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Utility of Knee Ultrasound in Management of Patients with Hemophilia in a Limited Resource Setting

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A B S T R A C T

Hemophilia is among the diseases that have not received adequate attention from the critical health decision-makers, despite the increasing number of patients diagnosed with the disease locally and across the world. Among the patients with hemophilia, bleeding into the joints, principally the knee joint, is common. A timely diagnosis of hemarthrosis and its complications is critical in optimal care for patients with hemophilia. MRI is the gold standard for the joint assessment in hemophilia, but access to MRI is limited by cost and scarcity. Ultrasonography is a valuable alternative, but the use of musculoskeletal sonography is not widespread locally. This study was designed to assess the utility of ultrasound in the assessment of the knee joint of patients with hemophilia who presented with knee pain or knee swelling at the hemophilia clinic in a hospital in Nairobi. A cross-sectional descriptive study was conducted over a period of four months from February 2021 to April 2021 at the National Hemophilia Clinic in a hospital Nairobi. Both clinical assessment of the knee and sonographic assessment of the knees was done, and results recorded in the data collection form. The mean age of the participants was 18.1 years (SD ± 11.8) with an age range between 3 and 60 years. The most common age group was 10-19 years that comprised 49% of the study population. Specific knee pathologies were identified by ultrasound in 88% of the participants, and there were both soft tissues and bony changes. Synovial hypertrophy was noted in 66% of the participants, hemarthrosis was seen in 51%, bone erosions 49%, articular cartilage thinning was seen in 39%, and subchondral cysts in 34%. The use of ultrasound for scanning patients presenting in hemophilia clinics with joint pain or swelling provides important imaging information about the status of the joints that can guide in management.

Introduction

Hemophilia is a coagulopathy characterized by increased bleeding tendency arising from deficiency of antihemophilic clotting factor VIII (Hemophilia A) or deficiency of plasma thromboplastin component clotting factor IX (Hemophilia B also called Christmas Disease). It is X-linked recessive disorder (Srivastava *et al.,* 2013).

Disease severity is classified based on the level of deficiency of the clotting factors in the individual patient. It can be mild, moderate, or severe. Bleeding can be in several regions of the body but common sites are joints, subcutaneous tissues, Intracranial, intra-abdominal, and retroperitoneal hemorrhage (Srivastava *et al.,* 2013).

Trauma is often the precipitating event, but spontaneous bleeds are also common especially in the joints, depending on disease severity. Post surgical bleeding is common after surgical procedures (Srivastava *et al.,* 2013).

Globally, hemophilia A's prevalence has been estimated at 1 in 10,000, and hemophilia B is estimated at 0.2 in 100,000 (Kerr, 2003). The global prevalence statistic shows that the disease puts considerable morbidity on the global populations.

Lorio *et al.,* (2019) study in several high-income countries across Europe found prevalence of hemophilia to be higher than previously estimated. In the report by Lorio *et al.,* (2019), the average life expectancy of Hemophilia males in Europe has historically been lower compared to the general population (as low as less than 30 years during 1970s). Currently, improved life expectancy has been observed due to improved health care for PLWH Lorio *et al.,* (2019).

Studies done as early as 1966 have consistently concluded that more cases will be identified with more awareness and testing (Forbes *et al.,* 1966). Low awareness and reporting rates limit the accurate determination of the prevalence. This is coupled with unfavorable attitudes by decision-makers who regard hemophilia management as a resource-intensive venture. Indeed, according to Ghosh *et al.,* (2004), high-cost and advanced technology requirements for successful therapy usually make hemophilia detection and management a low priority agenda for governments of the developing countries (Ghosh *et al.,* 2004). The recent Annual global survey conducted in 2017 by the "*world federation of hemophilia*" projected the number of patients with bleeding disorders worldwide as 315,423. The majority have hemophilia A, which predisposes them to frequent bleeding episodes, mostly without any defined precipitating event. However, the global survey points out that the number represents just a few already identified by the health systems, especially in the African continent.

The report by the World Hemophilia Federation further shows that Kenya has about 618 persons living with hemophilia that have been mapped and recorded (Brooker and Hemophilia, 2018). The number has been steadily rising, as shown by the previous reports by the same federation, likely due to increased awareness and incidence reporting by the affected persons.

