The value of HEAD-US system in detecting subclinical abnormalities in joints of patients in hemophilia

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The value of HEAD-US system in detecting subclinical abnormalities in joints of patients in hemophilia

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Abstract

Background: Prevention of hemarthrosis is the key factor in the adequate management of people with hemophilia (PWH). If hemarthrosis occurs, early diagnosis of joint damage is essential to make personalized treatments. This study is aimed at gaining an understanding of the ability of point-of-care ultrasound (US) using the `Hemophilia Early Arthropathy Detection with Ultrasound´ (HEAD-US) protocol to detect abnormalities in joints without history of hemarthrosis and clinically asymptomatic joints of PWH.

Research design and methods: The sample included 976 joints from 167 PWH (mean age 24.86 years). Data were collected from routine practice over a 3-year period and analyzed based on history of hemarthrosis and results of clinical (HJHS 2.1) and HEAD-US examinations.

Results: In our series, 14% of patients exhibited HEAD-US signs of incipient arthropathy in joints with no history of bleeding and with a HJHS 2.1 score of 0. The most severely involved joint was the right ankle. Synovitis, articular cartilage and subchondral bone damage scores in joints with subclinical findings were slower than in joints with previous hemarthroses or HJHS 2.1>1

Conclusions: Our study demonstrates that HEAD-US is better than hemarthrosis records and the HJHS 2.1 scale in detecting the early signs of joint damage in PWH.

Keywords: Hemophilia; Ultrasound (US); HEAD-US; Hemarthrosis; Clinical examination; HJHS 2.1
1. Introduction

Hemophilia A and B are X-linked recessive disorders caused by deficiency in coagulation factors VIII (FVIII) and IX (FIX) respectively. This deficiency results in repeated bleeding episodes that occur more frequently in the ankles, the knees and the elbows [1]. Intraarticular blood is harmful to the articular structures and causes severe complications, such as synovitis, chondrocyte apoptosis (chondral damage) and subchondral bone damage [1,2]. Although prophylactic therapy with factor concentrates has become a standard of care in the management of hemophilic patients, such treatment does not completely eliminate the risk of developing hemarthroses [3], and especially in patients with inhibitor [4,5]. In addition, prophylaxis is not yet available to many patients [6,7]. The amount of bleeding episodes experienced during childhood determines the severity of joint damage, which may be evaluated through imaging studies [8]. The number of intraarticular bleeding episodes (hemarthroses) is often recorded by the patient and/or the referring physician, but occult joint bleeds are not an uncommon occurrence [9]. Against this background, the notion of subclinical bleeding acquires greater significance. As long as there is a risk of a (symptomatic or subclinical) joint bleed, early detection becomes indispensable, particularly during childhood, in order to avoid long-term functional impairment [10-12].

In the absence of biomarkers or other laboratory tests that can diagnose and track musculoskeletal disorders in hemophilic patients [13], different methods are being investigated to increase the sensitivity of current joint testing procedures. Diagnostic imaging plays an essential role among such methods, as it provides objective information about the real joint status in these patients [14,15]. Magnetic resonance
imaging (MRI) and US are able to detect early soft-tissue and osteochondral changes in a joint before they become apparent on physical examination and on plain radiographs [15-17]. US is a sensitive imaging technique that provides instant functional and dynamic information on the status of a joint [18]. More specifically, US makes it possible to discover hemarthrosis, synovitis, chondral lesions and subchondral bone damage [11,19]. In addition, US has shown itself capable of detecting changes in joints which do not show radiographic or clinical abnormalities [20]. In the context of comprehensive patient care, the use of point-of-care US could enable detection of early articular changes in patients with hemophilia [19,21,22]. The HEAD-US (Hemophilia Early Arthropathy Detection with Ultrasound) system is a simple and rapid ultrasound-based diagnostic tool developed by Martinoli et al [22]. The system, addressed to physicians without specific training in imaging techniques, is capable of analyzing the six joints most typically affected by hemophilia (elbows, knees and ankles) in one single examination, providing information about synovial, cartilage and subchondral bone.

The purpose of this study is to determine the usefulness of the HEAD-US system in detecting subclinical abnormalities in joints of hemophilia patients with no history of hemarthrosis and clinically asymptomatic (Hemophilia Joint Health Score, HJHS 2.1 = 0).

