THE UTILITY OF KNEE ULTRASOUND IN PATIENTS WITH HEMOPHILIA WHO PRESENT WITH KNEE PAIN OR SWELLING AT THE HEMOPHILIA CLINIC IN KENYATTA NATIONAL HOSPITAL

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2022

DECLARATION

I declare that this dissertation is my original work written under the supervision of Dr. Callen Kwamboka Onyambu and Dr. Christine Mamai.

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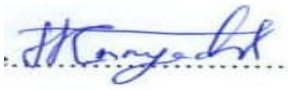

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DEDICATION

This work is dedicated to my loving wife Irene Anyango and my children Jahnel Havana and Mara Hawi for their steady patience and encouragement during this study

ACKNOWLEDGEMENT

I sincerely acknowledge my supervisors, Dr. Callen Kwamboka Onyambu and Dr. Christine Amo Mamai for their mentorship and insights during this study. I equally express much gratitude to the Kenyatta National Hospital management for allowing this study to be done within their facility. I appreciate the Hematology Clinic staff at the Kenyatta National Hospital for their effort and assistance toward this study.

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TABLE1: UNIVERSAL SIMPLIFIED PROTOCOL FOR HA ULTRASOUND

LIST OF ABBREVIATIONS

MRI	Magnetic Resonance Imaging
KNH	Kenyatta National Hospital
PLWH	People Living With Hemophilia
MSK-US	Musculoskeletal Ultrasonography
HA	Hemophilia arthropathy
POC-US	Point of Care Ultrasound
CT	Computed Tomography
US	Ultrasound
USP	Universal Simplified Protocol
TV-US	Toronto-Vellore protocol Universal Simplified
HEAD-US	Hemophilia Early Arthropathy Detection with Ultrasound
KNH/UON	Kenyatta National Hospital / University of Nairobi
SPSS	Statistical Package for Social Scientists

ABSTRACT

Background;

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. There is no available local data regarding the utility of ultrasound in the assessment of the knee joint of patients with hemophilia.

Objective;

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 Kenyatta National Hospital, Nairobi, Kenya.

Setting;

The National Hemophilia Clinic is located within the Kenyatta National Hospital in Nairobi, Kenya. Patients with hemophilia are followed in the Hemophilia clinic, where concentrate therapy and hemophilia complications are managed.

Study design;

This study was a cross-sectional descriptive study.

Study subjects;

A total of 41 patients with hemophilia and knee pain or knee swelling were assessed.

Study method;

This study was conducted over four months from February 2021 to April 2021. A total of 41 patients who have hemophilia and who attended the

routinely scheduled hemophilia clinic were recruited for the study. Both clinical assessment of the knee and sonographic assessment of the knees was done, and results recorded in the data collection form. Statistical analysis was done with SPSS version 2.0 to correlate the ultrasound findings with clinical findings.

Data management;

All the relevant data was obtained directly from the participant and recorded in the Data Collection Form attached.

The standard images obtained were filed and labeled accordingly.

Statistical analysis was done using the Statistical Package for Social Scientists (SPSS).

Expected main outcome measure(s);

It is expected that the number of MSK ultrasounds carried out in KNH hemophilia clinic will increase after this study resulting in early detection of hemophilic arthropathy. This outcome was measured by the primary register of ultrasound scans done on the KNH hemophilia clinic patients within the study period.

Chapter 1

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 (1).

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 (1).

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 (1).

Globally, hemophilia A's prevalence has been estimated at 1 in 10,000, and hemophilia B is estimated at 0.2 in 100,000 (2). The global prevalence statistic shows that the disease puts considerable morbidity on the global populations. Lorio *et al*. (3) study in several high-income countries across Europe found prevalence of hemophilia to be higher than previously estimated. Besides, the study by Lorio *et al*. (3) reports that hemophilia patient still have a significant life expectancy disadvantage. In the report by Lorio *et al.* (3), 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. (3)

Studies done as early as 1966 by Charles D. *et al*. have consistently concluded that more cases will be identified with more awareness and testing (4). 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 K. Ghosh *et al.* (5), 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. (5)

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. (6) 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 hemophilia (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 Dr. Srivastava *et al*. (1), 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 (1). 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. (7) There has not been widespread use of ultrasound for musculoskeletal imaging in Kenya. (8)

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 W. Foppen *et al*. in 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. (9)

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, (2) and to increase utilization of ultrasound in musculoskeletal imaging in Kenya and the region.