However, in Kenya, efforts aimed at increasing the detection and follow up of hemophilia patients have had good results, with clinics established in the major cities within Kenya to exclusively serve the medical needs of people living with haemophilia (PLWH). The aim is to take services closest possible to the patients and initiate follow-up programs that monitor and mitigate this disease's effects.

According to Srivastava *et al.,* (2013), the overall strategy for hemophilia management is replacing the missing clotting factor to prevent or treat the bleeding. Management is either done prophylactically (if prevention is the target) or prescribed for each bleeding episode in episodic care.

The recommendation is that comprehensive care should be prompt and include management of joint damage, muscle damage, and psychosocial support (Srivastava *et al.,* 2013). The clotting factors have become available locally in Kenya, despite their high cost. The health authorities make every effort to rationalize the prescription and administration of valuable hemophilia management resources.

Reliance has been on Magnetic Resonance Imaging (MRI) scanning for diagnosis of complications of hemophilia. MRI is expensive and not readily available in most regions in Kenya. Studies have identified ultrasound as an excellent modality for identifying hemophilia complications (Ceponis *et al.,* 2013). There has not been widespread use of ultrasound for musculoskeletal imaging in Kenya (Stevens *et al.,* 2016).

Ultrasound is readily available in most Kenyan regions. Ultrasound is less costly and can be used at the bedside. It does not have ionizing radiation. A study by Foppen *et al.,* (2018) found that if operated by an experienced operator using a standardized protocol, ultrasound is very reliable in assessing soft-tissue abnormalities of knee and ankle (Foppen *et al.,* 2018).

This study will evaluate ultrasound's utility in assessing the knees of the hemophilia patients who present with knee pain or knee swelling at the Hemophilia clinic in Kenyatta National Hospital. Results of this study, it is projected, will provide a baseline data on the spectrum of ultrasound findings in the knee joints in hemophilia patients and also help open the large potential of ultrasound as a powerful modality in evaluation, intervention and follow up of musculoskeletal conditions, (Kerr, 2003) and to increase utilization of ultrasound in musculoskeletal imaging in Kenya and the region.

A study in Kenyatta National Hospital (KNH) by Muthua and Julia (2019) among 140 patients with bleeding tendencies seen in KNH between 2010 and 2017 found hemophilia to be the commonest disorder among the study population at 82%.

The result from the study by Muthua and Julia (2019) approximately replicated the results seen much earlier by Kitonyi (1981), who found hemophilia in 63 % of the 105 patients with bleeding disorders seen in KNH. These Kenyan data show that hemophilia is not uncommon in Kenya and that with improving awareness, diagnostic and therapeutic facilities, more patients with the disease will be identified and assisted (Kitonyi, 1981).

The high cost of replacement therapy is a constant challenge to the patients and health systems. The challenge of accessing care is worsened by the statistic that shows that most PLWH live in developing countries where resources for health are limited (Ghosh *et al.,* 2004).

Foppen *et al.,* (2017) list bleeding as the most critical outcome measure used in evaluating the effectiveness of factor concentrate replacement therapy in hemophilia. Since bleeding is usually patient-reported, the severity of a bleeding episode is difficult to determine objectively.

Furthermore, hemarthrosis symptoms largely overlap with the symptoms of preexisting arthropathy and other non-bleed complaints of the joint that do not necessitate treatment with expensive clotting factors. Proper diagnosis, therefore, is key in successful follow-up and management. Timmer *et al.,* (2015) assert that timely accurate diagnosis is crucial for rational treatment and is a key strategy in reducing indiscriminate utilization of the concentrates (Foppen *et al.,* 2017).

Studies have identified discrepancies between objective Musculoskeletal Ultrasonography (MSK-US) and self-reported or physician identified joint pain etiology. MSK-US has been shown to be more accurate in determining the cause of joint pain compared to physician diagnosis.

Hemophilia is a lifelong condition and requires constant monitoring. The patient's bleeding status should be periodically assessed (Timmer *et al.,* 2015). Early signs of hemarthrosis (HA) are known to be detectable only by imaging if the patient is asymptomatic and has had just one or a few previous episodes of joint bleeding. The use of ultrasound is justifiable in such settings, especially due to its lower cost and availability.