2. Methods

This cross-sectional cohort study included patients with hemophilia treated at the Hematology Department of our hospital who presented for routine follow-up between January 2014 and December 2016. Patients’ age, type of hemophilia, severity of the
disease, inhibitor history, regimen of treatment (according to PedNet) [23] and type of physical activity were all recorded. We defined primary prophylaxis as the regular continuous treatment started after the first joint bleed and before the age of 2 years; secondary prophylaxis was defined as the regular continuous (long-term) treatment started after two or more joint bleeds or at an age >2 years; tertiary prophylaxis was considered as the regular treatment implanted after the diagnosis of joint damage; treatment was finally considered on demand when the deficient factor was administered in the episodes of bleeding. Exclusion criteria were other coagulopathies, patients with acute or subacute conditions, patients subjected to surgery or radiosynovectomy in more than three joints and patients with major disability as a result of supervening neurologic lesions (spinal cord injury, brain intracerebral hemorrhage or hereditary spastic paraparesis). In some instances, a patient was included in the study, but one or more of his joints were excluded if they underwent a bleeding episode in the past 6 weeks or had been previously treated with radiosynovectomy during the previous year [24].

As part of the evaluation process, the clinical record of the patient was examined to find out how many hemarthroses each of his joints had suffered over lifetime. Patients and/or family members were subsequently asked to confirm findings. In that same appointment, both physical, using HJHS 2.1 (Hemophilia Joint Health Score 2.1) and US examination, using HEAD-US were performed by the same physician specialized in physical medicine and rehabilitation with extensive experience in the management of patients with hemophilia. All patients (or their legal guardians) gave their consent to the examination.
In each patient, the physical examination involved the elbows, knees and ankles, in accordance with the HJHS 2.1 protocol [25-27]. Its use in this study is related to the fact that many of the subjects in this study were of pediatric age [26,27]. A score was calculated for each item of the HJHS 2.1, i.e. inflammation (0-3), duration of inflammation (0-1), atrophy (0-2), crepitus (0-2), range of motion (flexion 0-3, extension 0-3), muscle strength (0-4) and pain (0-2), which added up to a total score between 0 and 20 per joint. A separate score (0-4) was assigned to the gait category (0-4). Higher HJHS 2.1 scores indicate poorer joint function. US examination was carried out following physical examination at the same appointment. The same physician performed all US examination according to the HEAD-US protocol. She received formal HEAD-US training and had extensive experience in the use of the technique. Elbows, knees and ankles were assessed and scored for synovitis, chondral damage and subchondral bone damage. The scoring criteria have been clearly defined by the authors of the system and are based on pattern recognition [22]. For synovitis the score is 0: no or minimum synovitis, 1: mild or moderate synovitis; 2: severe synovitis; for cartilage the score is 0: normal cartilage; 1: partial/complete loss of cartilage thickness affecting <25% of the joint surface; 2: partial/complete loss of cartilage thickness affecting <50% of the joint surface; 3: partial/complete loss of cartilage thickness affecting >50% of the joint surface; 4: partial/complete loss of cartilage thickness all over the joint surface; for subchondral bone the score is 0: normal subchondral bone; 1: Mild irregularities in the subchondral bone with or without incipient periarticular osteophytes; 2: unstructured subchondral bone with or without erosions and prominent periarticular osteophytes. Scores for each joint could therefore range between 0 and 8, with higher scores indicating more severe abnormalities. One single US machine (Esaote, tipo MyLab25 Gold, Genoa, Italy) equipped with a 5-13 MHz linear probe was used.
Statistical tests analyzed the epidemiological data of the patient population, including bleeding history, joint status (assessed by means of the HJHS 2.1) and results of the US study (using the HEAD-US system). Mean values were calculated for each specific joint (elbows, knees, ankles). The analysis made a specific focus on patients who had joints with no history of hemarthrosis and no findings on the physical exam (HJHS 2.1=0) but which had shown signs of joint damage as manifested by synovitis, chondral damage or subchondral bone damage on HEAD-US. The purpose was to understand the extent at which the HEAD-US system is capable of disclosing hemophilia-derived derangement of joints when no clinical suspicion of damage exists. It was investigated whether these findings were more frequent in any particular joint. A comparison was also made between scores for synovitis, articular cartilage and subchondral bone damage of joints with unexpected articular damage with the scores of all other joints evaluated with the HEAD-US method. Finally, an attempt was made to determine whether any of the patient-related characteristics (age, type of hemophilia, severity of the disease, inhibitor history, regimen of hematologic treatment and type of physical activity) could predict subclinical joint damage on US. For this purpose, patients exhibiting unexpected findings on US were compared with those who had no hemarthrosis or any abnormal findings on HJHS 2.1 or HEAD-US. Qualitative data were expressed in the form of absolute frequencies and percentages whereas quantitative data were expressed as means and standard deviation and range (maximum-minimum). Comparison between quantitative data was performed using the Chi-Squared Test or Fisher’s Exact Test. Comparisons between two means were made using Student’s t Test or the Mann Whitney U Test, depending on data distribution. Hemarthrosis and the scores obtained on HJHS 2.1 and HEAD-US were categorized into two groups (0 and non 0) for each specific joint and for
all the joints studied as a whole. All the statistical analyses were conducted bilaterally and values were considered significant if $p<0.05$. The software used for the analysis was the SAS 9.3 package (SAS Institute, Cary, NC, USA).

