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ORIGINAL ARTICLE

# Ultrasonography of Knee Joint in Hemophilia A: What the Eyes Cannot See

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**Abstract** Haemophilia is the most common inherited coagulopathy. Approximately 94% patients suffer from joint disability. An imaging modality to detect joint damage can help in monitoring. Ultrasonography (USG) provides a low cost and reliable imaging alternative to magnetic resonance imaging. This study aims at the detection of subclinical knee-joint involvement by USG, in patients with moderate to severe Haemophilia. 27 patients suffering from moderate and severe Haemophilia and 27 age-matched controls were studied. USG of bilateral knee joints was done to analyse cartilage and synovial thickness, synovial vascularity and resistive index of vascular flow along with synovial collection. The relevant clinical parameters (age at diagnosis and study enrolment, severity of haemophilia A, annualized bleeding rates, total number of joint bleeds, spontaneous and provoked bleed, number of episodes treated with factor VIII injection) were noted. The USG findings were correlated to the clinical parameters and subclinical joint bleed detection looked for. 13 patients [18 out of 54 joints (33.33%)] showed increased vascular signals with mean resistive-index (RI) 0.67 (± 0.086; 95% CI: 0.62–0.70). The mean synovial thickness in persons with haemophilia (PwH) was higher than the control subset ($p < 0.05$ on all counts). The mean cartilage thickness was lower in PwH than in controls. On a subset analysis, there was significant difference between the mean cartilage thickness between moderate PwH and age matched controls ($p < 0.0001$). 3 patients (11.1%) showed evidence of joint collection (hemarthrosis) despite having no clinical evidence of joint involvement. Through the findings of our study, we do infer that ultrasonography can detect subclinical synovial inflammation and cartilage damage in haemophilia patients that may affect long term articular outcome. It is also a useful modality for detection of sub clinical joint bleed.

**Keywords** Haemophilia · Ultrasonography · Knee joint

## Introduction

India has more than 17,000 cases of haemophilia as per World Federation of Haemophilia (WFH) estimates with more than 93.9% suffering from disability [1, 2]. Less than 1% of patients with haemophilia A in India are on primary or secondary prophylaxis [2]. In this setting, joint damage becomes an inevitable and devastating complication in PwH, especially those with moderate and severe haemophilia.

Traditionally, radiography was used for estimation of joint damage. Radiography is suitable for the detection of bony changes associated with advanced arthropathy, but soft tissue changes of early disease remain undetected. MRI is the best option as it can accurately assess both soft tissue and bone [3]. In a country like India, this is not a feasible option because of financial constraints and restricted availability. However, USG has been shown to be an effective modality of assessing soft tissue abnormalities and osteochondral changes in haemophilia A [3]. USG is also a low-cost modality and can be easily repeated in follow-up to assess subsequent damage. This study aimed at comparing the USG findings and clinical parameters.

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## Materials and Methods

This was a cross-sectional, single-centre observational study. 27 consecutive patients of moderate and severe haemophilia A attending the haemostasis clinic of a tertiary-care hospital in West Bengal, India between June, 2016 and June, 2017 and not meeting the exclusion criteria, were enrolled. Prior approval was attained from the Institutional Ethics Committee (IEC). The patients were recruited to the study after obtaining their informed consent. The patients were on on-demand therapy with Factor VIII for joint-bleeds.

Exclusion criteria included (1) patients with radiologic (X-Ray) evidence of advanced knee-joint arthropathy (Arnold Hilgartner Stage IV or V), (2) clinically documented acute bleed in the knee-joints in the past 1 month, (3) history of intervention to the knee joints (radiation synovectomy, or any surgical procedure). Relevant clinical data (age at diagnosis and study enrolment, severity of haemophilia A, annualized bleeding rates (ABR), total number of joint bleeds, spontaneous and provoked bleed, number of episodes treated with F VIII inj.) was collected and clinical evaluation of the joint done. Ultrasonography of bilateral knee joints of each participant was performed using E Saote My Lab Gold 25 USG platform. A 10–15 MHz linear array transducer was used for this purpose. Cartilage (average of medial, central and lateral compartments) and synovial thickness were measured in B-mode scan. During USG evaluation of the knee joint, the person was kept in a supine position. For measurement of cartilage thickness, knee joint was kept in a position of maximum flexion and was scanned in a transverse plane across the lower femoral condyles. The hypoechoic cartilage was identified and measured in three areas (medial, central and lateral). Measurement of synovial thickness was done by keeping the knee joint in 30 degrees flexion. The supra patellar pouch was identified in a longitudinal mid-sagittal scan keeping the distal end of the transducer in apposition with the superior pole of the patella. Hypoechoic joint synovium was identified and measured in this plane. Assessment of synovial vascularity was performed by estimating the flow signals in the synovium using colour flow imaging. Following localisation of synovial flow signal, pulsed-wave doppler was used to obtain a spectral waveform and estimation of RI. Intra-articular collection was detected by B-mode USG. Hypoechoic or mixed echogenic area within knee joint recess with features of compressibility and displaceability was considered as joint collection. USG evaluation was performed by 2 independent radiologists experienced in musculo-skeletal radiology, who were blinded to the clinical background of the subjects and to each other's assessment. Similar parameters in 27 age-matched male controls were compared. Correlation analysis was done between USG findings (cartilage thickness, synovial vascularity) and the above clinical parameters. SPSS Version 21 was used in the statistical analysis.

