A Combined Ultrasonographic and Conventional Radiographic Assessment of Hemophilic Arthropathy

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Abstract Hemophilic arthropathy (HA) can be diagnosed by a number of imaging studies. However, it is difficult with conventional radiography to find soft tissue structures around joints, and ultrasonography has limited effectiveness in evaluating internal bony structures. We attempt to determine whether a combination of ultrasonography for soft tissue around joints and conventional radiography for bony structures can be used as a cost-effective imaging tool for evaluating HA and whether it reflects the functional status of hemophilic patients. Thirty-six males (median age 16.5 years; severe 34, mild 2) with hemophilia were recruited. We evaluated the severity of HA using combined imaging score that consisted of modified Petterson X-ray score (mPXS) and the modified ultrasonographic score (mUS). Joint impairment was clinically assessed using the World Federation of Hemophilia-Physical Examination (WFH-PE) scale and the Hemophilic joint health score (HJHS). We assessed the Hemophilia activities list (HAL) for the functional level. We performed a comparative analysis between the combined imaging score and the joint

impairment scores as well as the functional scores. The mean mUS was 4.97 ± 3.99 points, and the mean mPXS was 2.85 ± 2.91 points; the combined imaging score was 7.83 ± 6.31 points. The combined imaging score was significantly correlated with the HJHS ($p = 0.006$) and WFH-PE scores ($p = 0.019$) as well as the HAL score ($p = 0.002$). A combination of conventional radiological and ultrasonographic study might ultimately impact the optimal evaluation of joint impairment and functional status in hemophilic patients.

Keywords Hemophilia · Arthropathy · Ultrasonography · Radiography · Musculoskeletal · Function

Introduction

In hemophilia, accurate evaluation of joint condition is a prerequisite for a correct therapeutic approach. Therefore, evaluating joint conditions is very important not only for staging the joint damage but also for the prophylaxis follow-up and for assessing the outcomes of replacement therapy [1]. Hemophilic joint disease can be diagnosed by a number of imaging studies such as conventional radiography, ultrasonography and magnetic resonance imaging (MRI). With conventional radiography, it is difficult to establish early joint pathology and soft tissue structures such as the synovium and ligament structures [2–4]. Ultrasonography has limited effectiveness in evaluating internal bony structures and deep joint areas. Ultrasonography does not reflect subchondral sclerosis, bone cysts, or structural changes in the central portion of the joint [5]. MRI provides information about all of the pathology of the synovium, articular cartilage and bone, and it is useful for early detection of joint pathology [6, 7]. However, it is

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expensive, and it may be burdensome in young children who require sedation. Therefore, we here attempt to determine whether a combination of ultrasonography and conventional radiography can be used as a cost-effective imaging tool for evaluating hemophilic joints and adjacent structures and whether it indicates functional hemophilic joint status.

Materials and Methods

Subjects

Thirty-six males (hemophilia A, 35, hemophilia B, 1; median age 16.5 years, BMI 17.89 ± 3.68 ; sever 34, mild 2) with hemophilia were recruited at the hemophilic treatment center of OO between June 2012 and May 2014 to participate in this prospective study (Table 1). Exclusion criteria were presence of comorbidities that caused osteoarticular findings, which could have confounded the joint findings, need for sedation, study joint bleed less than 2 weeks before the examinations, and prior synovectomy. Informed consent from all individual participants is included in this study. After the ethical committee approval and informed consent were obtained, ultrasonography and conventional radiography in both knee and ankle joints were performed in all patients.

Ultrasonographic Score

We acquired ultrasonographic images using a 7.5 MHz transducer (Model L5-13S). The same probe and ultrasonography system (ACCUVIX V20, Samsung-Medison Co., Seoul, KOREA) were used. The knees and ankles were systematically studied in all patients. Static and dynamic examinations were carried out in all studied joints. The probe scanned the knee joint in the longitudinal and transverse view with patient in the supine position with the knee in full or moderate flexion (30–45°) to study the anterior suprapatellar region and lateral and medial patellar regions. The ankle was studied with the foot on the bed.