3. Results

A total of 167 patients with hemophilia were enrolled in the study. Mean age was 24.86 years (range 4-69). There were 14 patients who were older than 50 years (if we can consider that age as the beginning of osteoarthritis). Chondral and subchondral damage of hemophilic arthropathy and degenerative osteoarthritis cannot be differentiated by means of US; that’s why this fact could not be controlled in our study.

One-hundred and forty-five (86.82%) patients had hemophilia A and 22 (13.28%) had hemophilia B. There were no patients with hemophilia C (FXI deficiency). Of the total number of patients, 111 (66.4%) were affected by severe hemophilia, 24 (14.3%) by moderate hemophilia and 32 (19.2%) had the mild form of the disease. The number of patients with inhibitors was 26 (15.5%); the others didn't develop inhibitors. The regimen of hematologic treatment administered to patients at the time of enrolment was as follows: 51 patients (30.5%) received primary prophylaxis; 45 patients (26.9%) received secondary prophylaxis, 10 patients (6%) received tertiary prophylaxis; and 61 patients (36.5%) were being treated on demand. General patient data are shown in Table 1.

Overall, the study gathered data from 976 joints, which can be broken down as follows: 328 elbows (164 right and 164 left), 322 knees (161 right and 161 left), and 326 ankles (163 right and 163 left). Twenty-six joints had to be excluded and namely: 7 underwent
one or more intraarticular bleeding episodes in the preceding 6 weeks and 19 have been treated with radiosynovectomy in the previous year.

As far as the total number of haemarthroses was concerned, the mean number of haemarthroses suffered by patients (considering all patients) was 17.49 episodes (range 0-155). The mean of global hemarthrosis throughout life in our patients, according to the type of treatment, was distributed as follows: 2.18 in patients in primary prophylaxis; 3.8 in patients with secondary prophylaxis; 48.9 in patients with tertiary prophylaxis; and 34.2 in patients with on-demand treatment. It has to be noted that 55 patients (32.93%) had no recollection of having had a joint bleed in any of the 6 joints (mean age 19 years). The number of joints with hemarthrosis is shown in Figure 1. An analysis of the different joints revealed that the mean number of haemarthroses suffered was as follows: 2.17 (range 0-30) in the elbows; 2.77 (range 0-30) in the knees; and 3.78 (range 0-30) in the ankles.

As regard the joint status measured with the HJHS 2.1, the mean score for each patient was 8.44 (range 0-64). It must be noted that 92 patients (55.08%) obtained an overall score of 0 (their mean age was 17 years). We found 25 patients who having a HJHS 2.1 = 0, showed joint changes in the US assessment (measured with HEAD-US). The number of joints with the HJHS 2.1 ≥ 1 is shown in Figure 1. Mean HJHS 2.1 scores for each specific joint were as follows: 1.12 (range 0-15) for elbows, 1.2 (range 0-17) for knees and 1.89 (range 0-15) for ankles. Concerning gait abnormalities, 115 patients had a score of 0; 12 scored 1; 28 scored 2; 12 scored 3 and 0 scored 4 points.
Regarding the HEAD-US evaluation, we could not calculate a cumulative score because it is not a patient score. However, it must be emphasized that 72 patients (43.11%) obtained an US score of 0 points in all of their joints (mean age was 16.56 years). We found 4 patients were found that having HEAD-US = 0, showed changes in the physical examination (measured with HJHS 2.1). The number of joints with the HEAD-US ≥ 1 is shown in Figure 1. Mean HEAD-US scores for each specific joint were as follows: 0.86 (range 0-8) for elbows, 0.78 (range 0-8) for knees; and 1.41 (range 0-7) for ankles. Synovitis was observed in 13.83% of joints (135 of 976; 123 scored 1 and 12 scored 2 points); chondral damage was observed in 24.6% of joints (240 of 976: 65 scored 1, 59 scored 2, 45 scored 3 and 71 scored 4 points); whereas subchondral bone damage was found in 16.62% of joints (172 of 976: 96 scored 1 and 79 scored 2 points). These data are summarized in Figure 2.