LITERATURE REVIEW

A study in Kenyatta National Hospital (KNH) by Muthua *et al.* 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 majority of the hemophilia patients were males (97%). The researchers noted that the patients' locality of origin was widespread, representing 21 out of Kenya's 47 counties. In this study, hemarthrosis was noted to be a particularly common complication of hemophilia. Muthua *et al*. note that about 62.9% of all the hemophilia manifestations in Kenya are hemarthrosis. The knee joint, followed by the elbow and ankle joints are the most commonly affected. Hemorrhage usually starts within the synovium then eventually extends into joint space. (10)

The result from the study by Muthua *et al*. (10) approximately replicated the results seen much earlier by Prof. Kitonyi *et al*. (35), 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. (35)

R. Kerr *et al.* (2) have shown that globally, about 85% of the bleeding episodes in People Living with Hemophilia (PLWH) involve the joints, with hemarthrosis usually beginning as early as the first two decades of life. The researchers affirm that each bleeding episode often involves a single joint, but more joints are involved eventually. By age 20, they note, the number of involved joints tends to stabilize, and pathological changes involve no new joint. Over time, this condition usually manifests as joint contractures, unequal length of the limbs, and swollen painful joint. (2)

Normally the synovial tissue can clear a certain amount of intra-articular blood. Larger or small frequent bleeding into joints leads to progressive accumulation of hemosiderin in the synovial macrophages. The breakdown of accumulated hemosiderin involves the release of enzymes and cytokines into the joint. These contribute to synovial inflammation and articular cartilage destruction resulting in inflammation and the synovial tissue's villous hypertrophy. Once the synovium is

hypertrophied, it becomes hyperemic and predisposed to injury; thus, a vicious cycle of bleeding, hypertrophic synovitis, and further bleeding ensues. (2, 11) Blood in the joint also causes cartilage degradation by induction of chondrocyte apoptosis. Elevated intracapsular pressure from the bleeding also degrades cartilage function and contributes to cartilage destruction. The resulting increased blood flow causes periarticular osteoporosis. Other changes occasioned by hemarthrosis include epiphyseal overgrowth, subchondral cysts, premature physeal closure, and sub-synovial fibrosis, intra-articular and capsular fibrosis, leading to joint contracture. Over time, these pathological processes lead to metabolic and mechanical joint changes that manifest as severe joint disease called chronic hemophilic arthropathy. (2)

According to Dr. Srivastava *et al*. (1), prevention of bleeding through regular prophylactic therapy using clotting factor concentrates to a large extent, minimizes the development and progression of hemophilic arthropathy, and should be the "goal of therapy" to preserve normal musculoskeletal function. (1)

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. (5)

W. Foppen *et al.* (14) 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. M. A. Timmer *et al.* (12) assert that timely accurate diagnosis is crucial for rational treatment and is a key strategy in reducing indiscriminate utilization of the concentrates. (12)

A. Ceponis *et al.* (7) also assert that timely and accurate diagnosis of bleeding and complications of bleeding is practical in the management of PLWH. Also, A. Ceponis *et al*. (7) maintain that when concentrates are administered empirically to manage joint pain, it is ineffective in controlling pain if the cause is not a joint

bleed. In the opinion of A. Ceponis *et al*. (7), empirical administration of concentrates would invariably lead to poor utilization of resources; therefore, accurate determination of the cause of joint pain in PLWH is critical before initiation of therapy. (7)

Thorough clinical assessment of joints and muscles, and radiological evaluation annually or as indicated clinically is recommended by Dr. Srivastava *et al*. (1) for optimal management of PLWH. In their recommendation on how to investigate a single self-reported joint pain, Dr. Srivastava *et al*. (1) assert that only clinical evaluation without the need for X-ray and ultrasound is indicated in a single self-reported joint pain. However, P. De Moerloose *et al*. (13) asserts that routine evaluation of the joints require a longer interval of 4–5 years from age 8 (or even earlier if there is enough clinical reason). Therefore, both Dr. Srivastava *et al*. (1) and P. De Moerloose *et al*. (13) agree on the need for thorough joint assessment for optimal care of the patients but recommend varying intervals to assess affected joints. (1, 13)

