Haemophilia WILEY

ORIGINAL ARTICLE

Muskuloskeletal

Quantitative measurements of haemophilic joint tissues by point-of-care musculoskeletal ultrasound: Associations with clinical and functional joint outcome parameters

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Abstract

Background: Painful arthropathy is a long-term complication in patients with hemophilia (PWH), affecting mobility and quality of life. A major barrier for the appraisal of joint health is the absence of point-of-care (POC) imaging modalities to promptly identify and manage arthropathic changes. Accordingly, we developed the Joint tissue Activity and Damage Exam (JADE) POC musculoskeletal ultrasound (MSKUS) protocol. JADE is validated for haemophilic joint tissue recognition with high intra/inter-rater and inter-operator reliability.

Aims: Evaluate associations of JADE with clinical (Hemophilia Joint Health Score, [HJHS]) and functional (total arc [combined flexion and extension range of motion [ROM]]) parameters.

Methodology: In this multi-centre prospective study, we recruited PWH A or B with at least one arthropathic joint. We evaluated joint health (both elbows, knees, and ankles) by comparing JADE measurements (soft tissue and cartilage thickness, and osteochondral alterations) with HJHS and total arc.

Results: Of 44 PWH, most had hemophilia A (35/44), were severe (36/44) and had a median age of 36 years. Increasing HJHSs and declining total arc, indicating worsening arthropathy, were associated with JADE measurements in the expected direction, including (1) increasing length of osteochondral alterations, (2) diminished cartilage thickness, and (3) greater soft tissue expansion. The ankles had the highest proportion of joints without measurable (missing) cartilage. In multivariable models MSKUS measurements explained 68% and 71% of the variation in HJHS and total arc respectively for the elbow, 55% and 29% respectively for the knee, and 50% and 73% for the ankle.

Conclusions: This study highlights the associations of direct intra-articular ultrasonography measurements using the JADE protocol with clinical and functional parameters. Our findings underscore the clinical value of POC MSKUS using the JADE protocol

as a complementary instrument for the diagnosis and management of haemophilic arthropathy.

1 | INTRODUCTION

Recurrent hemarthroses are the hallmark of congenital haemophilia, an x-linked bleeding disorder. Joint bleeds lead to blood degradation, iron deposition, synovial inflammation, synovial hypertrophy, and ultimately, cartilage destruction and bone erosion.[1] Once joint damage occurs, it progresses over the patients' lifetime irrespective of further bleeding,[2] results in chronic arthropathic changes, and affects mobility and quality of life.[3] Intermittent arthritic flares, (a) symptomatic bleeding, and postural joint abnormalities may further aggravate the arthropathy.[4] Traditionally, most symptoms and findings were ascribed to joint bleeding and addressed mainly by optimizing clotting factor prophylaxis. Recently, a new emphasis is on early detection, diagnosis, and treatment of arthropathic abnormalities beyond improving clotting factor replacement strategies. There is rising awareness that prompt detection and management of not only symptomatic, but also asymptomatic findings are essential.

Clinical scoring systems, such as the Hemophilia Joint Health Score (HJHS),[5] along with radiographic,[6] magnetic resonance imaging (MRI),[7,8] and musculoskeletal ultrasound (MSKUS)[9–15] imaging modalities, can aid in the evaluation of joint health. MRI is considered the gold standard for arthritic joint evaluation, able to visualize soft tissue, fluid, hemosiderin, osteochondral, and other structural tissue abnormalities.[7] However, MRI is time-consuming, costly, and difficult to obtain in children or patients with claustrophobia. Recently, MSKUS, particularly point-of-care (POC) MSKUS, has emerged as a simple, inexpensive, convenient, and radiation-free imaging modality for the evaluation of arthritis.[16] POC MSKUS is attractive since it can detect soft tissue, osteochondral, and even vascular abnormalities, although the evaluation of deep joint structures is limited.[13,17] Both MRI and POC MSKUS appear superior to plain radiographs regarding soft tissue and vascular imaging.[18]

To enable POC MSKUS use for a standardized evaluation of haemophilic arthropathy, we developed the Joint $_{tissue}$ Activity and Damage Exam (JADE) protocol, which incorporates direct measurements of tissue abnormalities.[15] The JADE protocol quantitatively measures up to 1/10th of a millimetre soft tissue thickness, cartilage thickness, and osteochondral alterations with defined transducer positions in sentinel areas of the joint.[15] Thus far, the JADE protocol has been validated per Outcomes Measures in Rheumatology (OMERACT) guidelines[19] applying pathologic tissue annotation[17] and demonstrating high intra/inter-rater and inter-operator reliability.[15] OMERACT is an independent initiative of international health professionals who develop and validate clinical and radiographic outcome methodology tools for osteoarthritis and other rheumatic diseases.[19]