Different imaging modalities such as X-rays, magnetic resonance imaging (MRI), and ultrasound can assess the severity and effects of previous joint bleeds in hemophilia; therefore, knowing the particular imaging modalities' potential, utility and drawback is important in choosing the optimal tool for valuation of HA. The optimal modality chosen to evaluate HA depends on the patient's history, the clinical question to be answered, the modality's availability, and its affordability. The availability of MSK imaging experts is also crucial (De Moerloose *et al.,* 2012).

Hemophilia-related joint pathological changes that may be identified by appropriate imaging include synovial hypertrophy, joint effusion, hemosiderin deposits, cartilage degradation, and bone defects. Many periarticular structures, including tendons, muscles, and ligaments, can also be assessed by the use of appropriate imaging modality (Fischer *et al.,* 2002).

While plain radiographs can assess some chronic joint changes, the acute changes involve the soft tissues, making radiography unsuitable. MRI is the gold standard for the evaluation of soft tissues of the joints. Need for sedation of young children during scanning, limited access, and high-cost limit utilization of MRI. Ultrasound is gaining popularity as a modality of choice in the clinical setting due to its high sensitivity and specificity

in assessing soft tissue changes in HA. Ultrasound is readily available and is affordable. It is convenient since it can be used in many settings with little preparation (Hawana *et al.,* 2015).

Doria *et al.,* (2015), in a study involving 59 joints (25 knees and 34 ankles), found ultrasound to have high sensitivity (> 92%) for assessing synovial hypertrophy and hemosiderin in both ankles and knees. Similar findings were seen by Foppen *et al.,* (2017) in a study of the knees and ankles of 24 hemophilia patients (96 joints in total and age range of 18-34 years).

Synovial hypertrophy on MRI was confirmed in 19 joints. POC-US detection of synovial tissue was correct (overall accuracy) in 97%, and a positive predictive value of 94% (CI: 73-100) was observed. A negative predictive value of 97% was noted.

The overall accuracy of US for detection of cartilage abnormalities was 91% (CI: 83-96), and as for surface irregularities of the bones, the accuracy of 97% was achieved (CI: 91-99) (Doria *et al.,* 2015; Foppen and Vander, 2020).

In the Kenyan setup, radiography is often requested in most cases of joint pain. Equivocal radiograph reports are sent for MRI without ultrasonic evaluation. Thus, musculoskeletal ultrasonography remains inadequately utilized. Underutilization of MSK ultrasonography is largely due to inadequate expertise and limited experience amongst many of the MSK care providers (Stevens *et al.,* 2016).

However, in the recent past, much interest has developed in the use of MSK ultrasound imaging. There has been a steady rise in equipment availability and an ongoing increase in awareness and expertise in MSK ultrasonography.

Materials and Methods

Study Design

This study was a cross sectional descriptive study.

Study Area

This study was carried out at the Hemophilia Clinic in a hospital in Nairobi. The Hemophilia clinic provides care and follow-up of hemophilia patients and maintains the same patients' records within its catchment area. Upon inclusion into the study, the patients were guided from the hemophilia clinic to the Radiology department where scanning was done.

Study population

The study population consisted of patients with hemophilia and joint pain or swelling who ed the Hemophilia Clinic during the study period.

Scanning Procedure

The protocol chosen for this study was the Universal Simplified Protocol (USP) developed and validated by Kandagaddala *et al.,* (2019). This protocol was preferred for this study since it is a validated, simple, and suitable technique for quick and adequate assessment of the joints as shown in table 1 below.

USP avails a simpler and more clinically applicable technique, whereby 5 views are obtained for each knee joint. Doppler images and any other appropriate image is included to show pathologies encountered.

First the knee joint is divided by a transverse line through the joint space and a second sagittal line through the midline of the limb (Hawana *et al.,* 2015). For documentation purposes, the area proximal to the knee joint line is designated L1. L2 represents the joint line region and L3 is the area below the joint line. Each is further divided into medial and lateral parts (Lundin *et al.,* 2012; Timothy *et al.,* 2016).