The mean overall HEAD-US score for joints showing US signs of articular damage (260 joints, score ≥1) was 3.83 points (range 1-8). Mean scores for each specific joint were as follows: 1.2 points (range 1-2) for synovitis, 2.64 points (range 1-4) for chondral damage and 1.43 points (range 1-2) for subchondral bone damage.

To test the hypothesis of this study, we decided to select patients that showed some kind of articular involvement on the HEAD-US exam in joints with no bleeding episodes and HJHS 2.1=0. Of the total number of patients studied, 13.77% (23 out of 167) showed at least one unexpected US abnormality in one of their joints. The mean age of these 23 patients was 19.33 years (range 6-53 years). Figure 3 shows a comparison between these 23 patients and the rest of the sample. Of these patients, 18 showed US articular damage in 1 joint; 3 patients showed articular damage in 2 joints; 1 showed articular
damage in 4 joints; and 1 showed articular damage in 5 joints. The total number of joints exhibiting unexpected joint damage on HEAD-US exam was 33. These were distributed as follows: 4 right elbows, 7 left elbows, 3 right knees, 4 left knees, 9 right ankles and 6 left ankles. The number of patients with HEAD-US = 0 was 72; their mean age was 16.5 years (range 4-65). The mean number of joint bleeds in these patients was 1.2 (0-8). Of these, 62 had hemophilia A and 10 hemophilia B; 37 had severe hemophilia (32 in primary prophylaxis and 5 in secondary prophylaxis); 11 moderate hemophilia (7 in secondary prophylaxis and 4 on demand); and 24 mild hemophilia (all under on demand treatment). Some examples of the subclinical findings found in the different joints can be seen in Figure 4. Each patient’s characteristics and joint details are shown in Table 2. Taking into account that HJHS 2.1 scores <3 would be indicative of normal function [28], we found 6 joints more (in 5 patients) with no history of hemarthrosis and HJHS 2.1 score <3, who exhibited joint damage as detected by HEAD-US.

Statistical analysis of the 33 joints significantly showed that the right ankle exhibited more subclinical abnormalities than the other joints (p=0.008); with no statistically significant differences found between the other joints. No difference was observed when comparing the individual joints in terms of synovitis, chondral and subchondral bone damage. Figure 5 shows the scores of abnormal findings detected for each of the criteria evaluated by the HEAD-US system based on the joint type (elbows, knees and ankles). The most affected joint appears to be the ankle with the highest scores corresponding to chondral damage. The mean joint score obtained with the HEAD-US method in the series of patients with unexpected disease was 1.57 (range 0-8). More specifically, mean scores were 0.55 (range 0-2) for synovitis, 1.03 (range 0-4) for chondral damage and 0
for subchondral bone damage (range 0-2). These values were significantly lower (p<0.05) than in joints (elbows, knees and ankles) where, in addition to the HEAD-US score, previous hemarthroses and/or the HJHS 2.1 score were also considered. This means that HEAD-US made it possible to identify early signs of joint disease.

Regarding the question on whether any of the patients’ general characteristics (age, type of hemophilia, severity of the disease, inhibitor history, regimen of hematologic treatment and type of physical activity) could anticipate the appearance of unexpected US joint damage, none of those characteristics showed any statistical significance. This would suggest that none of them could help predict the existence of US joint damage in the absence of a history of hemarthrosis or an abnormal HJHS 2.1.

4. Discussion

The presence of damage in asymptomatic joints of patients with hemophilia has been previously reported in MRI studies. These studies included children with and without prophylaxis, in the absence of previous hemarthroses, and found between 38 and 69% joint damage in MRI of the ankles [29-31].