Additional opportunities to further validate the usefulness and applicability of the JADE protocol are inherent to comparisons with current clinical or functional tools that assess haemophilic arthropathy. If findings obtained by the JADE protocol could be shown to align well with other commonly used measures of joint change, then its value as a POC imaging tool for haemophilic arthropathy management would be enhanced. Herein, we compared the extent of measurable structural intra-articular changes, evaluated by JADE, and their association with clinical and functional joint assessments in a cross sectional analysis study.

2 | METHODS

2.1 | Patient selection

Adult patients with haemophilia (PWH) A or B of all severities (age ≥18 years) were recruited prospectively at three Haemophilia Treatment Centres in the United States (University of California San Diego, Washington Centre for Bleeding Disorders, and Los Angeles Orthopedic Haemophilia Treatment Centre) between May 2016 and April 2019. The results of the cross sectional analysis are reported here. Patients had to have at least one arthropathic joint. Arthropathic joints were defined by HJHS.[5,6] HJHSs had to have values that were at least three or higher[20,21] to suggest arthropathic changes. We also collected data on age and race. Written informed consent was obtained from all patients. The study was approved by the Institutional Review Boards of the participating institutions.

2.2 | Joint health evaluation

The health of each joint (elbows, knees, ankles) was evaluated by three measures: HJHS, total arc, and POC MSKUS. The HJHS version 2.1 is an established outcome measure, providing a clinical score for each joint summarizing swelling, duration of swelling, pain, strength, loss of range of motion (ROM), muscle atrophy, and crepitus (HJHS per joint: 0 best, 20 worst; total HJHS for six joints combined: zero best, 120 worst). The total arc of each joint measured by a goniometer provides a functional assessment by the sum of flexion and extension degrees of ROM.[22–24] As an example, an illustration of the ankle total arc is shown in supplement Figure 1. Higher HJHS and lower total arc measurements reflect worse joint health.
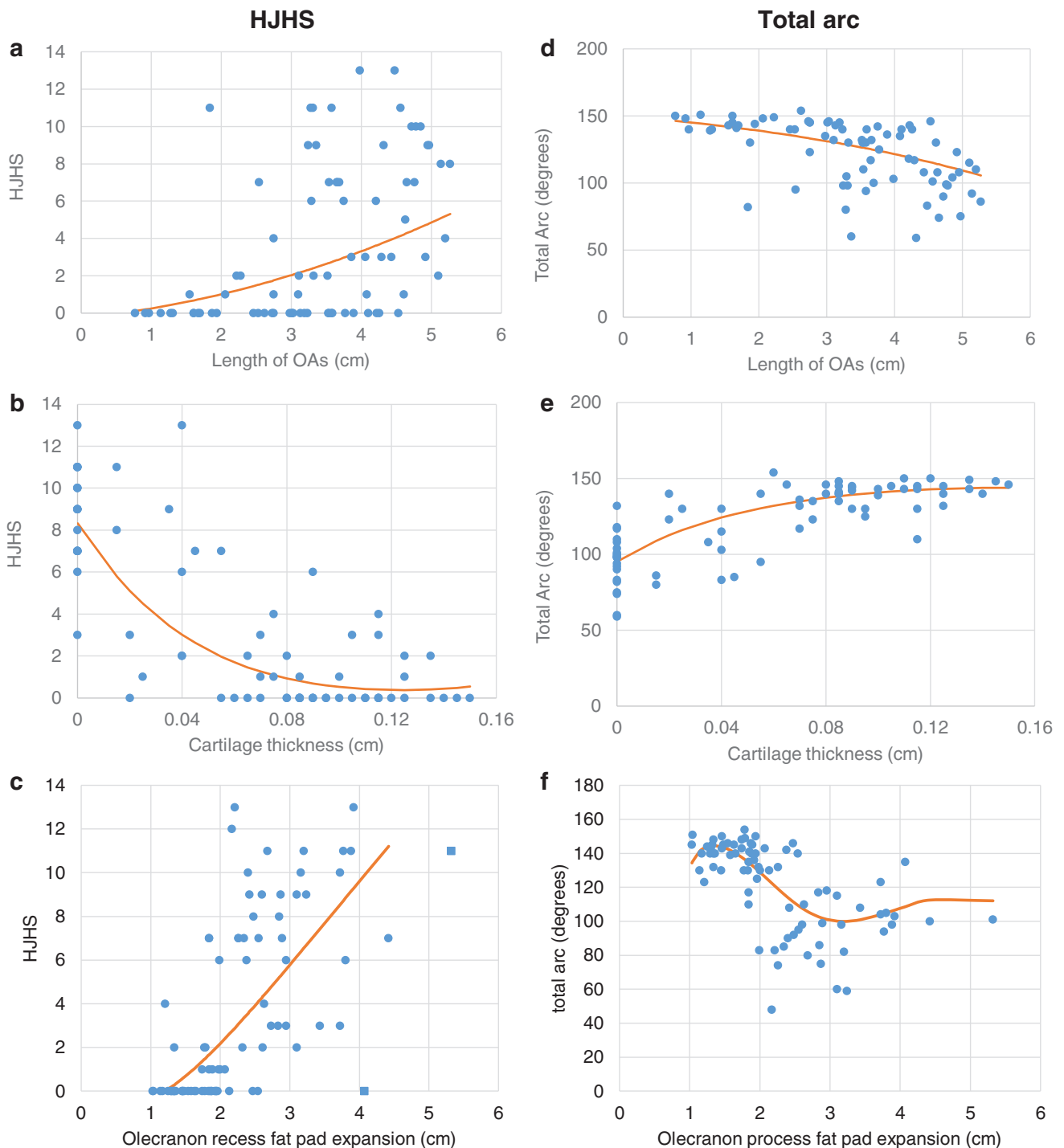
Figure 1 Elbow: Association of Joint $_{Tissue}$ Activity and Damage Exam (JADE) variables with HJHS and total arc. Association between hemophilia joint health score (HJHSs) with JADE variables of length of osteochondral alterations (A), cartilage thickness (B) and soft tissue expansion of the olecranon recess fat pad (C). Association between total arcs with JADE variables of length of osteochondral alterations (D), cartilage thickness (E) and soft tissue expansion of the olecranon recess fat pad.

