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Musculoskeletal ultrasonography for arthropathy assessment in patients with hemophilia

A single-center cross-sectional study from Shanxi Province, China

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Abstract

Magnetic resonance imaging (MRI) is currently considered the gold standard for assessing hemophilic arthropathy (HA) severity; however, MRI is often costly, time-consuming, and difficult to perform in children. In the present study, we evaluated the joint status of hemophilic patients from Shanxi Province, China, using musculoskeletal ultrasonography (MSKUS) and identified the factors that most strongly correlated with disease severity.

The study included 104 patients with hemophilia, who underwent MSKUS examination. A total of 1248 joints (including the shoulder, elbow, wrist, hip, knee, and ankle joints on both sides) from these patients were evaluated. Effusion, hypertrophy, cartilage modification, and bone erosion were assessed. The chi-square test was used to analyze categorical variables, and multivariate logistic regression was used to analyze the relationship between joint disease and risk factors.

MSKUS allowed clear visualization of synovial lesions, effusion, cartilage modification, and bone surface damage; however, it was unable to identify changes deep within bones. The distribution of damaged joints was as follows: shoulder, 2 (1.0%); elbow, 80 (38.5%); wrist, 4 (1.9%); hip, 4 (1.9%); knee, 126 (60.6%); and ankle, 90 (43.3%). Damage was more common in the knee, elbow, and ankle joints than in the shoulder, wrist, and hip joints ($P < .001$). Among the 1248 joints, 306 showed lesions, which included effusion in 102 (8.2%) joints, synovium hypertrophy in 176 (14.1%), cartilage modification in 193 (15.5%), and bone damage in 176 (14.1%). Many joints had multiple lesions at the same time. The chi-square test and multivariate logistic analysis showed that age and hemophilia severity were significantly associated with joint disease, while type of hemophilia and treatment categories were not associated with joint disease.

MSKUS is a convenient and cost-effective examination that can play an important role in the diagnosis and long-term monitoring of HA.

Abbreviations: HA = hemophilic arthropathy, MRI = magnetic resonance imaging, MSKUS = musculoskeletal ultrasonography.

Keywords: hemophilia, hemophilic arthropathy, musculoskeletal ultrasonography, ultrasonography

1. Introduction

Hemophilia is a sex-linked recessive genetic disorder, and it can be divided into 2 types (hemophilia A and hemophilia B). Hemophilia is more common in male individuals than in female individuals, and the most common symptom is an increased bleeding tendency.[1] Repeated joint bleeding is a serious complication that can cause hemophilic arthropathy (HA) and joint disability.[2] The pathological changes include effusion (hydrarthrosis or hemarthrosis), synovium hypertrophy and hyperemia, cartilage modification, bone erosion, osteophytes, and bone remodeling. The most commonly affected joints are the knee, elbow, and ankle joints,[3] but the shoulder, wrist, and hip joints can also be involved.[4]

For assessing joint status, an appropriate imaging system is needed to evaluate lesion severity and monitor joint disease progression. Conventional radiography has been used to evaluate HA.[5–7] Although radiography can demonstrate the early changes of bone lesions,[8] it only identifies the synovium, and analysis of other soft tissues is difficult.[7] Magnetic resonance imaging (MRI) is presently considered the gold standard for assessing HA severity. It can identify bleeding, synovium hypertrophy, cartilage damage, and osteochondral abnormalities accurately,[9,10] however, it is costly and time-consuming. Furthermore, young children require sedation for MRI examination. Therefore, its use has been greatly limited. Musculoskeletal ultrasonography (MSKUS) is a useful tool for diagnosing and monitoring musculoskeletal diseases.[11–13] It can identify some early changes, such as effusion (hydrarthrosis or hemathrosis), synovium hypertrophy and hyperemia, cartilage damage, and minor alterations of the bone surface. Additionally, many studies

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have shown a positive relationship between ultrasonography and MRI results.[14–18]

Shanxi Province is a northern province of China, and it is considered to be underdeveloped. In this region, MRI is too expensive for most patients with HA. Thus, in the present study, we assessed the joint status using MSKUS in patients with HA from Shanxi Province.

