imaging-guided diagnosis and interventions to enable efficient and immediate personalized care.[3,12,17,18] In patients with hemophilia, who have established arthropathy, it is not clinically possible to effectively distinguish between an acute bleeding event and a flare in inflammation—circumstances that call for very different interventions. Thus, there is a need to develop and validate US scales to provide an assessment of overall joint health outcomes longitudinally,[19,20] similar to what has been developed with MRI.[27,40,41] Pathologic tissue recognition with musculoskeletal US during the examination of hemophilic joints requires validation to answer pertinent diagnostic questions relevant to hemophilia care and to develop US scales. Current interpretation algorithms for tissue discrimination are derived from studies in rheumatoid arthritis or osteoarthritis and imply that the pathobiological characteristics of hemophilic arthropathy are comparable with those of these other arthritic conditions.

Figure 5. Soft tissue accumulation (blood clot). **A**, Long-axis US image shows hypoechoic tissue that was partially compressible on real-time imaging in the suprapatellar recess (thin arrow). **B** and **C**, Sagittal T1-weighted (**B**) and T2-weighted (**C**), fat-suppressed MR images show a heterogeneously hyperintense signal in the suprapatellar recess on both sequences, consistent with coagulated subacute blood products. Prefemoral (thick arrows) and suprapatellar (asterisks) fat pads are marked. Note that the prefemoral fat pad is more hyperintense proximally compared with distally.

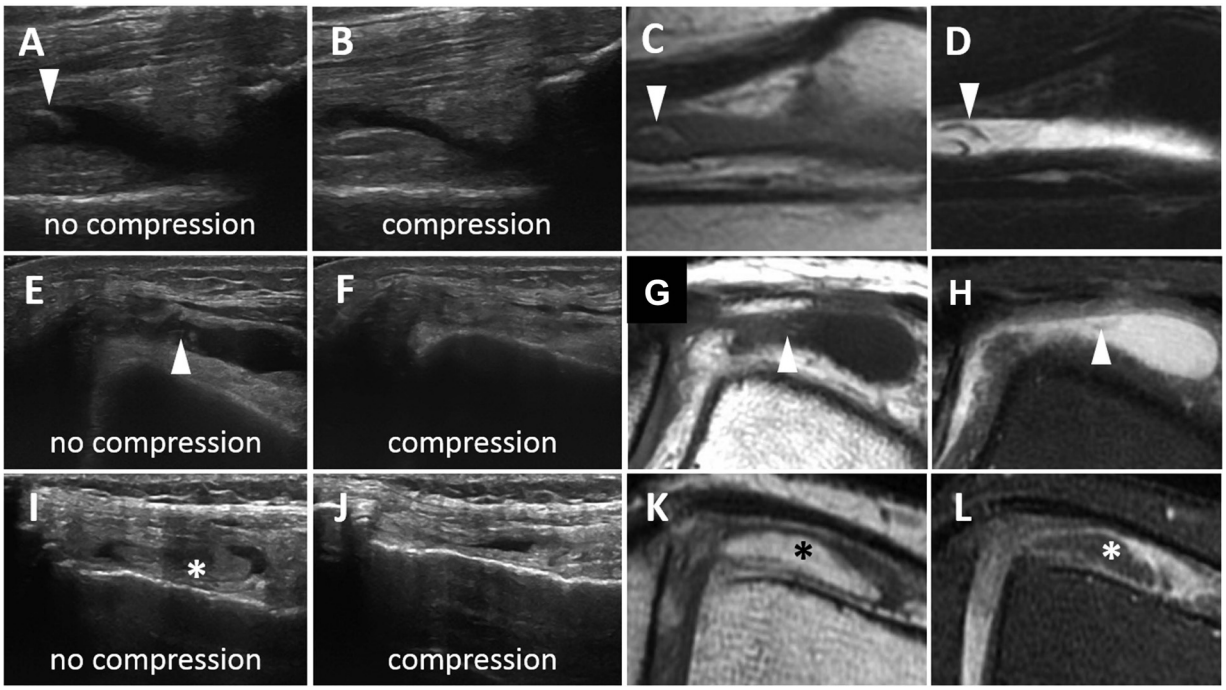


However, this implication may not be true, given numerous confounders inherent to the different etiology of hemophilic arthropathy. Examples of such confounders are bleeding with hemosiderin accumulation and extensive vascular remodeling with leaky vessels,[5,12,42] both unique to hemophilic arthropathy and not encountered in the other conditions. It is therefore important to perform validation studies to define the ability and limitations of musculoskeletal US to answer specific questions relevant to hemophilic arthropathy and define to what extent musculoskeletal US can discriminate between different pathologic soft tissue types or states.