2.3 | POC MSKUS imaging

POC MSKUS was performed using the JADE protocol.[15] At all three institutions, POC MSKUS examination was performed using a GE Logiq S8 high-resolution ultrasound machine (General Electrics, Fairfield, Connecticut) with real-time spatial compound imaging,

speckle reduction capabilities, and an 8–15 MHz high-frequency linear transducer using grayscale (B-mode) setting per accordance with the manufacturers. At each participating institution, images were obtained by haemophilia providers formally trained in POC MSKUS in the UCSD CME-accredited course (https://cme.ucsd.edu/httc/index.html). All imaging providers had at least 3 years of experience in POC

MSKUS imaging and two providers (AVD and BS) are certified in POC MSKUS by the American Registry for Diagnostic Medical Sonography. A detailed description of the JADE protocol, including transducer positions, atlas, and instructions for soft tissue, cartilage, and osteochondral measurements has been published.[15] In brief, the JADE protocol includes 17 standardized positions in the elbow, knee and ankle, permitting qualitative descriptions of critical intra-articular structures along with quantitative measurements evaluating three different POC MSKUS joint health domains: osteochondral alterations, cartilage thickness, and soft tissue expansion. Measurements of cartilage thickness and osteochondral alterations were performed on the humeral capitulum of the elbow, the femoral medial/lateral condyles of the knee, and the talar dome of the foot. Measurements of soft tissue expansion were performed in the olecranon fossa of the elbow, medial and radial knee recesses, and the anterior recess of the tibiotalar joint in the foot. These areas harbour fat pads, synovial and capsular soft tissue structures which are measured as a conglomerate since they cannot be discerned by POC MSKUS in pathological states.[17] Worse joint health is reflected by increased length of osteochondral alterations, decreased cartilage thickness, and/or increased soft tissue expansion.

2.4 | Statistical analyses

The results are presented at the joint level (JADE): elbow, knee, and ankle. We examined two outcomes for each joint: joint HJHS and total arc. The HJHS values were not normally distributed, resulting in positively skewed residuals when regression models were fitted. A square root transformation, where sqrtHJHS $= \sqrt{(0.5 + \text{HJHS})}$, ensured normally distributed residuals. The total arc was negatively skewed, and we used a reflecting transformation[25] where the transformed value Y = in (170 – Total arc).

The JADE variables came from MSKUS measurements of length of osteochondral alteration, cartilage thickness, soft tissue expansion and capsular thickness. Those with a lognormal rather than normal distribution were log transformed before analysis. Values that were more than 3.29 standard deviations from the mean were assumed to be drawn from a different population ($p < 0.001$) and classified as outliers.[25] They were excluded from analysis but shown on the graphs as filled squares.