The probe was positioned in longitudinal and transverse scans to evaluate the anterior, medial and lateral aspects of the tibio-talar region. The thickness of the synovial membrane was measured in mm, and an area with a thickness of 1.5 mm. was considered synovial hypertrophy [8]. The Power Doppler US (PDUS) was performed to detect synovial neo-angiogenesis, which was defined as color-flow signals in structures between the capsule and the bone surface [9, 10]. Flow was additionally demonstrated in two planes and confirmed by pulsed wave Doppler spectrum [11]. The intra-articular PDUS signal was scored on a semi-quantitative scale from 0 to 2: 0 = absence, no vessel signals; 1 = vessel signals in the region of interest (ROI) < 3 flags; 2 = vessel signals in ROI > 3 flags or in more than half of the intra-articular area. We used the modified ultrasonographic score (mUS) for the hemophilic arthropathy. In order to increase specificity for assessing soft tissue structures around joints, 3 items associated with bony structures—bony erosion, bone remodeling, and osteophytes—were excluded from the ultrasonographic scoring method proposed by Melchiorre et al. [12]. The joints were consecutively evaluated and scored (score ranging from 0 to 15) for effusion, cartilage damage, synovial hypertrophy with and without flags on PDUS, hemosiderin, hemarthrosis and fibrotic septa with ultrasonography (Appendix 1). There were images of some cases demonstrating early, moderate and advanced hemophilic arthropathy as evaluated by the ultrasonographic scoring system (Fig. 1).

Conventional Radiographic Score

For all patients, we were able to perform complete conventional radiography of the ankle and knee joints. All radiographic assessments were conducted by a radiologist, one of the authors. The severity of hemophilic arthropathy (HA) on conventional radiography was determined utilizing the Petterson scale [13], which incorporates the following eight aspects: osteoporosis, increased epiphyseal endplates, irregular subchondral surface, loss of joint space, subchondral cysts, erosion of the joint edges, incongruity of joint surfaces and deformity of the joint. The sum of these lead to the radiographic joint score (range 0–13), where 0 points suggests no radiographically evident pathological finding and 13 points shows a massively damaged joint on conventional radiography. We used modified Pettersson X-ray score (mPXS) as a conventional radiographic score. The mPXS is defined as the sum of the radiographic joint scores of ankle and knee joints (range 0–52 points) except elbow joints. There were images of some cases demonstrating early, moderated and advanced hemophilic arthropathy as evaluated by the conventional radiographic scoring system (Figs. 2 and 3).

Table 1 General characteristics

Parameters	
Age, median (interquartile ranges)	16.5 (7.25–27.75) years
Severity (N)	Severe (34), mild [2]
Deficit factor (N)	VIII (35), IX [1]
Primary prophylaxis (N)	23
Sex	All male

N Number of cases

Table 2 The results of imaging and functional studies in patients with hemophilic arthropathy

Classification	Assessment tools	Score
Imaging score	Modified ultrasonographic score	4.97 (3.99)
	modified Pettersson score	2.85 (2.91)
	Combination score	7.83 (6.31)
Joint impairment assessment	Hemophilic joint health score	2.97 (5.09)
	WFH-PE	3.53 (5.45)
ADL evaluation	Hemophilic activities lists	89.80 (15.11)
	FISH	30.29 (3.22)

Values are means (SD)

WFH-PE World Federation of Hemophilia-Physical Examination, FISH Functional Independence Score in Hemophilia, ADL Activities of daily living

Fig. 1 Figure a, b show longitudinal ultrasonographic findings of early hemophilic arthropathy in knee and ankle joint. These demonstrate a small effusion, no fibrotic septa, minimal synovial hypertrophy (<1.5 mm) without flags on PDUS, no hemosiderin deposition and no calcification. The suprapatellar recess (white arrow, a) is minimally distended; Figure c, d show moderate stage of hemophilic arthropathy in knee and ankle joint. These demonstrate a moderate effusion, no fibrotic septa, synovial hypertrophy