## Results

Among the 27 patients enrolled in the study, 9 patients had moderate Haemophilia A and 18 patients had severe haemophilia A. None of the patients was on any supportive medications (prophylactic factor concentrates, anti-fibrinolytics, etc.). The mean age of the haemophilia patients was 16.57 years (± 9.57). Mean number of joint bleeds were 36.04 and 29.85 in right and left knees respectively. The mean annualised joint bleed rates (ABR) for the study population was 7.74 (Fig. 1).

13 patients had knee as the target joints (7 in the right knee joint, 6 in left knee joint) (Table 1). Mean synovial thickness were 0.27 and 0.17 in haemophilia patients and controls. Mean right-cartilage thickness was 0.22 and 0.40 in patients and controls respectively. Mean left cartilage thickness were 0.23 and 0.38 in PwH and control population respectively. There was significant difference in all the above parameters between haemophilia patients and control population, across all age bands (Table 2). There was significant difference between the mean cartilage thickness between moderate PwH and age matched controls ($p < 0.0001$).

The mean right cartilage thickness, mean left cartilage thickness, right synovial thickness and left synovial thickness were compared between target knee-joints, non-target knee-joints and knee-joints of controls (Table 3). Intergroup-comparison showed that there was a significant difference in all the parameters between the target joints and non-target joints except in the right mean cartilage thickness ($p$ values were 0.568, 0.038, 0.04, 0.036 for right mean cartilage thickness, left mean cartilage thickness, right synovial thickness and left synovial thickness, respectively). There was significant difference in all the parameters between target joints and controls ($p$ values were $< 0.001$ for each of right mean cartilage thickness, left mean cartilage thickness, right synovial thickness and left synovial thickness, respectively).

There was a good inter-rater agreement between the imaging findings of two independent radiologists (Cohen's Kappa for cartilage thickness: 0.882, for synovial proliferation: 0.872).

13 patients (18 joints out of 54) showed increased vascular signals in the synovium indicating ongoing inflammation (synovitis) with mean RI 0.67 (± 0.086; 95% CI: 0.62–0.70).