Initial grey scale ultrasound and Doppler study was done on the knee joints and images were documented accordingly, by following the above mentioned protocol.

All the scans were done by the principal investigator with supervision from two senior radiologists with MSK bias.

Results and Discussion

Participants' demographic characteristics were as follows

A total of 41 patients with either knee joint pain or swelling were imaged during the study. The mean age of the patients was 18.1 years (SD ± 11.8) with an age range

between 3 and 60 years. The mode was 12 years and the median was 14 years. 40 were male and 1 was female. The most common age group was 10-19 years that comprised 49% of the study population as shown in figure 1 below.

Presenting Complaint

Knee joint pain was the commonest clinical complaint at 73% followed by knee joint swelling (56%). Only 44 % had reduced range of joint movement while 5%had warmness and redness around the joint.

Participants occupation; Majority were unemployed (78%). Only 12% were formally employed. This reflects the younger school going age of most of the participants.

Study findings of ultrasound scan

The study findings from ultrasound scanning. Only 12 % of the study population did not have any knee joint pathology detected by ultrasound despite having a clinical complaint of pain, swelling or reduced range of motion. Specific knee pathologies were identified by ultrasound in 88% of the participants, and there were both soft tissues and bony changes (Figure 2). Overall, synovial hypertrophy was the commonest finding across all the age groups.

The ultrasound findings grouped according to the participants' age groups are presented in Tables 1. Bone involvement was less common among the younger participants as compared to the older patients. The commonest pathology seen in the younger age groups was hemarthrosis followed by synovial hypertrophy.

Correlation of ultrasound findings in participants with their corresponding clinical complaints showed overlap of findings and complaints.

Sample images from the ultrasound are illustrated in figures 3, 4, 5 and 6 and show spectrum of findings ranging from knee hematoma to bony erosions.

Illustrations of Sample Cases

Knee joint complaints are common among the hemophilia patients visiting the hemophilia clinic at Kenyatta National Hospital. Our study demonstrated the heterogeneity of knee complaints seen at the hemophilia clinic. Knee joint pain was the commonest complaint at 68% followed by knee joint swelling that was seen in 53% of the participants. Reduced range of motion was present in 43% and only 5% had knee redness and warmth as a complaint.

In the present study detected hemarthrosis in 51% of all the joints studied. Hematrthrosis was noted to be the second most prevalent pathology in this study only surpassed by synovial hypertrophy. Hemarthrosis was detected most frequently in the suprapatellar recess. This finding highlighted the ongoing and active joint disease among the study participants. The study by Ceponis *et al.,* (2013) in Spain noted hemarthrosis in 13 out of 35 joints studied, a 37% prevalence. It is noted that the study by Ceponis *et al.,* (2013) was carried out in a setup where hemophilia management with factor replacement is both aggressive and often prophylactic, (60.7% were receiving factor replacement on demand, while 36.1% were on a prophylaxis programme) unlike in our study where 100 % of the participants were receiving factor replacement only on demand. The lower prevalence of hemarthrosis in the Ceponis study likely reflects better control of bleeding among their study population. However, both studies show a higher prevalence of knee hemarthrosis among hemophiliacs, and thus highlighting the severe burden hemophilia places on the patients as reported earlier in the study by Lorio *et al.,* (2019) who found a severe lifestyle disadvantage among the hemophilia patients.

Hemarthrosis is the initial pathology to occur in the hemophilia knee joint. Since ultrasound depicts hemarthrosis accurately, the use of ultrasound in follow up of hemophilia patients is key in timely diagnosis and management of hemophilic arthropathy. Targeted clinical interventions can follow once the evidence of hemarthrosis is availed by MSK ultrasound. The aim is to prevent progression of hemophilic arthropathy.

Synovial hypertrophy was noted in 66 % of all the studied knee joints. This was the most prevalent imaging finding among our study population. Ceponis *et al.,* (2013) similarly found synovial hypertrophy to be the most prevalent pathology (85 %) in their study population. Synovial hypertrophy was also noted to be the most prevalent finding in hemophilia knee joints in a study by Prasetyo *et al.,* who noted hypertrophied synovium in 57 out of 120 joints (48%). The lower percentage in the Prasetyo study was likely due to the fact that some of the participants in that study had no joint complaints unlike in our study, where inclusion

criteria was having a joint swelling or pain.