(1.5–2.5 mm) with 3 flags, no hemosiderin deposition and irregular cartilage profile (white arrow, d). Full amount of suprapatellar recess distension (white arrow, c) is observed; Figure e, f show advanced stage of hemophilic arthropathy in knee and ankle joint. These demonstrate a large effusion, no fibrotic septa, synovial hypertrophy (>2.5 mm) with over 3 flags (f), no hemosiderin deposition and cartilage calcification (white arrow, f). Marked distension of the suprapatellar recess with synovium is demonstrated (white arrow, e)

Combined Imaging Score

We created the combined imaging score in order to determine the correlation between the combined imaging and

functional scores; the mUS was added to the mPXS to make the combined imaging score. We performed a comparative analysis between the combined imaging score and the clinical joint impairment scores as well as the functional scores.

Fig. 2 Figure **a, b** show early stage of hemophilic arthropathy in knee joint: AP and lateral view. Note no osteoporosis, no enlarged epiphysis, no irregular subchondral surface, no narrowing of joint space, no subchondral cyst formation, no joint margin erosion, no gross incongruence of articulating bone ends and no joint deformity; Figure **c, d** show moderate stage of hemophilic arthropathy in knee joint: AP and lateral view. Note the osteoporosis, no enlarged epiphysis, no irregular subchondral surface, narrowing of joint space (>1 mm), no subchondral cyst formation, no joint margin erosion, no gross incongruence of articulating bone ends and no joint deformity. This is Petterson grade 2; Figure **e, f** show advanced stage of hemophilic arthropathy in knee joint: AP and lateral view. Note the osteoporosis, no enlarged epiphysis, partially irregular subchondral surface, narrowing of joint space (<1 mm), 1 subchondral cyst formation (*black arrow, e*), no joint margin erosion, slight gross incongruence of articulating bone ends and no joint deformity. This is Petterson grade 6

Early

Moderate

Advanced

Knee anterior-posterior

Knee lateral

Clinical Joint Impairment Score and Functional Score

The degree of joint impairment was assessed using the physical examination score of the World Federation of Hemophilia-Physical Examination (WFH-PE) scale and the Hemophilia Joint Health Score (HJHS). We assessed the Functional Independence Score in Hemophilia (FISH) and the Hemophilia Activities List (HAL) for the functional levels of activities of daily livings.

The HJHS is used to grade joints according to swelling, swelling duration, muscle atrophy, crepitus on motion, flexion loss, extension loss, instability, joint pain, strength, and global gait. A score of 0 to 24 is used for the both knee and ankle joints. Then, the individual scores are summed. A normal joint would receive a score of 0 points, and a score of 96 points corresponds to the worst level of arthropathy [14, 15]. Because more medical and surgical methods to improve function have become available, it has

been necessary to develop an instrument to compare physical outcome measures across different populations of patients with hemophilia. With this in mind, the WFH developed the Physical Examination Scale. This scoring system evaluates ROM, flexion deformity, swelling, crepitus, wasting, instability, axial deformity, joint bleeding and joint pain and in the both knee and ankle joints [16, 17].

The FISH was used to assess the functional status of patients in performing 8 tasks, which were divided into the following 3 categories: self-care (eating, grooming, bathing, and dressing), transfers (chair and squatting), and mobility (walking, going up stairs, and running). Each function was assigned a score of 1 to 4: 1 = the subject is unable to perform the activity, or needs complete assistance to perform the activity; 2 = the subject needs partial assistance/aids/modified instruments/modified environment to perform the activity; 3 = the subject is able to perform the activity without aids or assistance, but with slight