US is a well-established technique to diagnose synovitis, chondral damage and subchondral bone damage since the 1990’s [32]. It has shown itself to be a highly reliable technique to evaluate soft-tissue and osteochondral changes [33]. Fair evidence (grade B) exists nowadays to warrant the use of US as an accurate technique for early diagnosis of hemophilic arthropathy and, particularly, for detection of soft-tissue abnormalities [34]. US scores tend to correlate with clinical findings, and there is usually a connection between US scores and patients’ overall functional status [34]. In
addition, it has been reported that US could be a valid and reliable tool in the hands of non-radiologist physicians with specific training in US, to detect the presence of hemophilic arthropathy at the point of care [17,35].

Our Department started using the HEAD-US system to screen patients with hemophilia in 2013. It has proven a useful tool to obtain information about current joint status and to readjust therapeutic strategies in our patients. So far the point-of-care HEAD-US protocol has allowed us to evaluate the joints of our patient population. In fact, as far as we know, it is the study of these characteristics that includes the largest number of patients and joints. Patients of different ages (children and adults) were included, with different types of hemophilia and different treatment modalities. In our study there is a higher proportion of patients with severe hemophilia, since patients use to attending our hemophilia center more often. The treatment regimen used by the patients was prescribed by the hematologists involved in this study. The hematological treatment was administered in our center or the patients picked it up in it. In this study, data on adherence of patients were not collected. Patients with other clinical conditions, for example, neurological, were excluded from the study. The number of patients (sixty-one) treated “on-demand” is apparently high according to the WFH Guidelines. Our explanation is the following: 30 patients had mild hemophilia, 10 had moderate hemophilia, and 21 had severe hemophilia. In general, they were patients that had been treated “on demand” in the years before the implantation of prophylaxis and still continued with such a treatment regime, either by medical decision or by own decision.

As shown in the present paper, approximately 14% of our patients with hemophilia exhibited at least one joint with subclinical abnormality on US, regardless of age, type
of hemophilia, severity of disease and treatment administered. In this regard, we thought it was interesting to find out what percentage of patients had benefited from the information provided by US as existing reports only focus on the number of joints. Of the 23 patients (14%) who presented subclinical findings, the percentage of them with hemophilia A and B, or severe, moderate or mild hemophilia were similar to those in the general study population. Of patients with severe hemophilia, younger patients were on prophylaxis; only two patients aged 23 and 42 were on demand by their own decision. However, most patients with moderate or mild hemophilia were on demand. On the other hand, most patients performed some type of physical activity, similar to those in the general population, so this did not seem to be determinant for the development of subclinical joint damage. Notably, five patients were found in which HEAD-US found subclinical joint damage in more than one joint. The most affected joint was the ankle; this agrees with what has been published by other authors [37].

In current literature there are several studies published to date in which US assessment is used, to know the joint status of patients with hemophilia. These studies include different types of patients and different US protocols [16,18,20,25,37-39]. The characteristics of these studies are summarized in Table 3. The above mentioned publications provide heterogeneous data with respect to joint damage as identified by US. This is probably due to differences in patient age, type of treatment and/or in the interpretation of the results [41]. The results of this study are in agreement with those of other authors [20,37-39], on the fact that patients on prophylaxis may exhibit US signs of incipient arthropathy without any previous clinical suspicion, and that the ankle is the most commonly affected joint [37].
The fact that joints with subclinical findings after US assessment showed significantly low HEAD-US scores (in terms of synovitis and chondral damage) demonstrates its usefulness for early detection of joint damage. This early diagnosis in our hemophilia patients leads to more objective and individualized therapeutic decisions. From a multidisciplinary point of view, US information allows us to reconsider and modify hematological, rehabilitation and orthopedic treatments, and also to monitor the joint status. But this, like other US utilities, exceeds the objectives of this paper.

The findings in our study also made us consider the role played by micro-bleeds (subclinical bleeding) in joint damage [16,42]. It is widely known that maintenance of FVIII / FIX levels in patients on prophylaxis and mild or moderate hemophilia does not prevent all joint bleeds [43,44]. As newer modes of hematologic treatment become available and use of prophylaxis becomes more widespread, it is increasingly important to be able to resort to more sensitive diagnostic methods that can detect minor changes in apparently “healthy” joints. The success of future prevention and therapeutic strategies will depend on early detection of joint damage in patients without hemarthrosis and with absence of abnormal findings on physical examination and plain films. This is where US may play a decisive role as it allows detection of early changes in joints, especially nowadays in the absence of biomarkers that can diagnose and track musculoskeletal disorders in hemophilia patients [16,29].