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. In a study by A. Ceponis *et al*. (7) involving 40 patients with joint pain and swelling episodes, Patients were categorized by physicians as having joint pain or swelling due to several etiologies. The categories included intra-articular bleeding, inflammation, intramuscular bleeding, and other regional pain diseases. The patients were to be diagnosed by physicians, and also the patient self-report was assessed. A. Ceponis *et al*. (7) noted that most patients (33 out of 40) termed their symptoms as bleeding in joints. Physicians diagnosed five as arthritis, and two were not conclusively diagnosed in any category. However, only 12 were confirmed to be actual bleeds by MSK ultrasound. The other episodes were confirmed to be pathologies other than bleeding into the joint. Overall, physician diagnosis was incorrect in 18 of the 40 cases. (7)

The study by A. Ceponis *et al*. (7) illustrated the inaccuracy of self-reported or physician diagnosis alone for the determination of the actual cause of joint pain or swelling. Moreover, in the study by A. Ceponis *et al*. (7), the findings of the

objective Musculoskeletal Ultrasound (MSK US) scans changed the management in >70% of episodes, resulting in symptom improvement in more than 60% of the cases. The recommendation from the study is the inclusion of point-of-care imaging into hemophilia care since the practice of prescribing clotting factors or conservative measures based on reported pain perception and physical examination alone appears inadequate. (7)

Hemophilia is a lifelong condition and requires constant monitoring. The patient's bleeding status should be periodically assessed. (13) 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. (14)

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. (15)

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. (16)

Doria *et al.* (17), 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.* (14) 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). (17,18)

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. (8)

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.

1.1 GROSS ANATOMY OF THE KNEE JOINT

The knee joint is a modified synovial hinge joint formed between three bones: femur, tibia, and patella. The knee joint comprises the tibio-femoral joint and the patello-femoral joint and is the largest joint in the human body.

Principal articulating bones are the femur and the tibia through their medial and lateral condyles. There are articular cartilage and synovium enclosed within the joint capsule. Anterior and posterior cruciate ligaments are intracapsular ligaments. Extra capsular ligaments include ligamentum patella, transverse ligament, anterior inter meniscal ligament, medial, and lateral patellar retinacular ligaments of the extensor mechanism, anterior cruciate ligament, tibial and fibular collateral ligaments, posterior oblique ligament, oblique popliteal ligament,

posterior meniscofemoral ligament, popliteal tendon piercing the knee capsule. Medial and lateral menisci contribute to stability at the knee joint. (2, 7)

1.2 SONOGRAPHIC ANATOMY OF THE KNEE JOINT

E

chogenicity of tissues. (19, 20, 21)

S

kin- Appears as hyper echoic thin layer.

S

ubcutaneous Tissues- This layer appears just under the skin as a hypo echoic layer with interspersed linear echogenicity representing fibrous septa within the tissue.

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igaments- The appearance is similar to tendons on ultrasound (Hyper echoic).

B

one- Bone appears as a hyper echoic line. The hyper echoic line defines the outline of the bone, with posterior acoustic shadowing.

H

yaline Cartilage- Has hypo echoic appearance and does not alter shape with compression.

1.3 MODALITIES OF KNEE JOINT IMAGING IN HEMOPHILIA

Hemophilia being a manifestation of a genetic disorder is a lifelong condition. Fortunately, its effects can be managed well. Constant monitoring tailored to each patient's clinical condition and disease severity is recommended. (1)

Patients with severe cases warrant more frequent monitoring that involves thorough assessment of bleeding history and joint status at least once every year. Mild and moderate hemophilia cases can be evaluated less frequently. (13, 22)

1.3.1 Plain Radiography

Radiography is relatively cheap and widely available and can assess moderate to severe arthropathy manifestations of HA, but not the first joint changes. Moderate to severe joint effusion and narrowing of joint space and osteophytes are readily detected if present. (2) Serial radiographs done every 1-5 years are recommended for follow-up of joints' general status. (13, 14)