2. Methods

2.1. Participant

The study included 104 male patients (mean age, 20.8 ± 15.0 years; range 2–68 years) with mild, moderate, or severe hemophilia between April 2015 and April 2016. Among these patients, 1248 joints were evaluated, including the shoulder, elbow, wrist, hip, knee, and ankle joints on both sides. We excluded patients with rheumatoid arthritis and neuropathic arthropathy.

2.2. Diagnostic criteria of hemophilic arthropathy

MSKUS assessments and determination of lesion locations were based on the guidelines for musculoskeletal ultrasonographic examination,[19] and previously published protocols were used for reference.[20,21] Joint effusion was considered abnormal when effusion was >1 mm (knee joint effusion >2 mm), considering that healthy joints might show a small amount of fluid. Measurements were obtained for the shortest axis in the largest pocket of the joint. Synovial hypertrophy was defined as synovial thickness >1.5 mm on gray-scale sonography. The largest anterior–posterior diameter of a single synovial layer of the most affected bursa of the joint was measured.[14,18] Cartilage modification was defined as hyperechogenicity or an irregular profile showing rough or local erosion of the articular cartilage surface. Bone damage was defined as a cortical "break" when an irregular shape was observed in the longitudinal or coronal plane, osteophytes, or bone remodeling. As there is no clear standard for articular cartilage among joint locations, normal cartilage thicknesses were determined from the results of previous studies[22–25] and were compared with the findings of the contralateral joints (if there was no bleeding history) or the joints of 85 healthy volunteers matched by age and sex (if both joints were damaged).

2.3. Ultrasound setting

MSKUS was performed using the Philips IU22 Ultrasonic Diagnostic Apparatus (Philips, Amsterdam, the Netherlands) with a wideband high-frequency 12–5 MHz linear probe.

2.4. The main investigators

One professionally trained operator performed all examinations, who had 8 years of experience for performing MSKUS. All joints were evaluated by a physician on the day of MSKUS examination. Physical examination was performed according to version 2.1 of the hemophilia joint health score.[26]

2.5. Ethics statement

This study was approved by the local internal review boards and ethics committees. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

2.6. Statistical analysis

Continuous data are presented as mean ± standard deviation, while categorical data are presented as percentages. The chi-square test was used to analyze categorical data. To explore the risk factors of hemophilic arthropathy, we used multivariate logistic regression model. Hemophilic arthropathy was set as the dependent variable. The independent variables included the type of hemophilia, age, severity, and treatment categories. All findings were analyzed using two-tailed tests, with statistical significance assumed at $P < .05$. Analysis was performed using SPSS 22.0 statistical software (IBM Corp., Armonk, NY).

3. Results

The characteristics of all assessed patients are presented in Table 1. We noted that 21.2% of patients received no treatment, 71.2% received on-demand treatment, and only 7.7% received prophylactic treatment (Table 1). Among the 1248 joints examined, 306 showed deterioration (Table 2 and Fig. 1). These included 102 (8.2%) joints with effusion, 176 (14.1%) with synovium hypertrophy, 193 (15.5%) with cartilage modification, and 176 (14.1%) with bone damage. There were 647 lesions in 306 joints, and many joints had multiple lesions at the same time. The shoulder, wrist, and hip joints mainly showed soft tissue lesions and rarely showed osteochondral lesions. However, the knee, elbow, and ankle joints showed all 4 types of lesions. Among the involved joints, the shoulder, wrist, and hip joints

Table 1

Characteristics of the assessed patients.