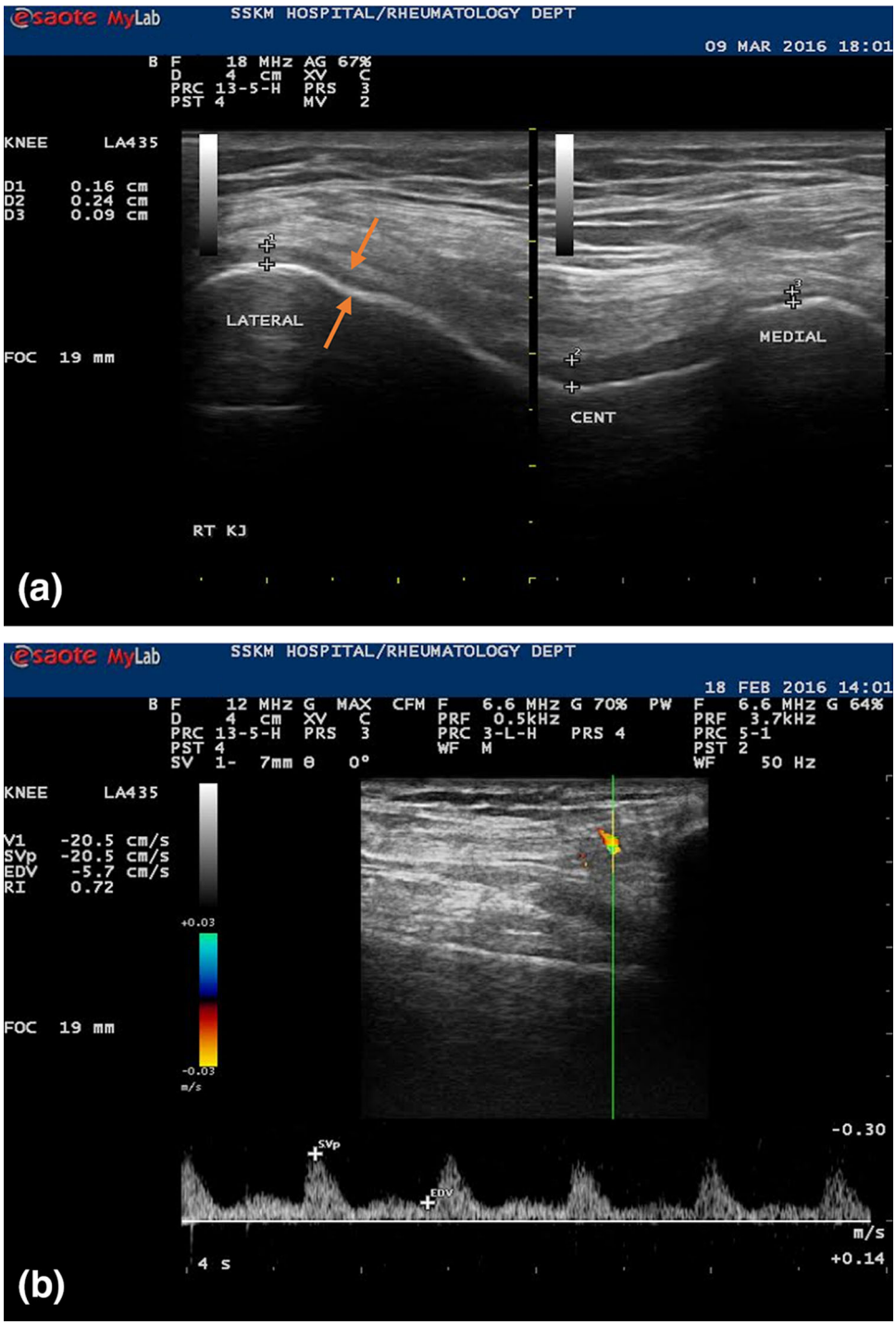


**Fig. 1** USG of knee joint showing **a** cartilage thickness in medial, lateral and central compartments with maximum erosion in medial compartment; and **b** vascularity in the synovium with decreased resistive index, suggestive of inflammation

3 patients showed presence of joint space collection (blood) despite having no clinical evidence or a recent history of hemarthrosis, indicating subclinical bleed. These patients had moderate haemophilia and their documented mean annualized bleeding rates was 0.2. The mean cartilage thickness (Right: 0.2, Left: 0.22) was significantly less than the age matched control population (Rt: 0.4, Lt: 0.38). The mean synovial thickness in these patients was also higher (0.22) as compared to the age-matched controls (0.12).

There was no significant correlation between the joint parameters (synovial thickness, cartilage thickness) and clinical parameters (age, no. of clinically documented bleeds, severity of disease, or treatment received (all correlation coefficients $< 0.3$).

**Table 1** Baseline characteristics in moderate and severe hemophilacs and control (healthy) subjects

| Type | No. (n) | Age (years) | ABR (range) | Knee target joint (n) | Right mean synovial thickness (cm) | Left mean synovial thickness (cm) | Right mean cartilage thickness (cm) | Left mean cartilage thickness (cm) | Vascularity increased (n) | Mean resistive index (R.I.) |
|---|---|---|---|---|---|---|---|---|---|---|
| Moderate | 9 | 14.83 | 5.33 (4–10) | 3 | 0.27 ± 0.19 | 0.24 ± 0.15 | 0.24 ± 0.1 | 0.25 ± 0.12 | 6 | 0.68 ± 0.06 |
| Severe | 18 | 17.44 | 8.94 (3–30) | 10 | 0.3 ± 0.11 | 0.25 ± 0.12 | 0.18 ± 0.08 | 0.18 ± 0.05 | 10 | 0.67 ± 0.09 |
| Control | 27 | 16.75 | 0 | – | 0.16 ± 0.04 | 0.17 ± 0.06 | 0.4 ± 0.06 | 0.38 ± 0.09 | 0 | – |