We examined the association between joint status (joint HJHS and total arc) and each JADE variable by plotting graphs and calculating the curve of best fit. Because each subject had left and right joints we adjusted for the intra-individual correlation by fitting random intercept models[26] in order to calculate the line that best described the association between the outcome and JADE measurement. Curves were fitted by adding polynomial terms. The association between the outcome and JADE variable was shown by the regression coefficient b and 95% confidence interval. The use of a reflecting transformation for total arc means that a negative regression coefficient indicates a positive association between the outcome and the independent variable, and viceversa. With a quadratic model the association was described by two regression coefficients b_1 and b_2. Similarly, a third-order polynomial

resulted in three regression coefficients b_1, b_2 and b_3. We also calculated the percentage variation in the outcome that was explained by the JADE variable; this is analogous to r^2 in an ordinary least-squares regression.

We next examined joint status in relation to the combined JADE variables and age by fitting multivariable models. However, there was the risk of collinearity since these JADE variables were correlated with each other. Also, those associations with quadratic or third-order polynomials, resulted in multivariable models of excessive complexity. This would risk overfitting given the sample size. To avoid collinearity and overfitting, we transformed the set of predictor variables for each joint into a smaller set of uncorrelated variables by principal component analysis.[27] We discarded those principal components with an eigenvalue <70/P percent of the total variance where P is the number of principal components. We then fitted multivariable models with the selected principal components as the independent variables to estimate how much of the outcome could be explained by the JADE variables in combination. In each case, we used the transformed outcome variable and we fitted random intercept models.[26] The models that provided the best fit to the data were selected after examining the residuals, the Akaike Information Criterion (AIC),[28] and the percentage of the total variation of the outcome that was explained by the independent variables.

We used Pearson's chi-square test to test the overall null hypothesis that all three joints had equal proportions of cartilage degradation, defined by no cartilage thickness. If that hypothesis was rejected, then a post hoc analysis using the Holm correction was performed.

3 | RESULTS

3.1 | Baseline characteristics

There were 44 patients, evenly distributed between the three centres with a median age of 36 years [19 to 70 years]. Most patients (80%, 35/44) had haemophilia A and were severe (82%, 36/44) (Table 1).

3.2 | Elbow

Increasing HJHSs, signifying worsening arthropathy clinically, were associated with increasing length of osteochondral alterations, diminished cartilage thickness of the humeral capitulum, and greater soft tissue expansion in the olecranon fossa (Figures 1A–1C, Table S1). Similarly, declining total arcs, indicating joint dysfunction, were associated with increasing osteochondral alterations and reduced cartilage thickness of the humeral capitulum (Figures 1D–1E, Table S2). Concerning soft tissue expansion in the olecranon fossa, joints fell into two groups: those with a fat pad area <2 cm^2 were in good condition with a median total arc of 140 degrees (range 83–158 [IQR 130–145], normal 140-150), while those with a larger fat pad area ≥2 had a lower median of 101 degrees [range 48–146, IQR 86–118] (Figure 1F).

TABLE 1 Baseline characteristics

Characteristic	
Centre[a]	
LA	14 (32)
Seattle	15 (34)
San Diego	15 (34)
Haemophilia type[a]	
A	35 (80)
B	9 (20)
Severity[a]	
Mild	1 (2)
Moderate	7 (16)
Severe	36 (82)
Treatment	38 (86)
Prophylaxis	6 (14)
On demand	
Race/ethnicity[a]	
Hispanic	7 (16)
White	26 (59)
African American	4 (9)
Asian	2 (5)
Other	5 (11)
Age (years)[b]	36 [28, 49]
Total HJHS[b]	27 [18, 42]
Joint HJHS[b]	
Elbow	2 [0, 7]
Knee	2 [0, 7]
Ankle	6 [1, 9]
HJHS[b]	
Elbow: Left	2 [0, 7]
Right	2 [0, 7]
Knee: Left	2 [0, 7]
Right	2 [0, 8]
Ankle: Left	6 [1, 9]
Right	6 [2, 9]
Joint Total arcs[b]	
Elbow	130 [100, 143]
Knee	130 [105, 140]
Ankle	32 [22, 56]
Total arcs[b]	
Elbow: Left	130 [99, 143]
Right	130 [100, 143]
Knee: Left	131 [105, 140]
Right	130 [97, 140]
Ankle: Left	32 [22, 56]
Right	30 [22, 53]

[a]Values expressed as N (%).
[b]Values expressed as median [interquartile range].