	n/N%
Type of hemophilia	
A	86 (82.7)
B	18 (17.3)
Severity*	
Mild	6 (5.8)
Moderate	40 (38.4)
Severe	58 (55.8)
Age	
<6 years	13 (12.5)
6–17 years	40 (38.5)
18–34 years	36 (34.6)
≥35 years	15 (14.4)
Joint with history of bleeding	
Shoulder	80 (38.5†)
Elbow	129 (62.0)
Wrist	66 (31.7)
Hip	85 (40.9)
Knee	145 (69.7)
Ankle	145 (69.7)
Treatment categories	
Prophylactic treatment	8 (7.7)
On-demand treatment	74 (71.1)
Occasionally treatment or no treatment	22 (21.1)
Type of hemorrage	
Spontaneous	74 (71.1)
Injuries	30 (28.9)
Inhibitors	
(+)	6 (5.8)
(–)	98 (94.2)

The percentage may not total to 100% because of rounding.

* Severity is classified according to the activity of FVIII/FIX as follows: mild: >5 to <40%; moderate: 1%–5%; severe: <1%.

† Percentage of this column refers to the proportion at each location.

Table 2

Ultrasonography findings of lesions at each location in patients with hemophilia.

L	n	LS (%)	RS (%)	LE (%)	RE (%)	LW (%)	RW (%)	LH (%)	RH (%)	LK (%)	RK (%)	LA (%)	RA (%)
E	102	0 (0)	1 (1.0)	11 (10.8)	11 (10.8)	1 (1.0)	1 (1.0)	0 (0)	1 (1.0)	29 (28.4)	25 (24.5)	14 (13.7)	8 (7.8)
S	176	1 (0.6)	1 (0.6)	27 (15.2)	31 (17.6)	1 (0.6)	1 (0.6)	1 (0.6)	1 (0.6)	34 (19.3)	29 (16.5)	28 (15.9)	21 (11.9)
C	193	0 (0)	1 (0.5)	20 (10.4)	30 (15.5)	0 (0)	0 (0)	2 (1.0)	0 (0)	41 (21.2)	45 (23.3)	26 (13.5)	28 (14.5)
B	176	0 (0)	1 (0.6)	20 (11.4)	27 (15.3)	0 (0)	0 (0)	2 (1.1)	0 (0)	38 (21.6)	35 (19.9)	26 (14.8)	27 (15.3)

Percentage may not total 100% because of rounding.

B = bone damage, C = cartilage modifications, E = effusion, L = lesion, LA = left ankle, LE = left elbow, LH = left hip, LK = left knee, LS = left shoulder, LW = left wrist, RA = right ankle, RE = right elbow, RH = right hip, RK = right knee, RS = right shoulder, RW = right wrist, S = synovium hypertrophy.

accounted for 0.8% of joints with damage, while the knee, elbow, and ankle joints accounted for 99.2% of joints with damage (chi-square test, $P < .001$) (Fig. 2). The distribution of damaged joints at each location was as follows: shoulder, 2 (1.0%); elbow, 80 (38.5%); wrist, 4 (1.9%); hip, 4 (1.9%); knee, 126 (60.6%); and ankle, 90 (43.3%).

On dividing patients into 4 age groups (<6, 6–17, 18–34, and ≥35 years), we found that synovium hypertrophy, cartilage modification, and bone damage significantly increased with age (trend chi-square test, $P < .001$), while effusion did not increase with age ($P > .05$) (Fig. 3).

The chi-square test and multivariate logistic regression analysis (Tables 3 and 4) showed that age and hemophilia severity were significantly associated with joint disease (chi-square test: $P = .004$ and $P = .016$, respectively; multivariate logistic analysis: $P = .015$ and $P = .010$, respectively), while type of hemophilia and treatment categories were not associated with joint disease (chi-square test: $P = .557$ and $P = .261$, respectively; multivariate logistic analysis: $P = .325$ and $P = .609$, respectively).