Since radiography involves the use of ionizing radiation and does not show soft tissue details, it is of limited use in hemophilia arthropathy. Arnold-Hilgartner and Patterson scores are used to grade the severity of joint involvement by plain radiography. (23, 15, 2, 24)

1.3.2 Computed Tomography

The advantage of CT is its better demonstration of bone structure as well as soft tissue details compared to plain radiography and gives good cross-sectional information. However, it is not suitable for long-term follow-up of hemophilia patients since it is costly and uses ionizing radiation. It has limited soft-tissue contrast resolution compared to MRI. (14)

1.3.3 Magnetic Resonance Imaging

This modality remains the reference standard for joint evaluation and enables a thorough evaluation of all soft tissues and bones. It gives cross-sectional multi-planar information and has no ionizing radiation. Besides, a contrast MRI allows more detailed intra-articular soft tissue evaluation. However, it is limited by its high cost, longer duration of image acquisition, and low availability. Some patients have contraindications that may limit its use e.g., metal implants and some pacemakers. Hemosiderin deposits appear as dark areas due to susceptibility

artifacts. A severe deposition may limit the utility of MRI in the joint assessment MRI. (14)

Several scoring systems exist that use MRI to quantify hemophilia joint changes, notably the *International Prophylaxis Study Group (IPSG) MRI scale*. (25) MRI scales have been shown to reliably predict 5-year joint bleeding patterns and the development of HA's chronic changes. (18)

1.3.4 Sonography

Several studies have demonstrated the utility and accuracy of ultrasound as a modality for evaluation and monitoring HA. (14) Compared to MRI, US requires shorter examination time, costs less, is more readily available, and is less affected by motion during acquisition; thus, no sedation or anesthesia is needed even in children. Dynamic image acquisition also enables interventional procedures to be carried out without ionizing radiation dose to the patient or caregiver. The US's main limitation is the inability to penetrate the bone cortex and high operator dependence. (21)

K. Zukotynski *et al*. (20) in a study to systematically review ultrasound as a tool for evaluation HA showed there is fair evidence (Grade B) to recommend US as an accurate technique for early diagnosis of HA and that US score correlates with clinical/US constructs. These researchers also confirmed that US findings in HA correlate to the functional status of the joints. (20)

Lack of universal standardized evaluation and reporting protocol for the HA has continued to be a challenge making comparison and follow-up of patients across different facilities difficult. However, useful protocols have been developed in an attempt to standardize scanning approaches in different joints in PWH notably;

The Universal Simplified Protocol (USP) (25), Disease-specific quality-of-life measurement tool for hemophilia patients, (26) Toronto-Vellore protocol (TV-US), and Hemophilia Early Arthropathy Detection With Ultrasound(HEAD-US). (27, 28, 29)

The choice of the protocol to use depends on the local facility guideline. The ideal protocol should be simple enough to shorten the examination and interpretation time but comprehensive enough to assess all the knee's relevant structures. Good

inter observer and intra observer reliability is desirable. Ease of learning by non-expert MSK sonologists and applicability to easily accessible machines is critical.

A study by Monica S. (30) asserts that the USP protocol can provide adequate joint status details with less duration of examination and fewer images, thus making this protocol particularly suited for point of care ultrasound assessment in the Hemophilia clinic setting. The entire joint can be assessed in "approximately 10 minutes," according to Monica, S. (30) This protocol scans the entire joint and documents five standard views from the TV-US protocol. Additional images using Doppler are acquired and documented with appropriate labeling like in TV-US if relevant findings are noted. For annotation, each joint is divided as L1 (above the joint line), L2 (joint line), and L3 (below the joint line). (30)

In a prospective study to determine the accuracy of diagnosis and quantification of HA by use of the HEAD-US protocol in comparison to the MRI, Domen, *et al*. (31) demonstrated US protocol and scoring method to be a quick, reliable, and accurate for the detection and quantification of hemophilic arthropathy in comparison to MRI. Thus, HEAD-US could justify prophylactic treatment initiation to prevent the occurrence of hemophilic arthropathy, especially in children, or prevent disease progression in established disease. It is suited for quick evaluation of the six mostly involved joints during a single scanning session. (20, 31) However, this protocol has been found to have fixed views of the knee joint (i.e., only five images for knee joints and four images for ankle joints) and may fail to demonstrate some abnormalities. (32)