In a multivariable model, 68% of the variation in HJHS and 71% of the variation in total arc were explained by a combination of these MSKUS measurements (Table S3).

3.3 | Knee

Increasing HJHSs were associated with increasing length of osteochondral alterations and thinner cartilage in the 'sunrise view' (depicting the trochlea and medial/lateral femoral condyles) as well as greater soft tissue expansion in the medial and lateral recesses (Figures 2A–2C, Table S4). Similarly, declining total arcs were associated with longer osteochondral alterations and decreasing cartilage thickness in the 'sunrise view' as well as greater soft tissue expansion in the medial and lateral recesses (Figures 2D–2F, Table S5).

In a multivariable model, these MSKUS measurements explained 55% and 29% of the variation in HJHS and total arc, respectively (Table S6).

Associations between HJHSs and/or total arcs with length of osteochondral alterations and/or cartilage thickness could not be established when the femoral condyles were assessed in longitudinal axis anteriorly or posteriorly.

3.4 | Ankle

Deteriorating HJHSs were associated with increasing length of osteochondral alterations on the talar dome and greater soft tissue expansion in the anterior tibiotalar recess (Figures 3A–3B, Table S7). A large proportion of ankles had no cartilage left (Figure 3C, Table S7), and there was no apparent association between ankle joint HJHS and cartilage thickness. Of note, more than half of the joints in the ankle (51%) had lost all their cartilage compared to the elbow and knee (27% and 7% respectively, $p < 0.001$).

The measurements of ankle total arc showed considerable scatter when plotted against osteochondral alterations, capsular thickness, and cartilage thickness (Figures 3D–3F, Table S8). But when combined in a multivariable model they explained 73% of the variation in total arc. Similarly, the MSKUS measurements explained 50% of the variation in HJHS (Table S9).

4 | DISCUSSION

This study demonstrates relationships between measurements of intra-articular structural changes using POC MSKUS (JADE protocol), with clinical HJHSs and functional arc measures in PWH. Overall, these results establish the clinical value of ultrasound-derived direct measurements of intra-articular tissues involved in pathological processes in haemophilic joints in the ambulatory setting. Importantly, these results add to the validation of the JADE protocol to provide the tissue measurements, especially in terms of the construct validity of sentinel areas examined by JADE to interrogate intra-articular defects and changes.
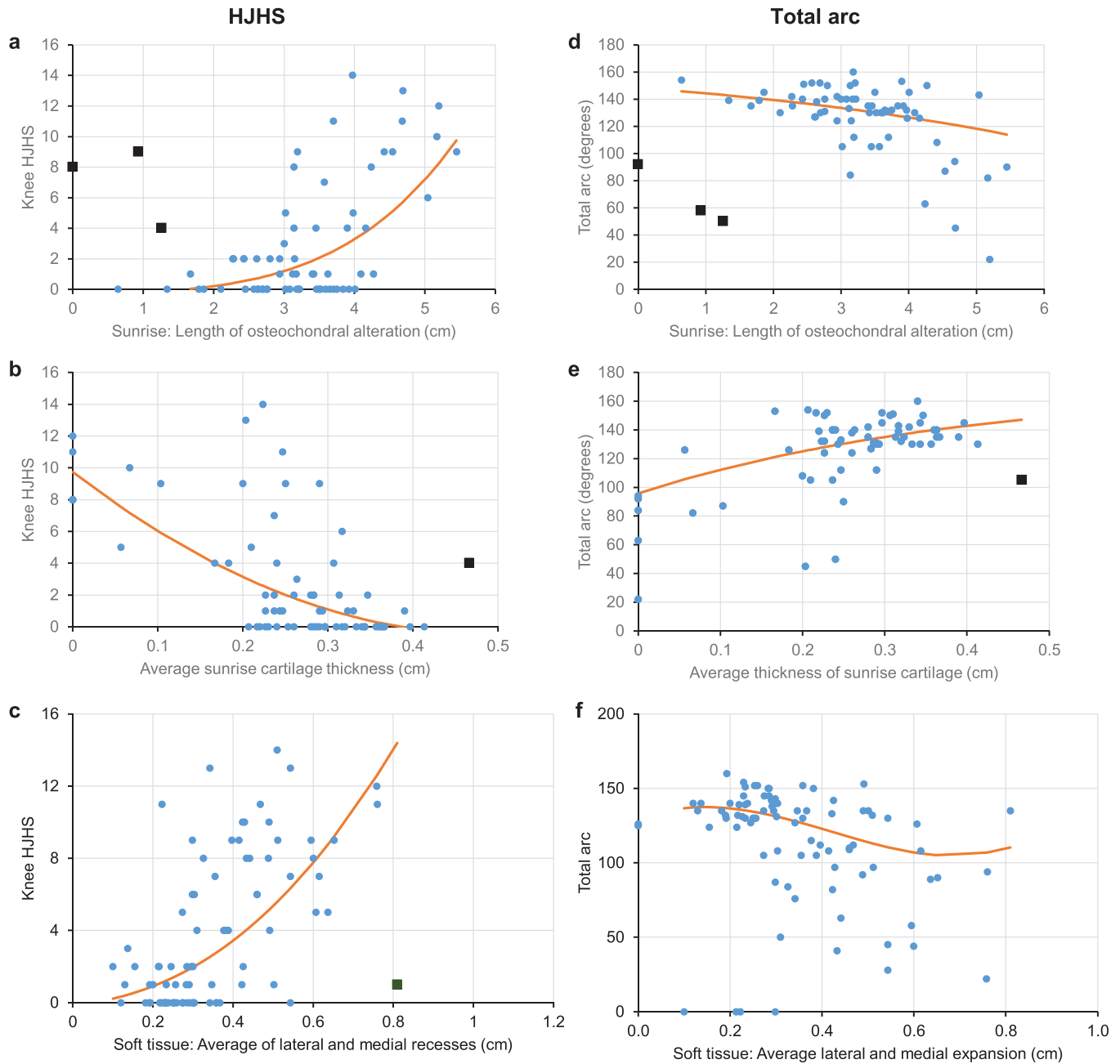
Figure 2 Knee: Association of Joint $_{Tissue}$ Activity and Damage Exam (JADE) variables with HJHS and total arc. Association between hemophilia joint health score (HJHSs) with JADE variables of length of osteochondral alterations (A), cartilage thickness (B) and soft tissue expansion of the average of lateral and medial recess (C). Association between total arcs with JADE variables of length of osteochondral alterations (D), cartilage thickness (E) and soft tissue expansion of the average of lateral and medial recess (F). Osteochondral alterations and cartilage thickness measurements were taken in the sunrise view.