Fig. 3 Figure **a, b** show early stage of hemophilic arthropathy in ankle joint: AP and lateral view. Note no osteoporosis, no enlarged epiphysis, no irregular subchondral surface, no narrowing of joint space, no subchondral cyst formation, no joint margin erosion, no gross incongruence of articulating bone ends and no joint deformity; Figure **c, d** show moderate stage of hemophilic arthropathy in ankle joint: AP and lateral view. Note the osteoporosis, no enlarged epiphysis, no irregular subchondral surface, narrowing of joint space (>1 mm), no subchondral cyst formation, no joint margin erosion, no

gross incongruence of articulating bone ends and no joint deformity. This is Peterson grade 2; Figure **e, f** show advanced stage of hemophilic arthropathy in ankle joint: AP and lateral view. Note the osteoporosis, no enlarged epiphysis, partially irregular subchondral surface, narrowing of joint space (<1 mm), 2 subchondral cyst formation (black arrow, **e**), joint margin erosion (black arrow, **f**), gross incongruence of articulating bone ends and no joint deformity. This is Peterson grade 7

discomfort. He is unable to perform the activity like his healthy peers; and 4 = the subject is able to perform the activity without any difficulty like other healthy peers [18]. Scores ranging from 8 (the worst) to 32 (the best) were used to assess the functional status of the hemophilia patients [19]. The HAL is a hemophilia-specific, self-assessment questionnaire that was developed in close collaboration with the patients themselves and that can be administered in approximately 5 min. It consists of 42 activity items, divided among seven domains: “Lying down/sitting/kneeling/standing,” “Functions of the legs,” “Functions of the arms,” “Use of transportation,” “Self

Care,” “Household tasks” and “Leisure activities and sports.” Scores can be obtained for each domain separately, but an overall sum score for the complete questionnaire can also be calculated [20, 21].

Statistical Analysis

Statistical analysis by Spearman’s rho correlation coefficient was performed for each alteration. In all patients, the score from the combined imaging study and the functional scores were compared. The statistical analysis was

Fig. 4 This figure shows that there were significant correlation between combined imaging score and Hemophilic Joint Health Score (HJHS), World Federation of Hemophilia-Physical Examination

(WFH-PE) score as well as Hemophilic activities lists (HAL) score, however, this method was no significant correlation with Functional Independence Score in Hemophilia (FISH)

performed using SPSS 10.0 software (Chicago, Illinois, USA). A two-tailed p value less than 0.05 was considered to show statistical significance.

Results

Table 2 shows the results of the study population. The mean mUS score was 4.97 ± 3.99 points, and the mean mPXS score was 2.85 ± 2.91 points; the combination score was 7.83 ± 6.31 points. The mean HJHS score was 2.97 ± 5.09 , and the mean WFH-PE score was 3.53 ± 5.45 . The HAL score was 89.80 ± 15.11 , and the FISH score was 30.29 ± 3.22 . Figure 4 shows that the combination score was significantly correlated with the HJHS ($p = 0.006$, $r = 0.463$) and WFH-PE ($p = 0.019$, $r = 0.452$) scores as

well as the HAL score ($p = 0.002$, $r = -0.531$). However, there was no significant correlation with the FISH score ($p = 0.79$, $r = 0.04$).

Discussion

In hemophilia management, measuring impairment and functional ability is recognized as increasingly important for assessing and monitoring joint status and for evaluating the range of therapeutic interventions. Impairments can result from abnormalities of body structures and physiological functions [22]. The presence of impairments can be assessed clinically and radiographically, and imaging studies of the musculoskeletal system in patients with HA help to quantify outcomes, in addition to providing criteria

by which physiatrists, hematologists, orthopedists physiotherapists, pediatricians, radiologists and occupational therapists can decide whether current treatment is still effective or other interventions are needed. Usually, HA severity is scored with the PXS, but this assesses bone modifications only and cannot identify soft tissue modifications and bleeding. Pettersson et al. [13] introduced a score based on radiological changes only; sensitivity and good correlation to clinical findings were shown mainly in non-adult hemophiliacs of different severity levels. MRI is a sensitive diagnostic tool for documenting early arthritic changes in hemophilic children with no obvious clinical signs of arthropathy. In addition, it can unmask more advanced arthritic alterations than those detected by conventional radiography. Furthermore, MRI can be used for long-term follow-up of joints, as well as for studying the precise sequences of events before the completion of HA. The provided knowledge might distinguish reversible and non-reversible phenomena during the process of developing HA [23]. However, MRI is a time-consuming and expensive technique, and it is not widely available. The ability of ultrasonography to detect structural changes in rheumatic diseases has been compared with other imaging techniques such as conventional radiography and MRI in inflammatory arthritis and in osteoarthritis [24]. Ultrasonography is an imaging method that detects superficial joint structures, muscles, tendons, sheaths and entheses [25]. Additionally, it is now well-known that PDUS may identify synovial blood flow [26]. One disadvantage that is frequently cited is that ultrasonography does not allow for full evaluation of cartilage thickness or bone changes such as subchondral cysts or marginal erosions [3]. Obviously, the ultrasonography has advantages in assessing soft tissue structures, and radiography has advantages in evaluating bony structures. Therefore, we developed a method of combining the modified ultrasonographic scores with the conventional radiographic scores.