4. Discussion

In recent years, MSKUS has been more extensively applied.[27–31] The present study comprehensively evaluated 12 specific joints in hemophilic patients, using MSKUS. We found that MSKUS can be used to clearly visualise synovial lesions, effusion, cartilage modification, and bone surface damage, but cannot be used to visualise lesions deep within bones. Episodes of bleeding were less common in the shoulder, wrist, and hip joints than in the knee, elbow, and ankle joints, but bleeding was not rare. Additionally, osteochondral damage was lower in the shoulder, wrist, and hip joints than in the knee, elbow, and ankle joints. Similarly, damage to the knee, elbow, and ankle joints was generally more severe, and the incidence of lesions was the highest in the knee joint, followed by the ankle and elbow joints. These findings differ from the results of a study in a Taiwan province that was based on Pettersson scores, in which the prevalence of ankle arthropathy was the highest.[32]

In China, many patients with hemophilia receive either on-demand treatment or no treatment, and few patients receive prophylactic treatment. In this study, 8 patients had received prophylactic treatment, and 6 of these patients had abnormal joints. Notably, there was no positive impact of treatment on joint damage, and this finding differs from the results of previous studies.[33–35] After a telephonic interview, we noted that the 2 patients with normal joints were young children (aged 2 and 5 years) who had undergone primary preventative treatment.

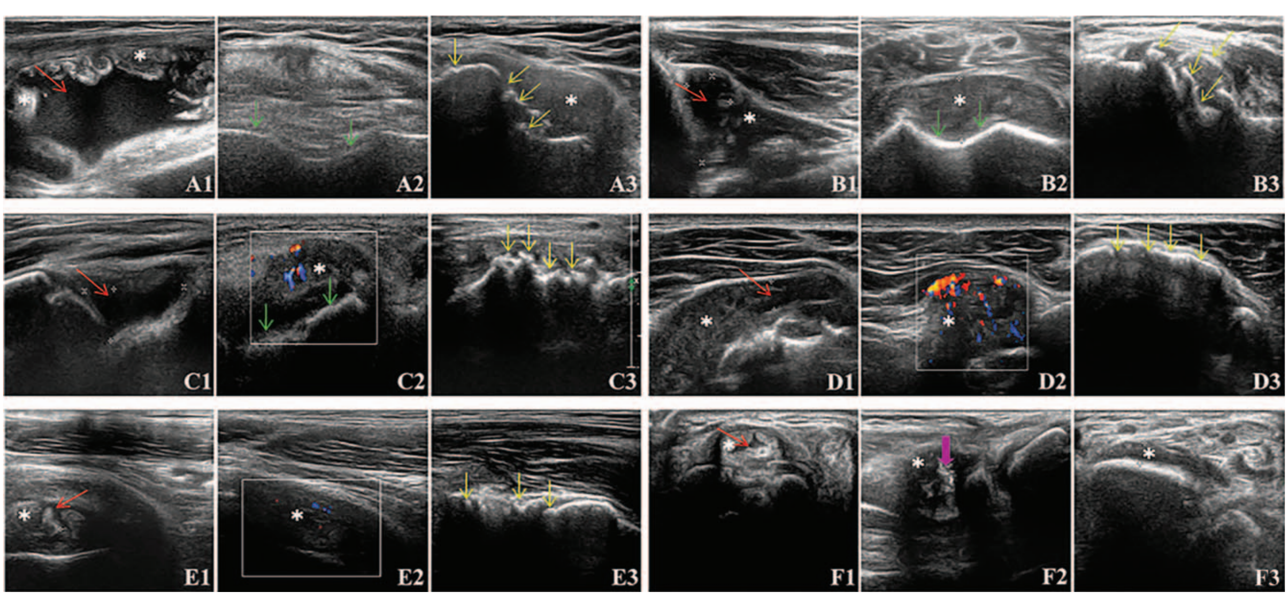

Figure 1. (A1)–(A3): knee joint, (B1)–(B3): elbow joint, (C1)–(C3): ankle joint, (D1)–(D3): shoulder joint, (E1)–(E3): hip joint, (F1)–(F3): wrist joint. The red arrows (between calipers) indicate effusion or hemorrhage (between calipers). Asterisk (*) represents hypertrophic synovium, and some parts are accompanied by increased color Doppler flow signals. The purple solid arrow indicates the hyperechoic hemosiderin after hemorrhage absorption. The hypoechoic cartilage band is destroyed, shows thinning, or disappears, and the echo shows an increase and nonuniformity (green arrow). The yellow arrow indicates cartilage disappearance, irregular bone surface, or an osteophyte.