The Toronto-Vellore protocol is comprehensive and reliable with findings that compare well to MRI but is time-consuming and cumbersome when used in point of care practice. It involves acquiring 27 grayscale images and 11 Doppler images in predetermined scan planes. (30) Using ultrasound, the knee joint's soft tissues, including synovium, articular cartilage, capsule of the knee joint, and ligaments are assessed. Limited assessment of the bonny cortices is possible with ultrasound. (26)

Locally in Kenya, the use of US in HA has not been widely adopted, partly due to hemophilia's status as a relatively rare condition despite the severe consequences the disease has on the patients. (8)

1.4 Study Justification

Hemarthrosis is the commonest manifestation of hemophilia locally, with the knee joint most frequently affected. Complications of hemarthrosis such as synovial hypertrophy and joint cartilage destruction, if detected early enough, can be managed, and their effect on loss of joint function alleviated.

Plain radiography is not sensitive enough to be of any significance in the early evaluation of these joint changes. MRI, while being the gold standard, is limited by its higher cost and its availability only in major Kenyan cities. No local Kenyan study has been done to assess the spectrum of findings in Knee joint Hemarthrosis in people with Hemophilia.

This study aims to avail baseline data for such findings with the anticipation that this will benefit the patients and increase the local care-provider's awareness and utilization of ultrasound in musculoskeletal diseases.

1.5 Study question

What is the spectrum of ultrasound findings in the knee joint of hemophilia patients with joint pains or swelling at the Hemophilia clinic in Kenyatta National Hospital, Nairobi?

1.6 Study Objective

The objective of this study was to determine the types of abnormalities detectable by ultrasound, in the knee joints of patients with hemophilia who have knee joint pain or knee joint swelling, at the Hemophilia clinic in Kenyatta National Hospital, Nairobi.

1.7 Broad Objective

To establish local baseline data of the utility of ultrasound in the assessment of swollen or painful knee joints of patients with hemophilia.

1.8 Specific Objective.

The specific objective of this study is as follows;

1. To establish the types of abnormalities detectable by ultrasound in the knee joint of patients with hemophilia who have knee joint pain or knee joint swelling at the Hemophilia clinic in Kenyatta National Hospital, Nairobi.

Chapter 2 S

TUDY DESIGN AND METHODOLOGY.

2.1 Study design.

This study was a cross sectional descriptive study.

2.2 Study area.

This study was carried out at the Hemophilia Clinic in Kenyatta National Hospital, Nairobi, Kenya. 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 of Kenyatta National Hospital where scanning was done.

2.3 Study Population.

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

2.4 Inclusion Criteria

The principal investigator included any patient with hemophilia and knee joint pain or swelling who visited the hemophilia clinic during the study period into the study. The study period was between the months of February 2020 to April 2020.

2.5 Exclusion Criteria

1. Patients who declined to consent to the study.

2. Patients who did not have joint pain or swelling at the time of their visit to the hemophilia clinic.

2.6 Sample size calculation

The sample size of 39 patients was used. This was arrived at using Fisher's formula for prevalence studies in finite population's correction as highlighted by Daniels (33) as follows;

$$n = \frac{NZ^2P(1-P)}{}$$

$d^2(N-1) + Z^2P(1-P)$

N = Total number of the PLWH patients who have joint pain or swelling and visit the hemophilia clinic during the period of study (estimated as 4 per week for 11 weeks giving a population of 44 patients).

P = prevalence of knee joint bleeding in hemophilia patient population. The available Kenyan statistic by Muthua *et al.* (10) found the prevalence of knee joint bleeding as 62.9 % in PLWH. (10)

Z = Z statistic representing confidence level of 95% (1.96).

d = the desired precision level for confidence interval of 95% is 5.0 %.