Table.1 Ultrasound findings by age groups

	Finding	Percentage involvement of joints by the pathology					
		0-9 years	**10-19 years**	**20-29 years**	**30-39 years**	**40-49 years**	**60-69 years**
1	Hemarthrosis	87.5	50	42.86	0	100	0
2	Synovial Hypertrophy	62.5	65	71.48	75	100	0
3	Cartilage erosion	37.5	71.4	57.14	50	0	100
4	Simple effusion	0	87.5	28.57	0	0	0
5	Osteophytes	12.5	12.5	85.71	50	100	100
6	Subchondral cysts	12.5	25	57.14	50	0	100
7	Bone erosion	25	37.5	85.71	50	100	100
8	Cartilage thinning	0	12.5	42.86	25	0	100

Figure.1 Participant's age distribution

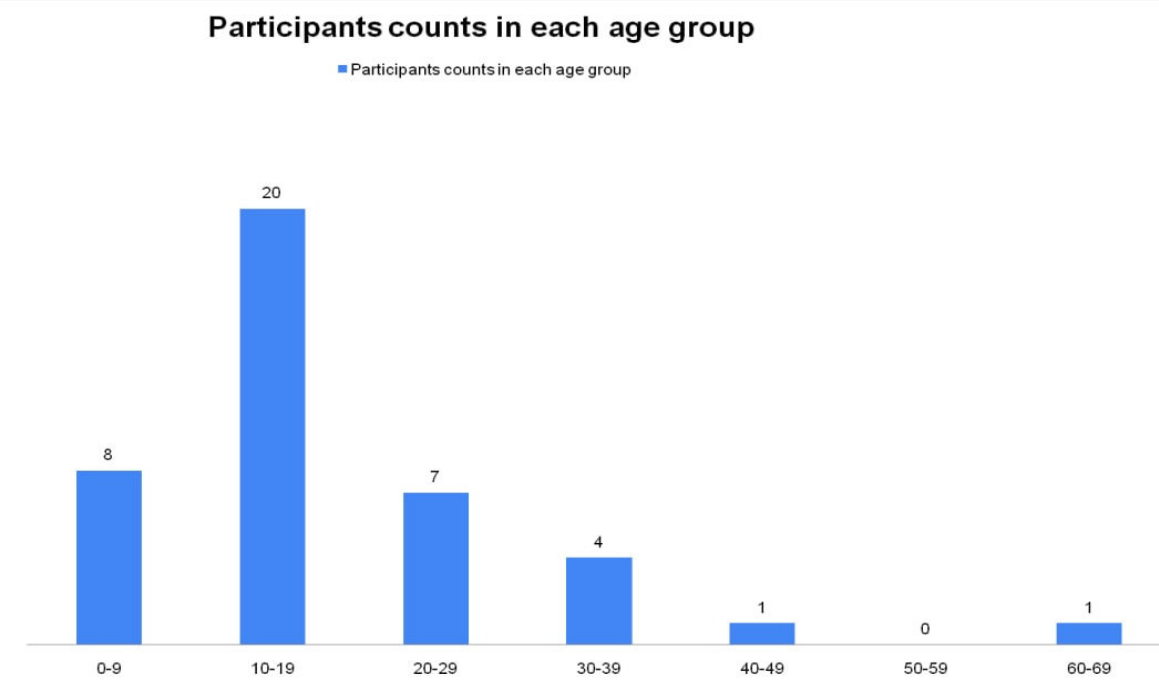


Figure.2 Pathologies seen at ultrasound scanning

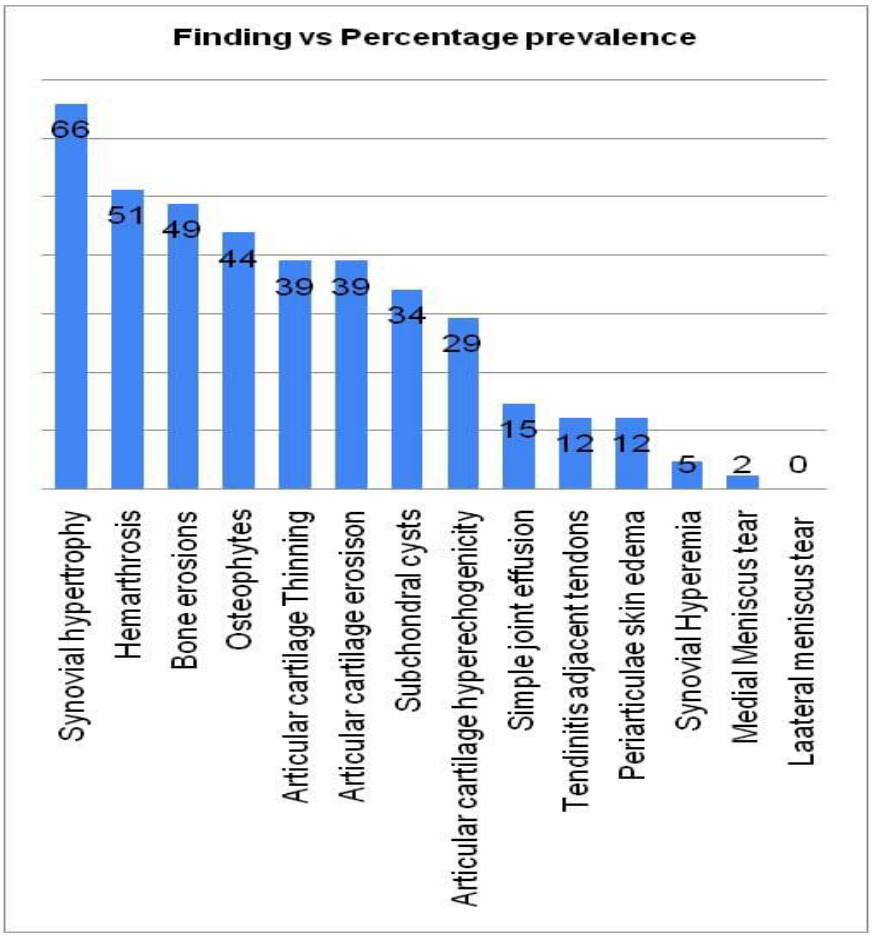