The goal of treatment for HA is to minimize structural damage to joints and maximize patients' functioning. The WFH developed the Physical Examination Scale. This scoring system does not take into account the normal physiologic changes that occur in children, and the score does not assess strength, which is an important function that affects physical activity. The HJHS is easily performed and is a highly sensitive means of assessment in hemophilia patients. This system was invented to produce a score that would be sensitive to early changes, account for normal development in children, and be reliable, valid, and practical to administer [15]. Therefore, we checked both the WFH-PE and the HJHS scores to assess clinical impairment. A number of studies have reported a positive relationship between age and HJHS [27, 28]; in one, a cohort of 39 individuals

with hemophilia from Brazil showed a significant positive correlation of WFH-PE score with age [29]. In our study, the mean HJHS score and the mean WFH-PE score were consistent with the findings for age group <12 years in Khanum's study [27]. We believe that these results relate to the fact that the majority of our study group had undergone prophylactic therapy.

We conducted two hemophilia-specific measures of activities of daily living, one, a performance-based measure, the FISH, and the other, a self-report measure, the HAL. It is known from the literature that both instruments assess different constructs of physical functioning [30, 31]. Therefore, we determined that using both would more fully assess a patient's functional health status. The FISH had good correlation with the clinical HJHS and WFH-PE scores. However, the functional score had poor correlation with the radiological score. Many patients with hemophilia appear to function reasonably well despite having poor conventional radiographic scores [19]. In our study, the FISH was not significantly correlated with the combined imaging score, which we attributed to the lack of correlation with the radiologic scores, which were based only on structural alterations. The FISH was originally designed to compare a patient's basic functional ability with that of normal healthy individuals [32]. Therefore, it may have had a ceiling effect when applied to those with minimal musculoskeletal changes. We believed that this could have been another reason for the poor correlation between the mean FISH and combined imaging scores.

There are some limitations in this study. We could not analyze data according to age or severity because of the relatively small sample size. Additional studies with larger samples are necessary to firmly establish the usefulness of our combined imaging study. Further research is needed to compare and analyze the data between the combined study and MRI, which is the imaging method of choice for evaluating HA. In conclusion, a combination of conventional radiological and ultrasonographic evaluation might ultimately impact the optimal evaluation of joint impairment and functional status in hemophilic patients.

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Compliance With Ethical Standards

Conflict of interest Jae-Hyung Kim has received research Grants from Eulji University (No. 2013-EMBRI-DJ0003).

Appendix

See Table 3.

Table 3 Modified ultrasonographic score

	Evaluation	Score
1	Effusion: hydrarthrosis or hemarthrosis	Absent = 0; small = 1; moderate = 2; large = 3 Absent = 0; small = 1; moderate = 2; large = 3
2	Fibrotic septa	Absent = 0; present = 1
3	Synovial hypertrophy with flags on PDUS	1 = <3 flags; 2 = >3 flags
4	Synovial hypertrophy, thickness measured in mm	Score 1: < 1.5 mm; score 2: 1.5–2.5 mm; score 3: > 2.5 mm
5	Hemosiderin deposition: it appears as a diffuse hyperechoic signal	Absent = 0; small = 1; moderate = 2; large = 3
6	Cartilage modifications	Hyperechogenicity = 1; irregular profile = 2; calcification = 3
Total score (max. 15 points)		

PDUS: power Doppler ultrasonography

Ultrasonographic score based on a method, proposed by Melchiorre et al. [12]

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