Thus;

$$n = \frac{44 \times 1.96^2 \times 0.629 (1 - 0.629)}{0.05^2(44-1) + 1.96^2 \times 0.629 (1 - 0.629)} = \frac{39.4448}{0.1075 + 0.89647}$$

$$= \frac{39.4448}{1.00397} = 39.289$$

Therefore n = Minimum of 39 patients. 41 patients were scanned during the study.

2.7 Sampling Method

Consecutive hemophilia patients who attended the KNH hemophilia clinic were included upon giving informed consent.

2.8 Consent and Recruitment process

Every patient who met the criteria for inclusion was informed about the overall study objective and requested to volunteer into the study.

Those who consented signed the informed consent form shown in Appendix 1 and were subsequently scanned as outlined in the knee ultrasound procedure as outlined in section 2.9. The process was done by the principal investigator.

2.9 Data Collection Procedure

The patient's biodata and summary of clinical information was collected and recorded in the patient biodata questionnaire, Appendix 4. The names of the patients were excluded in the data collection for confidentiality purposes.

After the knees were scanned by the principal investigator, the sonographic findings was recorded in the Ultrasound findings section of the biodata questionnaire.

2.10 MATERIAL AND EQUIPMENT

2.11 Ultrasound machine

Scanning was done by the principal investigator using the high-frequency (7.5-12 MH) linear transducer. The ultrasound Machine used was Logiq 6 and the preset was the musculoskeletal preset available in the machine presets.

2.12 Scanning procedure

The protocol chosen for this study was the Universal Simplified Protocol (USP) developed and validated by M. Kandagaddala. This protocol was preferred for this study since it is a validated, simple, and suitable technique for quick and adequate assessment of the joints. (26)

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. (16) 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. (25, 34)

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

Table 1.0

L1 - Area above joint line.

L2 -At joint line.

L3- Area below joint line.

These give the following standard views:

1. Supra-patellar sagittal view (L1 Anterior Sagittal Central)
2. Medial coronal (L2 Medial Coronal)
3. Lateral coronal (L2 Lateral Coronal)
4. Posterior medial sagittal (L2 Posterior Sagittal Medial)
5. Posterior lateral sagittal (L2 Posterior Sagittal Lateral)

2.14 Personel

All the scans were done by the principal investigator with supervision from two senior radiologists with MSK bias. A biostatistician advised in the sample size calculation and statistical analysis.

2.15 Quality Assurance Procedure

To ensure quality, the images were analyzed by the principal investigator and the two supervisors before filing.

The USP protocol was consistently used during each scanning to ensure uniformity.

2.16. Ethical Considerations

Before the study began, a research proposal was submitted to the KNH/UON Research and Ethics Committee for approval.

Each participant in the study voluntarily signed the informed consent before they were included in the study.

No patient identifiers were used. Instead each patient was given a unique code number.

The information given by the patients was intended to be used solely for the study. The management of each patient was not interfered with.

The following precautions were observed by both the research team and participants to prevent covid-19 infections during the study.

-Hand washing and donning the KNH recommended PPEs by both teams prior to, during and after each scan was done.

-Ultrasound probes were covered appropriately with disposable covers.

- Disinfection of the probes and the machine was done before and after every scan using 0.5 % chlorine / 0.5 % solution of hydrogen peroxide.

2.17 Data management and Statistical analysis

All the relevant data was obtained directly from the participant and recorded in the Data Collection Form attached.

The standard images obtained were filed and labeled accordingly.

Statistical analysis was done using the Statistical Package for Social Scientists (SPSS).

Timelines for the study

Activity	May 2020 to Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	Mar 2021	Apr 2021	May 2021
1. Completion of research proposal								
2. Submission of thesis to KNH-UON ERC for approval								
3. Collection of data								
4. Data analysis								
5. Thesis defense								
6. Publication								