Of note, and to provide a perspective, the validation process for the use of musculoskeletal US in rheumatoid arthritis is still ongoing,[43] and only recently, after a decade of progress, was MRI deemed valid.[44] The Outcome Measures in Rheumatology group, an international initiative focused on standardization in rheumatology, has set forth clear guidelines for validation that first involve a consensus definition of pathologic conditions visible by a certain imaging modality, preferentially supported by cross-reference to another validated imaging modality, and, secondarily, determination of the effectiveness of pathologic recognition and discrimination. Others have begun the validation process of US in hemophilic arthropathy[20,45] but predominantly in children and youth in early stages of the disease. Therefore, musculoskeletal US tissue validation studies in hemophilic arthropathy, especially for findings in more advanced stages and adults, remain an unmet clinical need and are urgently required to advance diagnostic recognition patterns in the point-of-care setting.

Our study, involving direct comparison of musculoskeletal US with MRI, begins to fill this gap, delineating to what extent musculoskeletal US can show the presence of abnormal soft tissue and discriminate between various soft tissue abnormalities. This objective was accomplished by comparing imaging findings on musculoskeletal US with the accepted reference standard of MRI, with inclusion of both routine clinical sequences

Figure 6. Appearance of fat in joint recesses of 3 patients. **A** and **B**, Suprapatellar recess. Longitudinal US images show a frond of hyperechoic material surrounded by fluid that was compressible on real-time imaging (arrowheads). **C** and **D**, Sagittal T1-weighted (**C**) and T2-weighted (**D**), fat-suppressed MR images elucidate the soft tissue frond as fat metaplasia (arrowheads). **E** and **F**, Transverse US images show compressible, anechoic fluid with few fronds of hyperechoic material (arrowhead), consistent with an effusion and solid material. **G** and **H**, Axial T1-weighted (**G**) and T2-weighted (**H**), fat-suppressed MR images confirm the effusion and show that the solid material is fat (arrowheads). **I** and **J**, Transverse US images show a thickened tongue of tissue (asterisk), which displaces out of plane on compression. **K** and **L**, T1-weighted (**K**) and intermediate-weighted (**L**), fat-suppressed MR images show that this tissue is an inferior projection of the extrasynovial, prefemoral fat pad (asterisks).



and sensitive 3-dimensional multiecho ultrashort TE sequences. Although not yet available on most clinical MRI machines, the multiecho ultrashort TE sequence (with TEs ranging from 0.03 to 9 milliseconds) is analogous to gradient echo sequences and facilitates optimal detection of various amounts of hemosiderin, including a low burden (which is less apparent on images with a TE of 0.03 milliseconds but more apparent at longer TEs) to a very high burden (visible on all images, including those with a TE of 0.03 milliseconds).