**Table 2** Comparison of mean synovial thickness and mean cartilage thickness among haemophilia patients and corresponding healthy controls as per age-bands

| | Mean synovial thickness (± SD) | *p* value | Rt. mean cartilage thickness (± SD) | *p* value | Lt. mean cartilage thickness (± SD) | *p* value |
|---|---|---|---|---|---|---|
| Patients 0–10 years | 0.27 (± 0.13) | 0.0379 | 0.20 (± 0.08) | 0.0006 | 0.19 (± 0.08) | 0.0006 |
| Control 0–10 years | 0.12 (± 0.02) | | 0.45 (± 0.06) | | 0.46 (± 0.07) | |
| Patients 11–20 years | 0.25 (± 0.09) | 0.0383 | 0.24 (± 0.12) | 0.0005 | 0.26 (± 0.14) | 0.0229 |
| Control 11–20 years | 0.18 (± 0.04) | | 0.41 (± 0.05) | | 0.36 (± 0.09) | |
| Patients > 20 years | 0.33 (± 0.08) | 0.0022 | 0.21 (± 0.12) | 0.0159 | 0.22 (± 0.05) | 0.0379 |
| Control > 20 years | 0.20 (± 0.02) | | 0.32 (± 0.04) | | 0.32 (± 0.04) | |

All measurements in cm

**Table 3** Comparison of the cartilage thickness and synovial thickness between target-joints, non-target joints and controls

| | Right mean cartilage thickness | Left mean cartilage thickness | Right mean synovial thickness | Left mean synovial thickness |
|---|---|---|---|---|
| Target joints | 0.20 ± 0.06 (n = 7) | 0.21 ± 0.06 (n = 6) | 0.31 ± 0.13 (n = 7) | 0.3 ± 0.11 (n = 6) |
| Non-target joints | 0.23 ± 0.12 (n = 14) | 0.26 ± 0.13 (n = 14) | 0.27 ± 0.14 (n = 14) | 0.21 ± 0.12 (n = 14) |
| Controls | 0.40 ± 0.06 (n = 27) | 0.38 ± 0.09 (n = 27) | 0.16 ± 0.04 (n = 27) | 0.17 ± 0.06 (n = 27) |

## Discussion

There have been few published data looking at the correlation of the USG findings and the clinical parameters. In the study by Foppen et al. [4] joints without reported bleeding did not show abnormalities at physical examination and/or ultrasound assessment. In contrast, we found synovial proliferation, hyper vascularity and lower cartilage thickness in the patients with lower ABR and even without any clinically documented bleed. Synovial proliferation, vascularity and decrease in RI are well known features of ongoing inflammation. RI is a parameter which is measured from arterial waveform. It indicates the resistance offered by the vascular bed to the blood flowing through it. In the setting of an inflammation, RI of local arteries is relatively lower than the normal. In multiple studies these USG parameters were used to detect synovial inflammation in rheumatoid arthritis [5]. In addition to rheumatoid arthritis, USG is also used in osteoarthritis to detect synovial pathologies in clinically silent joints [6, 7]. Ongoing sub-clinical joint-bleed may be a plausible explanation of these findings [8]. This is an interesting finding suggesting a possible role of periodic monitoring of joint damage status on USG irrespective of the status of clinical bleeding (Fig. 2).

Utility of USG to detect various aspects of haemophilic arthropathy has been documented in some previous studies [9]. An important initiative was to develop an USG based