The HJHS, based on the Gilbert score, was developed to identify early clinical signs of joint degeneration in PWH.[5,20] In contrast to MRI and MSKUS, clinical scores do not determine which intra-articular structural abnormalities contribute to clinical manifestations.[8] MRI can predict bleeding and radiographic changes even 5 years later.[29] However, during the last decade, several POC MSKUS protocols have been developed as an attractive alternative to MRI.[9–15] Technical advances over the past two decades have made ultrasound extremely powerful and more sensitive than MRI to detect superficial structural changes due to resolution in the μm range, far exceeding spatial resolution achieved with routine MRI. Even fine structures such as tendon fibre (dis) arrangements or individual nerve fascicles can be visualized[30] and cartilage thickness can be accurately measured in locations accessible to the ultrasound beam.[31,32] The development of the JADE protocol took advantage of the high tissue resolution afforded by ultrasound. Since most structures in the joint are
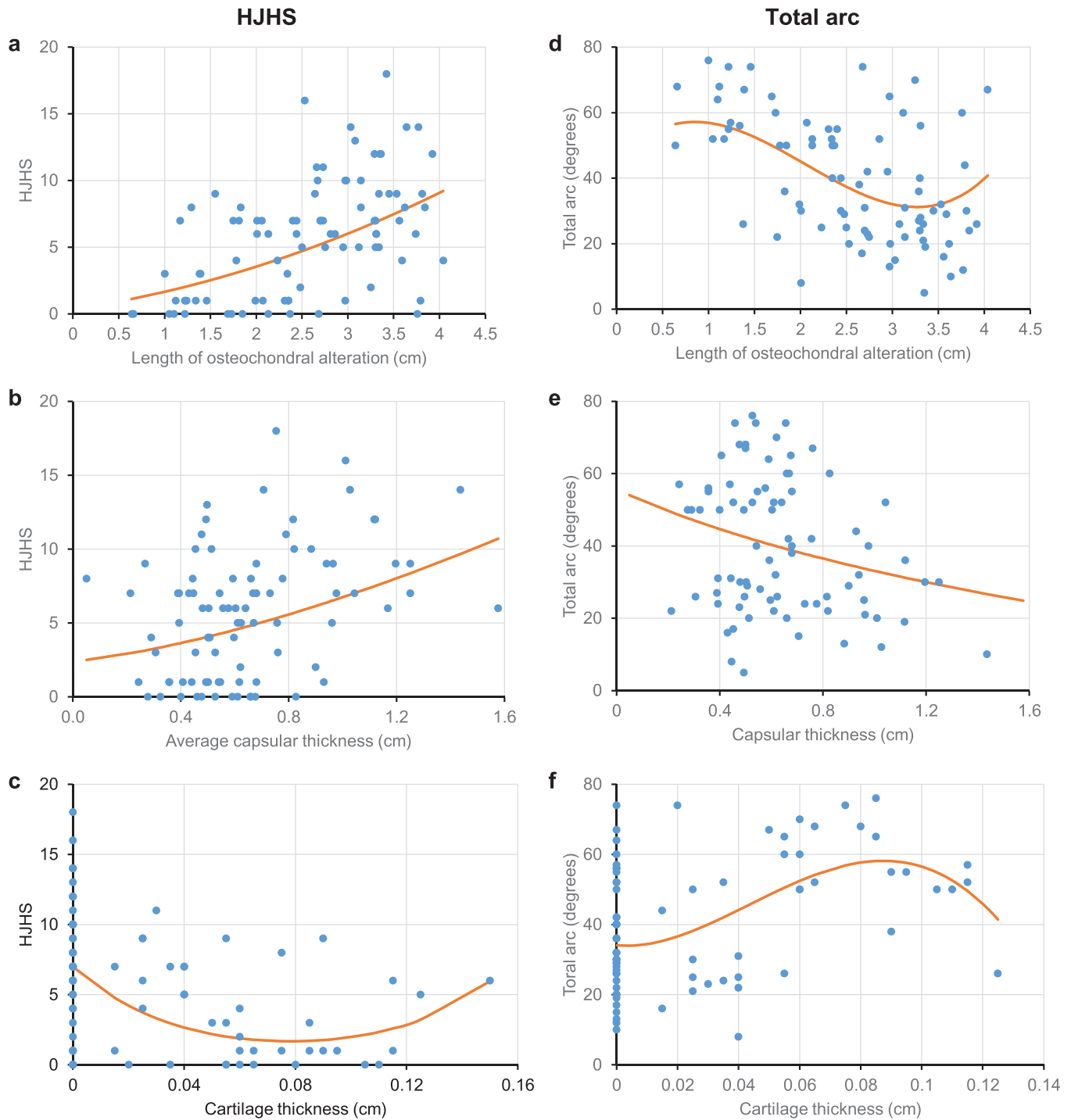
FIGURE 3 Ankle: Association of Joint $_{Tissue}$ Activity and Damage Exam (JADE) variables with HJHS and total arc. Association between Hemophilia Joint Health Score (HJHSs) with JADE variables of length of osteochondral alterations (A), capsular thickness (B) and cartilage thickness (C). Association between total arcs with JADE variables of length of osteochondral alterations (D), capsular thickness (E) and cartilage thickness