Figure.3 Sample image from ultrasound scanning during the study. Suprapatellar sagittal view [L1 anterior sagittal central view]. Shows suprapatellar bursa hematoma**.**

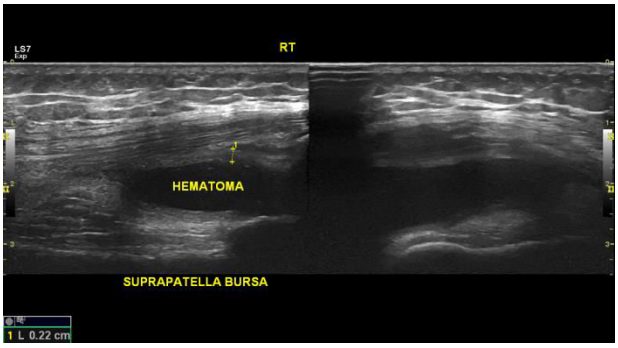


Figure.4 Sample image from ultrasound scanning during the study, showing bony erosion in the right knee. The left knee is normal. Medial coronal [L2 Medial coronal].

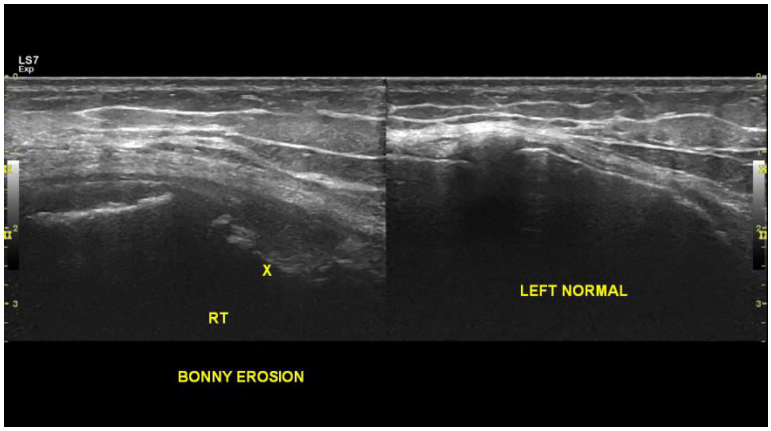


Figure.5 Sample images from ultrasound scanning during the study. Suprapatellar sagittal view [L1 anterior sagittal central view] and L2 at joint line showing hematoma in the suprapatellar recess and thinning of the femoral trochlea cartilage.