Budget for the study

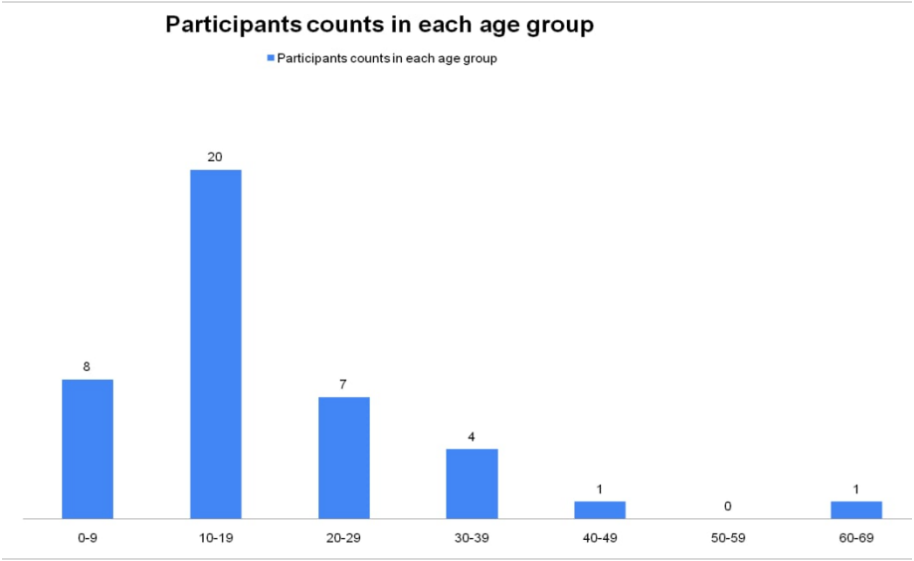
	Item	**Budget Justification**	**Cost KSh.**	**Quantity**	**Total KSh.**	**Source of funding**

	Proposal development, reference materials	Research materials, Internet bundles	0,000		0,000	rincipal investigator
	Ultrasound scanning fees (30 patients+5 Extra for Contingency)	Cost of scanning since there is no waiver obtained	,600	9	40,400	rincipal investigator
	Data analysis	Fees paid to statistician	0,000		0,000	rincipal investigator
	Cost of Publication		0,000		0,000	rincipal investigator
TOTAL					10,400	rincipal investigator

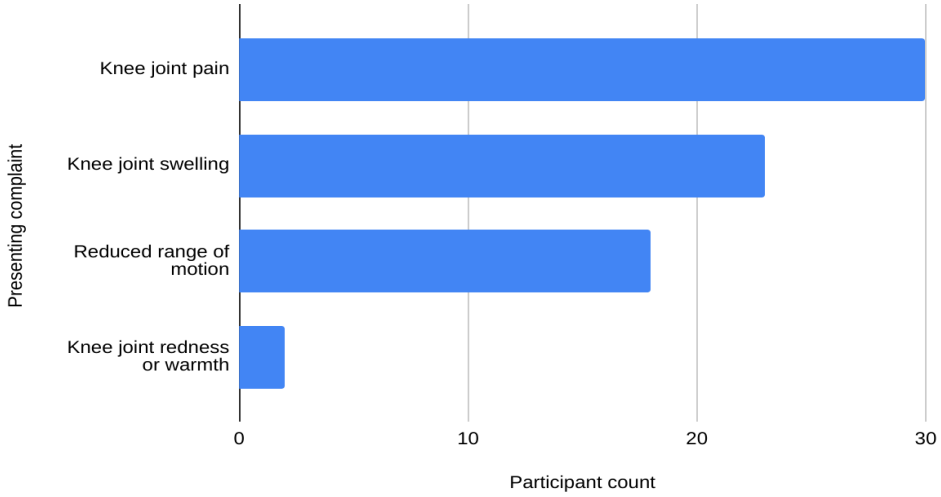
Chapter 3 RESULTS.

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 2.0 below.