Our study is nonetheless constrained with a few limitations, among them the fact that the results obtained depend on the validity of the diagnostic tools used and the quality of the measurements made. Moreover, the entire study was carried out by one person with no reference comparison for the analysis. The incidence and the risks of subclinical
intra-articular bleeds leading to changes in joint status have not been well established. The absence of controls for elderly patients who would have developed osteoarthritic changes in the joints due to their age could be another limitation. Also, clinical function was evaluated by means of the HJHS 2.1, which has demonstrated higher sensitivity than the Gilbert scale but has not been shown to be valid for older adults [27]. The reproducibility of HEAD-US measurements when used by non-radiologists is currently under analysis [17]. Rigorous validation studies are needed that compare the scores provided by HEAD-US with those obtained with MRI in order to establish the sensitivity threshold of this US system [45].

5. Conclusions

In conclusion, subclinical bleeding/micro-hemorrhage in the joints of patients with hemophilia is a common occurrence that may result in hemophilic arthropathy despite new modalities of hematological treatment. Analyzing joint changes with objective tools that are able to detect early damage is nowadays an essential component of a comprehensive care delivery model. The HEAD-US protocol is a simple US method that allows physicians to analyze the joint status of patients with hemophilia at the point of care, detecting potential damage to the synovium (synovitis), the cartilage or the subchondral bone. The HEAD-US system appears to be a useful tool to detect incipient signs of disease activity and joint damage in cases with no history of hemarthrosis or where physical examination (HJHS 2.1) is negative. Nearly 14% of patients in our series exhibited US findings compatible with incipient arthropathy in apparently healthy joints. Right ankles were the most frequently affected joints. No connection was observed between the degree of joint damage observed and age, type of hemophilia,
severity of the disease, inhibitor history, regimen of hematologic treatment and type of physical activity.

6. Key Issues

- Early diagnosis of articular damage is paramount in hemophilia patients.
- The study was performed in a university hospital. HEAD-US protocol was used.
- HEAD-US was superior to hemarthrosis records in detecting the early signs of joint damage.
- HEAD-US was better than the HJHS 2.1 scale in detecting the early signs of joint damage.

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Declaration of interest

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest


** This author recently reported that unimaginable biotechnological progress has augmented life expectancy for hemophilia patients through a growing list of very secure and efficacious recombinant factor VIII and plasma-derived factor VIII concentrates for musculoskeletal bleeding treatment and prophylaxis. Extensive use of primary strategies of bleeding prophylaxis has doubtless minimized musculoskeletal morbidity, which has long been the symbol of hemophilia.


** These authors have reported a general outlook of the FVIII/FIX treatment practice and results for patients with hemophilia A and hemophilia B across
Europe. They observed that treatment practice vary considerably between centers and countries and patients treated on-demand and prophylactically both had bleeds, stressing the need for additional optimization of treatment.


**These authors evaluated the relationship between biomarkers and compatible additive magnetic resonance imaging (MRI) scores in patients with severe hemophilia A. They found no clear correlations with any of the potential biomarkers for hemophilic arthropathy in the overall population. CS846 levels were significantly correlated with MRI scores in patients treated on demand.


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**These authors reported in 1992 that ultrasonography (US) is a good diagnostic tool in the initial stages of hemophilia. In fact they observed that US allowed differentiation between hemarthrosis and synovitis. It also revealed early cartilaginous involvement.


Figure 1. Joints that suffered hemarthrosis, scored ≥ 1 on HJHS 2.1 (Hemophilia Health Joint Score version 2.1) and exhibited abnormal findings on HEAD-US (Hemophilia Early Arthropathy Detection with UltraSound).