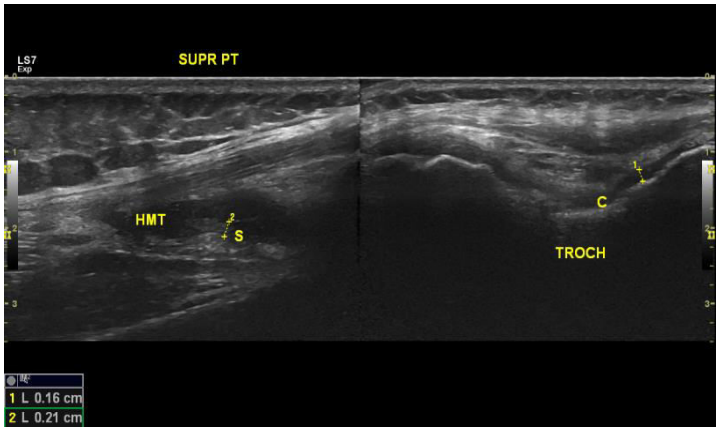
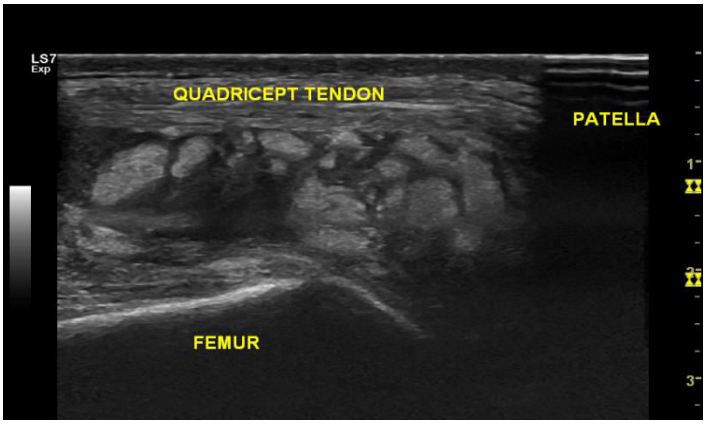


Figure.6 Sample images from ultrasound scanning during the study showing rice bodies within the suprapatellar bursa.



Synovial tissue invasion by inflammatory immunocytes triggered by bleeding into the joint leads to this villous synovial hypertrophy. Synovial hypertrophy reflects both acute and prior joint bleeds and depicts the risk of further joint destruction since the pannus formed is the main driver of joint destruction in hemophilia.

Articular cartilage thinning was noted in 39% of all the knee joints scanned. A cutoff of 1.6 mm for adults and 3.7 mm for children were used in our study based on the available references.

Our study showed cartilage thinning was more prevalent in the elderly patients as compared to younger patients, similar to findings by Kerr (2003) who noted that findings of hemophilic arthropathy depend on the age of the patient at onset and that the patients who have chronic disease have thinner cartilage.

In addition, the study found that among the younger patients, the main pathological findings were soft tissue changes, including synovial hypertrophy, hemarthrosis, and cartilage erosions. Osteophytes, bone erosions and osteophytes were rarer in the younger participants as compared to the elderly patients. Among the 0-9 year old participants, only 13% had osteophytes and subchondral cysts while all the patients aged above 40 year old had osteophytes and bone erosions.

Bonny changes indicate the chronicity of the pathological process and the study noted the prevalence of the chronic pathologies in the older participants. Since the bleeding into joints is the central pathophysiological process, this observation supports the routine prophylactic medication to prevent any such bleed as the cumulative effects of bleeding that was noted in the elderly patients were worse, although studies are needed to assess the clinical effects of prophylactic medications and factor replacement in the local set up.