considered superficial (in contrast to deep abdominal structures, for instance), ultrasonographic measurements provide the opportunity to capture very subtle tissue changes easily and precisely in the 10th of a millimetre range, with high intra-/inter-rater and inter-operator reliability.[15] Except for the JADE protocol, other POC MSKUS protocols to date are based on semi-quantitative scoring, combining osteo-

chondral and soft tissue abnormalities. Semi-quantitative scores can be subjective, are constrained by ceiling effects, and provide joint health estimates instead of precise tissue-specific alterations. These alterations may be dynamic, without affecting semi-quantitative scores, and go unnoticed with scoring. In comparison, the JADE protocol takes advantage of continuous measurements (1/10th of a millimetre) of

intra-articular changes which allows a more dynamic and accurate assessment of alterations, providing more opportunities for targeted interventions.

OMERACT guidelines recommend three pillars - 'truth, discrimination, and feasibility' - be met to ascertain the validity of imaging protocols.[19] These require (1) delineating which pathological tissues can be identified, (2) determining intra- and inter-rater/operator reliability, and (3) defining areas of clinical applicability. Thus far, the JADE protocol has been validated for pathological tissue recognition[17] and demonstrated high intra-rater, inter-rater, and inter-operator reliability.[15] Here, we provide first insights into OMERACT's pillar of 'feasibility', that is, correlations of ultrasonographic tissue measurements with clinical findings in a cohort of adult PWH.