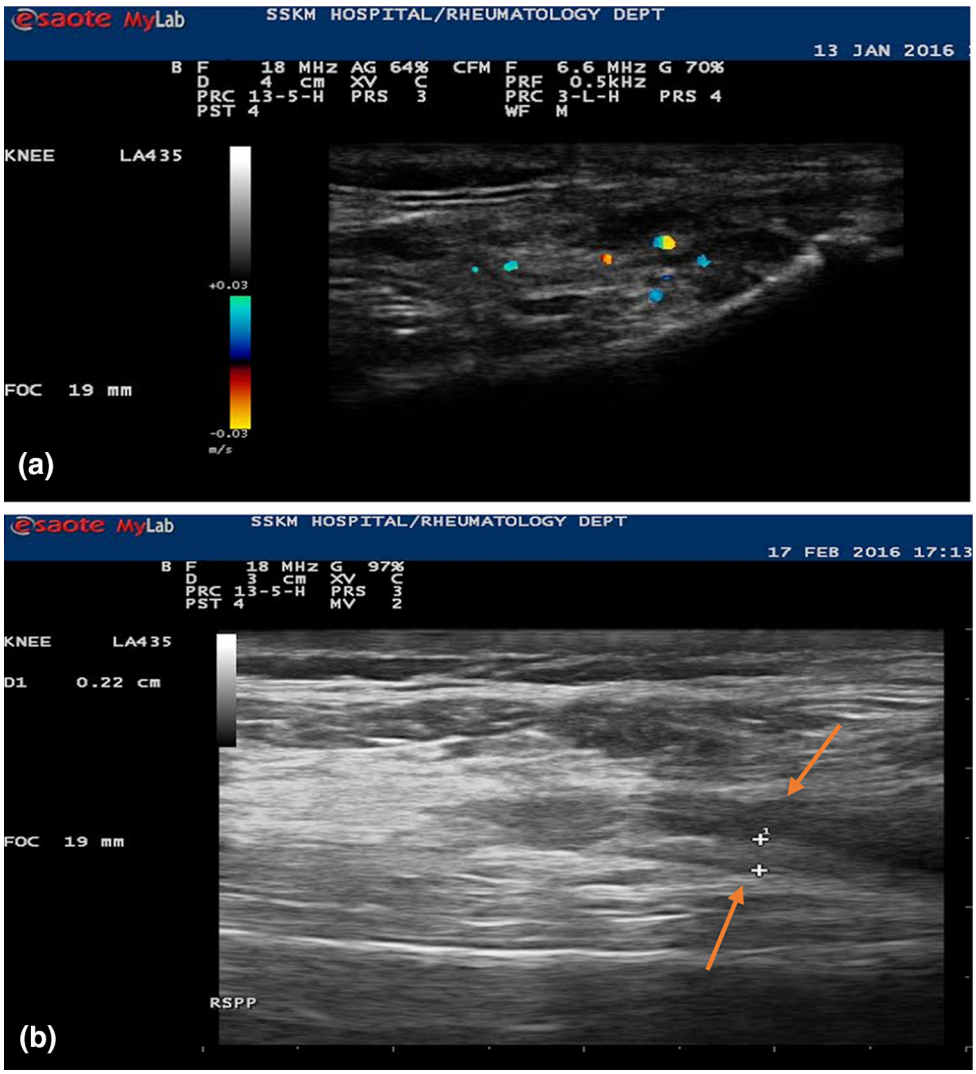


**Fig. 2** USG of knee joint showing **a** hyper-vascularity of synovium, and **b** synovial thickening (red arrows)

scoring system in haemophilia patients, incorporating both inflammatory activity and damage in three sets of joints. This HEAD-US scoring system includes bony abnormalities in addition to synovial and cartilage changes [10]. In our study, synovial inflammation and cartilage damage were looked for. Sub-chondral bony changes were not assessed, as scoring of the joint changes on USG was not the aim of our study. Moreover, we included synovial flow signals and RI to estimate the inflammatory burden in haemophilia patients as synovial inflammation is the harbinger of future joint damage.

In our clinical practice, we often find patients who have significant osteochondral damage on imaging (MRI/USG) despite less number of clinically documented joint bleeds. This is reflected in our finding of having no correlation between USG and clinical parameters.

We have compared the indices (right mean cartilage thickness, left mean cartilage thickness, right synovial thickness and left synovial thickness) in between target joints and non-target joints in PwH (Table 3). Most of the parameters were significantly worse in the target joints which is expected, with more bleeds amounting to greater joint damage. However, the difference between the right mean cartilage thickness was not statistically significant between the two groups (0.23 in non-target joints and 0.2 in target joints). We believe that this may be due to the small number of patients in each subset (7 PwH with right knee as target joint).

We hereby also show that there is significant difference in corresponding parameters between PwH and age-matched male controls ($p < 0.05$, Table 1) as assessed by USG as was demonstrated in background studies [3, 11, 12]. This is expected as the joint damage is not expected in control (normal) samples as compared to those with moderate to severe haemophilia. This difference was also significant between moderate PwH and controls suggesting a potential role for serial joint monitoring by USG in this distinct subset of moderate PwH.

It has been documented that sub-clinical bleeds do represent a major cause for joint-damage [13]. Once chronic arthropathy has set in, the patient usually lands up with joint deformity and/or synovial proliferation for which surgical procedures (joint replacement or arthrodesis) or radiation synovectomy become imperative [14]. USG is a reliable imaging modality, especially considering the cost-constraints in India. The ability to pick-up sub-clinical joint damage may help to monitor the joint damage in serial USGs. In our study, subgroup analysis showed relevance of USG findings in moderate haemophilia A. However, less number of patients is a limitation of the study. Further studies with larger patient numbers are required to validate this observation.

## Conclusion

Subclinical synovial inflammation and premature knee cartilage degeneration occurs in haemophilic patients, irrespective of the age, severity, number of bleeds or treatment.

Ultrasonography can detect subclinical hemarthrosis, even in moderate PwH. This may affect long term articular outcome in these patients.

**Compliance with Ethical Standards**

**Conflict of interest** All the authors declare that they have no conflict of interest.

**Informed Consent** Informed consent was obtained from all the patients.

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