Figure 2. Scores obtained by the joints on the different parameters of the HEAD-US exam (Hemophilia Early Arthropathy Detection with UltraSound). The pies represent the number of joints with synovium (S0: no or minimum synovitis, S1: mild or moderate synovitis; S2: severe synovitis); cartilage (C0: normal cartilage; C1: partial/complete loss of cartilage thickness affecting <25% of the joint surface; C2: partial/complete loss of cartilage thickness affecting <50% of the joint surface; C3: partial/complete loss of cartilage thickness affecting >50% of the joint surface; C4: partial/complete loss of cartilage thickness all over the joint surface); and subchondral bone (B0: normal subchondral bone; B1: Mild irregularities in the subcondral bone with or without incipient periarticular osteophytes; B2: unstructured subcondral bone with or without erosions and prominent periarticular osteophytes).
Figure 3. Patients with joint damage as measured by HEAD-US when hemarthrosis and HJHS 2.1 was 0, patients with joint damage as measured by HEAD-US when hemarthrosis and HJHS 2.1 was $\geq$ 1, and patients without joint damage as measured by HEAD-US.

Figure 4. Examples of subclinical ultrasound findings. A: Grade 1 synovitis in the radial recess of the elbow (arrow). B: Grade 1 chondral damage in the femoral trochlea of the knee (arrow). C: Grade 1 chondral damage in the talar dome of the ankle (arrow).
Figure 5. Scores obtained on the different items of the HEAD-US scale (Hemophilia Early Arthropathy Detection with UltraSound) by the 33 joints where there were no previous hemarthrosis records and physical findings in HJHS 2.1. S1: mild or moderate synovitis; C1: partial/complete loss of cartilage thickness affecting <25% of the joint surface; C2: partial/complete loss of cartilage thickness affecting <50% of the joint surface; C3: partial/complete loss of cartilage thickness affecting >50% of the joint surface. Note that no grade 2 synovitis, grade 4 chondral damage or subchondral bone damage were detected.
### Table 1. General patient data

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<tr>
<td>B</td>
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<td>Severity of hemophilia</td>
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<tr>
<td>History of hemarthrosis</td>
<td>112 (67%)</td>
</tr>
<tr>
<td>HJHS 2.1 score ≥ 1</td>
<td>75 (44.9%)</td>
</tr>
<tr>
<td>HEAD-US score ≥ 1</td>
<td>95 (56.9%)</td>
</tr>
</tbody>
</table>

HJHS 2.1= Hemophilia Joint Health Score version 2.1; HEAD-US= Hemophilia Early Arthropathy Detection with Ultrasound; PP=primary prophylaxis; SP=secondary prophylaxis; TP=tertiary prophylaxis; OD=on demand treatment
Table 2. Data corresponding to patients where the hemarthrosis record and HJHS 2.1 were = 0 but who nevertheless exhibited subclinical joint damage on US.