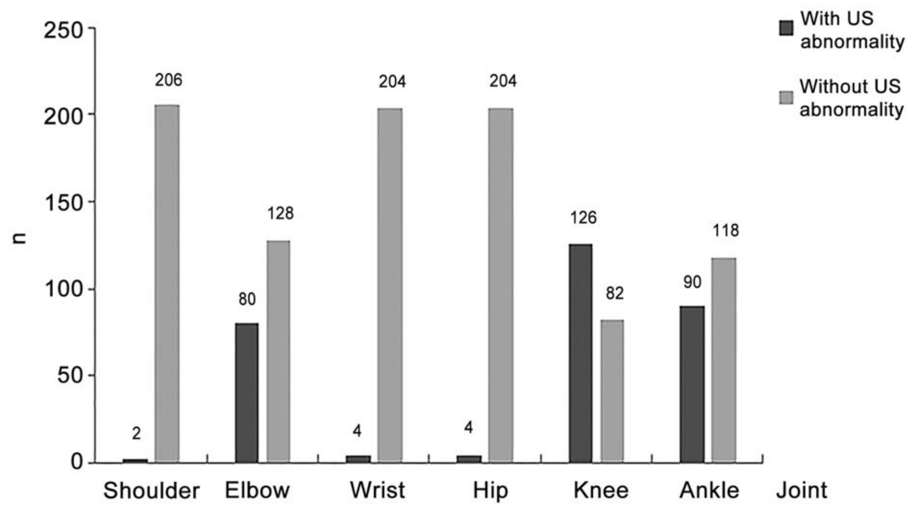

Figure 2. A total of 1248 joints from 104 hemophilia patients were examined. There were 306 abnormal joints on musculoskeletal ultrasonography (black column). Comparison of the incidences of involvement among the various joints according to the chi-square test ($P<.001$). There is a significant difference between the knee, elbow, and ankle joints and the shoulder, wrist, and hip joints.

Additionally, we noted that 4 of the 6 patients with abnormal joints (aged 2–10 years) had mild synovial hypertrophy (3 patients had mild knee lesions and 1 had a mild ankle lesion) and that they had undergone primary preventative treatment. The other 2 patients with abnormal joint cartilage and bone (aged 23 and 27 years) had undergone tertiary preventative treatment and had started prophylaxis nearly 3 years prior. We found that prophylaxis was more effective when initiated early and at a sufficient dose.

In our study, joint damage increased significantly with increasing age and hemophilia severity, both of which were related to a high number of accumulative bleeding episodes and bleeding-related joint damage. However, we found that they were not influenced by the type of hemophilia or treatment modality. Muça-Perja et al[36] similarly found that the degree of joint involvement was not influenced by the type of hemophilia. Further research with a large sample size may be needed.

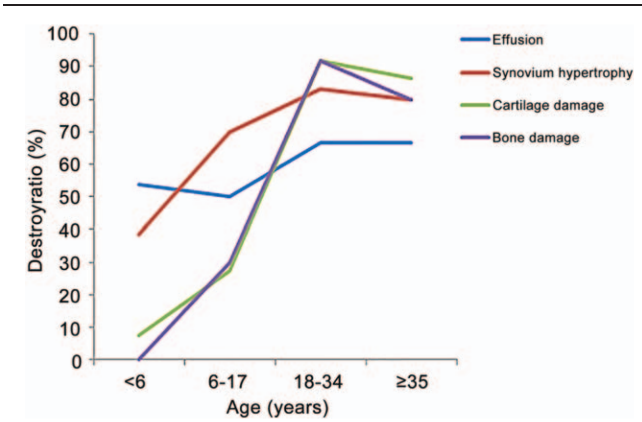

Figure 3. Effusion, synovium hypertrophy, cartilage destruction, and bone destruction show increases with age. There are significant differences across ages with regard to synovium hypertrophy, cartilage destruction, and bone destruction (trend chi-square test, $P<.001$), but not effusion ($P>.05$).