Towards that end, deteriorating elbow and knee HJHS correlated in the expected direction with all POC MSKUS joint domains (e.g., osteochondral alterations, cartilage thickness, and soft tissue expansion). Worsening ankle HJHS correlated with osteochondral alterations and soft tissue expansion. However, no apparent association between HJHS and cartilage thickness was found likely because many ankles had no cartilage left (bare talus surface). Indeed, the number of joints without measurable cartilage was highest for ankles, exceeding elbows and knees. This observation aligns with recent studies, assigning a new role for the ankle as the arthropathic joint indicator for PWH[2]. Other ultrasound protocols previously evaluated the association between clinical and ultrasound findings. For example, the HEAD-US protocol showed good correlation with HJHS.[33,34] However, the findings by Timmer et al. were based on a retrospective cohort and the ultrasound measurements were performed by a single provider. In general, the HEAD-US protocol is designed to detect early arthopathy, whereas the JADE protocol can be applied reliably to all stages of arthropathy as exemplified by the current cohort demonstrating a wide range or arthropathic manifestations.

Haemophilic arthropathy is a slowly progressive pathological process leading to different compensatory mechanisms to adapt against ROM limitations.[35] To capture this process, we utilized total arc, a composite of flexion and extension ranges for each joint.[22–24] Total arc provides a functional joint assessment and may be normal despite extension or flexion ROM deficits.[36] For example, a joint may have a flexion ROM deficit, but be hyperextended, thereby preserving a normal total arc and function through compensation mechanisms. Although total arc ROM has not been widely adapted or validated in prospective haemophilic arthropathy studies, we learned informally from patients that deficits in the total arc are perceived more detrimental than isolated flexion or extension ROM deficits. Resembling HJHS findings, decreasing elbow and knee total arcs were associated with deteriorating values of all three JADE joint parameters. For the knee, JADE measurements were less predictive of clinical and functional changes. Likely a larger sample size is needed to explain this predictive variability. As with HJHSs, each parameter showed wider variability in association with total arc in the ankle compared to elbows and knees. Similarly, this could be explained by many ankles without talar cartilage and/or complicated assessment of the ankle anatomy involving multiple articulations. However, combining the three param-

eters (soft tissue expansion, osteochondral alterations, and cartilage thickness) in a multivariable model explained a considerable amount (73%) of the ankle total arc variation. Overall, JADE measurements appeared to correlate better with total arc than HJHS, highlighting the relevance of the JADE protocol not only with clinical but functional, more patient-relevant outcomes.

Based on these findings, objective imaging delineation of structural abnormalities using the JADE protocol will complement the HJHS or clinical exam for monitoring haemophilic arthropathy progression at the tissue level, in clinical practice and in clinical trials. For example, the classical endpoint in clinical trials of new systemic therapies for PWH is a reduction in bleeding frequency estimated by a patient's report. However, there is no consensus on a clear definition of bleeding for haemophilia research.[37] In PWH with pre-existing arthropathy, pain due to arthropathy versus hemarthrosis can be indistinguishable, which may lead to over-reporting of bleeding frequency.[38] Moreover, silent or non-symptomatic presence of intra-articular blood may go unnoticed. Overall, the current imprecision of patient estimated bleeding frequency as an outcome parameter may affect joint health, with a clear role for more objective assessment tools.[39] For instance, effects of therapeutic interventions to halt or reverse synovial growth, as a biomarker in response to (often asymptomatic) bleeding, could be measured precisely by POC MSKUS approach[40,41] using the JADE protocol.

This study has several limitations. First, the target population was adults limiting the applicability of the results to children with immature joint anatomy. Second, the HJHS has been validated only in children, adolescents, and young adults, although in clinical practice it is commonly used in adults.[5,20] Third, MSKUS cannot delineate deep joint structures. Fourth, providers performing ultrasound were not blinded to the HJHS and total arc. Acquisition of HJHS parameters, flexion and extension measurements, and ultrasound images were performed by the physical therapist at each centre. Although providers were not blinded, calculation of HJHS scoring, total arc, and JADE measurement were performed at later time points and were asynchronous. In addition, total arc and JADE measurements are objective variables which limit bias. Fifth, the JADE protocol uses specific sentinel positions for tissue measurements. It is not meant to provide a full diagnostic ultrasound exam which is distinct from POC MSKUS, a distinction that has been previously defined.[42] Lastly, the biological meaning of small changes identified clinically by HJHSs or by ultrasound, and thresholds of normal versus pathology, is not yet defined.[13] Towards that end, studies to determine the sensitivity of the JADE protocol to detect longitudinal changes in association with clinical findings are ongoing.

In conclusion, this study highlights the utility of direct tissue-specific measurements by ultrasound using the JADE protocol to objectively quantify intra-articular haemophilic changes, associated with clinical and functional outcomes. These findings provide evidence that POC MSKUS using the JADE protocol is a meaningful tool to guide management of haemophilic arthropathy.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.