We demonstrated that musculoskeletal US effectively detected expanded or heterotopic soft tissue, but it was not able to discriminate between soft tissue types based on echogenicity alone, such as coagulated blood, synovial proliferation (of any subtype, including intrasynovial fatty tissue), or fat pad expansion. Interestingly, our observations also suggest that hemophilic joint bleeding is not limited to intracavitary hemarthrosis but can also manifest as soft tissue or synovial hemorrhages, as illustrated by the case presented in Figure 4. These hemorrhages cannot be detected by US or easily by MRI. This finding was unexpected and highlights the idea that our understanding of the pathobiological characteristics of hemophilic joint bleeding and imaging modalities for detection is incomplete. We found that intra-articular tissues in hemophilic joints can lose their usual US-discriminating features, including morphologic characteristics, echogenicity, and the expected location, in pathologic states. For instance, extrasynovial fat pads, which are typically smooth and hyperechoic, may become irregular and hypoechoic and may form extensions into joint recesses, potentially resembling hypertrophic synovium. We also observed that lipoma arborescens, which signifies fatty synovial metaplasia,[46,47] can be easily misinterpreted as nonfatty synovial proliferation on musculoskeletal US images when present in smaller amounts. Extrasynovial fat pad extension into the adjacent medial and lateral recesses has not been previously described, to the best of our knowledge, although we have seen this phenomenon in patients without hemophilia. The frequency and importance of this finding remain to be elucidated. We have also shown that the usual hyperechoic fat pad appearance may change on US images, in analogy to what was previously described with MRI in other arthritic conditions.[48,49] Although echogenic features of pathologic fat pad alterations have not yet been described systematically, observations from this study suggest that alterations are present and complicate the distinction of fat expansion or displacement from hypertrophic synovium.

Importantly, musculoskeletal US was unable to detect hemosiderin deposits in our study. There were no distinct echogenic features that permitted the determination of whether synovium was hemosiderin laden. This observation was in contrast to previous findings,[20,24] describing hemosiderin-laden synovium as relatively hypoechoic, an observation considered controversial by other experts in the field.[23] Toward that end, it has to be noted that the hemosiderin-laden synovium tended to appear hypoechoic in a substantial number of cases in our study, but the difference from non–hemosiderin-laden synovial proliferation was not statistically significant. Based on our findings, it appears that musculoskeletal US cannot detect hemosiderin, and if clinically relevant, requires MRI to make the distinction.

With respect to the use of point-of-care musculoskeletal US for the evaluation of hemophilic arthropathy in everyday clinical practice, our findings support musculoskeletal US as a highly sensitive modality for detecting the presence of soft tissue alterations, albeit without discrimination between synovial, fatty, and blood origins. Recognizing this limitation appears valuable and relevant when comparing findings to baseline examinations in clinical follow-up over time, as well as for the development of US scales to quantify and describe the progression of arthropathic changes. On the basis of our findings, we suggest that soft tissue proliferation is best reported nonspecifically as "soft tissue expansion" rather than "synovial proliferation," and soft tissue alterations are described by applying usual US nomenclature, but without assignment to specific structures such as synovium. The discrete tissue delineation using US and MRI, with conventional and ultrashort TE MRI sequences, revealed a key finding: namely, that expanding tissues in hemophilic joints are not just synovial, as widely assumed. In the acute clinical setting, it may not be important to delineate which tissue is expanding, whereas the ability to distinguish between expanding tissue and the presence of hemarthrosis (including blood clots) is critical. Both have similar clinical presentations encompassing loss of range of motion, swelling, and pain,[3] but treatment approaches differ, in that only hemarthrosis requires clotting factor replacement therapy. Based on the findings of this study, and the fact that musculoskeletal US is considered highly sensitive for distinguishing effusions from soft tissue, the most

important utility of point-of-care musculoskeletal US in hemophilia clinics may therefore be the diagnosis of hemarthrosis. In the chronic setting, when following arthropathic joints longitudinally, the clinical and pathobiological meaning of limited soft tissue discrimination is unknown and requires further study.

A limitation of this study may have been that most of the imaged joints were affected by advanced arthropathy. It is conceivable that tissue discrimination by musculoskeletal US is easier in early arthropathy, when tissue characteristics may resemble their original state more closely.

This study reinforces the importance of following Outcome Measures in Rheumatology guidelines when developing new imaging modalities for arthritic conditions and highlights the importance of providing objective evidence regarding advantages and limitations of musculoskeletal US. The integration of point-of-care musculoskeletal US to afford insightful, timely, convenient, and targeted management of hemophilic arthropathy remains a major advancement for hemophilia care but requires ongoing validation and standardization. It is imperative that providers recognize the advantages and limitations of musculoskeletal US to decide which imaging modality may be most appropriate based on current knowledge to answer a specific question.

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