We did not consider cartilage calcification for cartilage modification, as epiphyseal plate ossification increases with age in adolescents. Calcification often accompanies hyperechogenicity and an irregular profile. Occasionally, a thickened synovium and fat pads are difficult to differentiate, and color Doppler flow imaging and power Doppler imaging can help distinguish between a thickened synovium and fat pads. In this study, most patients had received on-demand or occasional treatment, thereby resulting in frequent joint bleeding and related joint damage. Among the tools available for monitoring joint status, MRI is often costly and time-consuming. In the Second

Table 3

Chi-square test to analyze internal differences for the 4 factors with regard to the incidence of the involved joints identified on musculoskeletal ultrasonography.

Variable	Patients with normal joints (n)		Patients with abnormal joints (n)	*P*
Type of hemophilia*				
A	12	74	0.346	.557
B	1	17		
Age (years)†				
<6	4	9	8.216	.004
6–17	8	32		
18–34	0	36		
≥35	1	14		
Severity#				
Mild	3	3	7.711	.016
Moderate	6	34		
Severe	4	54		
Treatment categories#				
Prophylactic treatment	2	6	2.559	.261
On-demand treatment	10	64		
Occasionally treatment or no treatment	1	21		

* Data analysis using the continuity correction chi-square test.
† Data analysis using the trend chi-square test.
# Data analysis using Fisher's exact test.

Table 4

Multivariate logistic regression analysis to analyze the risk factors associated with joint disease identified on musculoskeletal ultrasonography.

Variable	Regression coefficient	Standard error	Wald	*P*	OR	OR (95%CI)
constant	−5.781	2.406	5.772	.016		
Type of hemophilia	1.146	1.164	0.971	.325	3.147	(0.322,30.778)
Age, years	1.107	0.455	5.914	.015	3.024	(1.240,7.378)
Severity	1.394	0.538	6.704	.01	4.029	(1.403,11.571)
Treatment categories	0.347	0.678	0.262	.609	1.415	(0.375,5.342)

CI = confidence interval, OR = odds ratio.

Hospital of Shanxi Medical University, MRI examination of a joint costs 895¥ and takes 15–20 minutes irrespective of whether the joint is normal, while MSKUS examination of a joint costs 90¥ and takes about 5–8 minutes (the examination takes less time if the joint is normal). On the other hand, radiography is associated with poor soft tissue resolution. The advantages of MSKUS are unique as they are beneficial to both patients and physicians,[37–39] and MSKUS is emerging as an important modality for the diagnosis of treatable musculoskeletal abnormalities that contribute to pain in patients with HA.[40,41] Therefore, MSKUS appears to have a potentially critical role in the development of personalized hemophilia care.[13,40]

The present study has some limitations. First, there was no clear definition of articular cartilage thickness according to joint location or patient age. Additionally, there was no specified definition of abnormal joint effusion in joint capsules at different locations. Second, MSKUS was not compared with MRI owing to sample size issues and the expensive nature of MRI. A further study with a large sample size is required to determine normal articular cartilage thickness and abnormal joint effusion. Moreover, comparisons with MRI are needed to determine the efficacy of MSKUS.

5. Conclusion

MSKUS is an economical and convenient imaging approach. It can provide clear images of soft tissue changes and damage to the osteochondral surface. Moreover, it can play an important role in the diagnosis and long-term monitoring of HA, and it may become the first-choice imaging approach for diagnosis, follow-up, and preoperative and postoperative evaluations.

Author contributions

Conceptualization: Cui-ming Zhang, Yu-lin Guo, Lin-hua Yang.
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Supervision: Lin-hua Yang.
Writing – original draft: Cui-ming Zhang, Lin-hua Yang.
Writing – review & editing: Cui-ming Zhang, Lin-hua Yang.

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