<table>
<thead>
<tr>
<th>Age</th>
<th>Type of hemophilia</th>
<th>Severity</th>
<th>Inhibitor</th>
<th>Treatment</th>
<th>Type of physical activity</th>
<th>HEAD-US Elbows</th>
<th>HEAD-US Knees</th>
<th>HEAD-US Ankles</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>PP</td>
<td>Swimming</td>
<td>S1C0B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>Severe</td>
<td>Yes</td>
<td>PP</td>
<td>Swimming</td>
<td>S1C0B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>No</td>
<td>S1C0B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>PP</td>
<td>Basketball</td>
<td>S1C0B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>A</td>
<td>Severe</td>
<td>Yes</td>
<td>PP</td>
<td>No</td>
<td>S1C0B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>No</td>
<td>S0C1B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>No</td>
<td>S0C1B0 (L)</td>
<td></td>
<td>S1C0B0 (L)</td>
</tr>
<tr>
<td>18</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>Soccer</td>
<td>S1C0B0 (L)</td>
<td></td>
<td>S1C0B0 (L)</td>
</tr>
<tr>
<td>20</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>PP</td>
<td>Swimming</td>
<td>S0C1B0 (R)</td>
<td>S0C1B0 (R)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>PP</td>
<td>Soccer</td>
<td>S0C1B0 (R)</td>
<td>S0C1B0 (R)</td>
<td>S0C2B0 (L)</td>
</tr>
<tr>
<td>22</td>
<td>A</td>
<td>Mild</td>
<td>No</td>
<td>OD</td>
<td>No</td>
<td>S1C1B0 (R)</td>
<td>S0C1B0 (R)</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>A</td>
<td>Severe</td>
<td>Yes</td>
<td>OD</td>
<td>Swimming</td>
<td>S0C1B0 (R)</td>
<td>S1C1B0 (R)</td>
<td>S1C2B0 (L)</td>
</tr>
<tr>
<td>28</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>No</td>
<td>S1C0B0 (R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>Walking</td>
<td>S0C1B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>B</td>
<td>Moderate</td>
<td>No</td>
<td>TP</td>
<td>Cycling</td>
<td>S1C1B0 (R)</td>
<td>S0C1B0 (L)</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>No</td>
<td>S0C1B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>A</td>
<td>Mild</td>
<td>No</td>
<td>OD</td>
<td>No</td>
<td>S1C1B0 (R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>Cycling</td>
<td>S1C0B0 (R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>A</td>
<td>Severe</td>
<td>Yes</td>
<td>OD</td>
<td>Walking</td>
<td>S1C2B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>A</td>
<td>Severe</td>
<td>No</td>
<td>SP</td>
<td>Table tennis</td>
<td>S1C1B0 (R)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>B</td>
<td>Moderate</td>
<td>No</td>
<td>OD</td>
<td>Hunting</td>
<td>S1C1B0 (L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>A</td>
<td>Moderate</td>
<td>No</td>
<td>TP</td>
<td>Walking</td>
<td>S0C1B0 (L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HEAD-US = Hemophilia Early Arthropathy Detection with UltraSound; PP=primary prophylaxis; SP=secondary prophylaxis; TP=tertiary prophylaxis; OD=on demand treatment; S=synovitis; C=chondral damage; B=subchondral bone damage; R=right; L=left
Table 3. Previously reported studies on the role of US to know the articular status of hemophilia patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients number</th>
<th>Age (median)</th>
<th>Treatment regimen</th>
<th>Number of joints</th>
<th>History of hemarthroses</th>
<th>Clinical signs</th>
<th>US protocol</th>
<th>Articular abnormalities in US when no hemarthroses or clinical findings</th>
<th>Articular abnormalities in US</th>
<th>Articular abnormalities in US when no hemarthroses or clinical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altisent et al [37]</td>
<td>25</td>
<td>8.3 (median)</td>
<td>Prophylaxis</td>
<td>124</td>
<td>Annual rate 0.2 (median)</td>
<td>HJHS 1.8 (mean)</td>
<td>HEAD-US [22]</td>
<td>21% 19.6% when HJHS 2.1 = 0 (n=107)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foppen et al [20]</td>
<td>32</td>
<td>11.5 (median)</td>
<td>Prophylaxis</td>
<td>64</td>
<td>Lifetime 3 (median)</td>
<td>HJHS 0 (mean)</td>
<td>HEAD-US [22]</td>
<td>7.9% 0% when bleeding = 0 1.8% when HJHS 2.1 = 0 (n=56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timmer et al [25]</td>
<td>15</td>
<td>53 (median)</td>
<td>Different regimens</td>
<td>76</td>
<td>-</td>
<td>HJHS 0 (median)</td>
<td>HEAD-US [22]</td>
<td>36% 2% when HJHS 2.1 = 0 (n=46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Minno et al [38]</td>
<td>20</td>
<td>23.9 (mean)</td>
<td>Different regimens</td>
<td>40</td>
<td>Lifetime 0 (mean)</td>
<td>Asymptomatic joints</td>
<td>Zukotynski protocol [40]</td>
<td>55% synovitis, 80% chondral damage when no hemarthroses or clinical findings (n=40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poonnoose et al [16]</td>
<td>51</td>
<td>15 (median)</td>
<td>-</td>
<td>55</td>
<td>At least 1</td>
<td>HJHS 0-16 (range)</td>
<td>Doria protocol [33]</td>
<td>100% 100% synovitis and 75% osteochondral damage when HJHS 2.1 = 0 (n=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sierra et al [39]</td>
<td>30</td>
<td>4.82 (range)</td>
<td>Different regimens</td>
<td>120</td>
<td>-</td>
<td>Different signs in Gilbert score</td>
<td>Zukotynski protocol [40]</td>
<td>29% of the knees and 51% of the ankle. Up to 76.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidder et al [18]</td>
<td>34</td>
<td>39.3 (mean)</td>
<td>-</td>
<td>65</td>
<td>-</td>
<td>Acute or chronic articular pain</td>
<td>Full joint US assessment</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*HJHS 2.1 = Hemophilia Joint Health Score version 2.1; HEAD-US = Hemophilia Early Arthropathy Detection with Ultrasound; US = Ultrasound*