Early detection of the pathological changes may also trigger urgent clinical interventions to stop progression of joint degeneration. Indeed, ultrasound scanning of the knee joint in hemophilia, since it can detect hemarthrosis earlier and reliably, can be used as a critical, objective clinical outcome measure in evaluating the effectiveness of factor concentrate replacement therapy in hemophilia

When the patients are categorized according to their clinical complaint of pain, swelling, reduced range of motion and warmth, the study found no pattern of pathological findings in any of these groups. Instead, the pathological changes noted were distributed randomly among the patients. The significance of this finding is that the clinical complaints of pain, swelling and reduced range are nonspecific and may not reliably predict the specific pathological state of knee joint structures as detected by ultrasound scan. Similar findings were noted by the study by Ceponis *et al.,* (2013) who identified discrepancies between objective Musculoskeletal Ultrasonography and self-reported or physician identified joint pain etiology.

To illustrate, among the patients who had knee pain, 62% had synovial hypertrophy, 48% had hemarthrosis, 49% had bone erosions and 49% had osteophytes, while in the patients who had knee joint swelling, 73% had synovial hypertrophy, 57% had hemarthrosis, 57% had bone erosions and 53% had osteophytes. In the group with reduced knee joint range, synovial hypertrophy was seen in 61%, hemarthrosis was noted in 72%, bone erosions in 57% and osteophytes in 56%.

The finding emphasizes the need for imaging evaluation in each patient in order to identify the specific pathology inorder to guide the clinical intervention approach. Each of the clinical complaints of pain, swelling and reduced range of motion carry equal weight in predicting the joint changes seen in hemarthrosis.

It was noted that only 2 patients scanned were female versus 39 males. This reflected the known predilection of hemophilia to male patients, with a male to female ratio of 3.1:1 and 5.2:1 reported in literature. This is because hemophilia is X-linked recessive disorder and rarely occurs in females (Soucie *et al.,* 1998).

The use of ultrasound for scanning patients who present in hemophilia clinics yields a lot of critical clinicopathological information about the status of the joints. The information detectable includes both soft tissues and periarticular bone status. This information is valuable for the patients since knowing the status of their joints alerts them to the urgent need for intervention. In particular, hemarthrosis of the knee joint was noted to be higher in our study population compared to other similar studies.

This may reflect a gap in the factor replacement in our study population. The information gained from

ultrasound scanning of the joint in hemophilia is critical for the care provider, as ultrasound easily and accurately depicts the pathological processes in both soft tissues and bones. This information helps the clinician to plan for the patient management guided by objective evidence of the pathologies in the joint to enable the clinician to address the real need of each patient.

Limitations of the Study

Sample size was relatively small (41) thus limiting generalization of results, although it is noted that hemophilia is a rare disease in the Kenyan population.

Recommendations

The use of ultrasound in the clinical set up of hemophilia management is feasible and provides a lot of key information that may be useful for patient management, the routine use of ultrasound in diagnostic and follow up of patients with hemophilia is recommended.

Training of more care providers in musculoskeletal ultrasonography to equip them with necessary skills and build confidence in the utility of ultrasound in musculoskeletal system imaging.

Updating of local hemophilia patient follow-up guidelines to emphasize the need for timely radiological assessment of the joints to enable earlier detection and characterization of joint pathologies. This would stop progression of the joint pathologies and potentially avail opportunity of clinical intervention in a more timely and more effective manner.

Declarations

Ethics approval and consent to participate

The study approval was obtained from the Kenyatta National Hospital and University of Nairobi ethical and research committee (KNH-UoN ERC) with approval number- P604/11/2020.

Consent for publication

Not applicable

Availability of data and materials

The data sets analysed during this study are available from the corresponding author on reasonable request

Competing interests

There are no competing interests to declare

Funding

No external funding was obtained for this study

Author contribution

Dennis Odiwuor Obuon and Callen Kwamboka Onyambu wrote the main manuscript. Dennis Odiwuor Obuon prepared the figures and tables. Christine Amo Mamai appraised the manuscript for critical content. All authors reviewed the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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