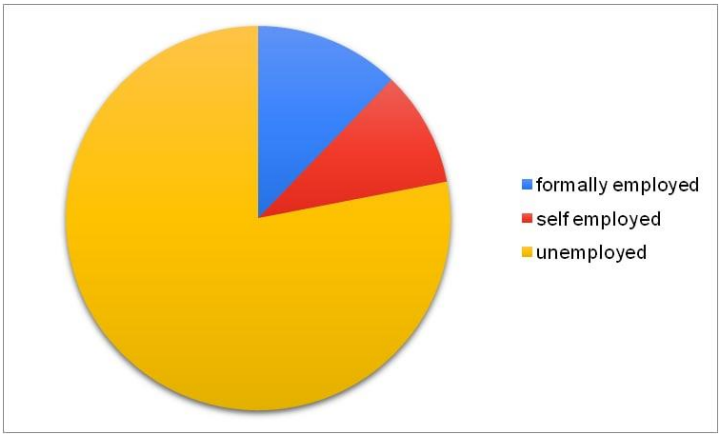
Figure 2.0



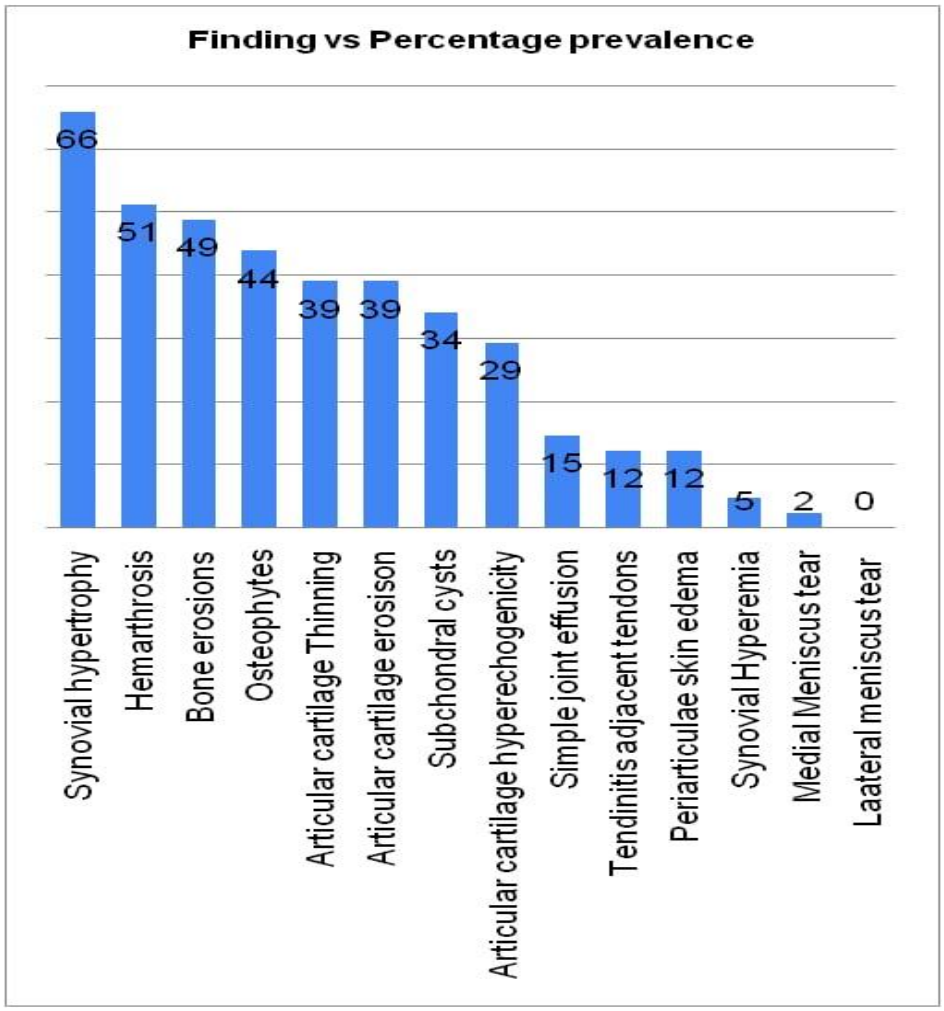
Presenting complaint; Knee joint pain was the commonest clinical complaint at 73% followed by knee joint swelling (56%). Only 44 % had reduced range of joint movement while 5%had warmness and redness around the joint. (figure 3.0).



Participants occupation; Majority were unemployed (78%). Only 12% were formally employed. This reflects the younger school going age of most of the participants(figure 4.0).



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. Overall, synovial hypertrophy was the commonest finding across all the age groups.
(figure 5.0).



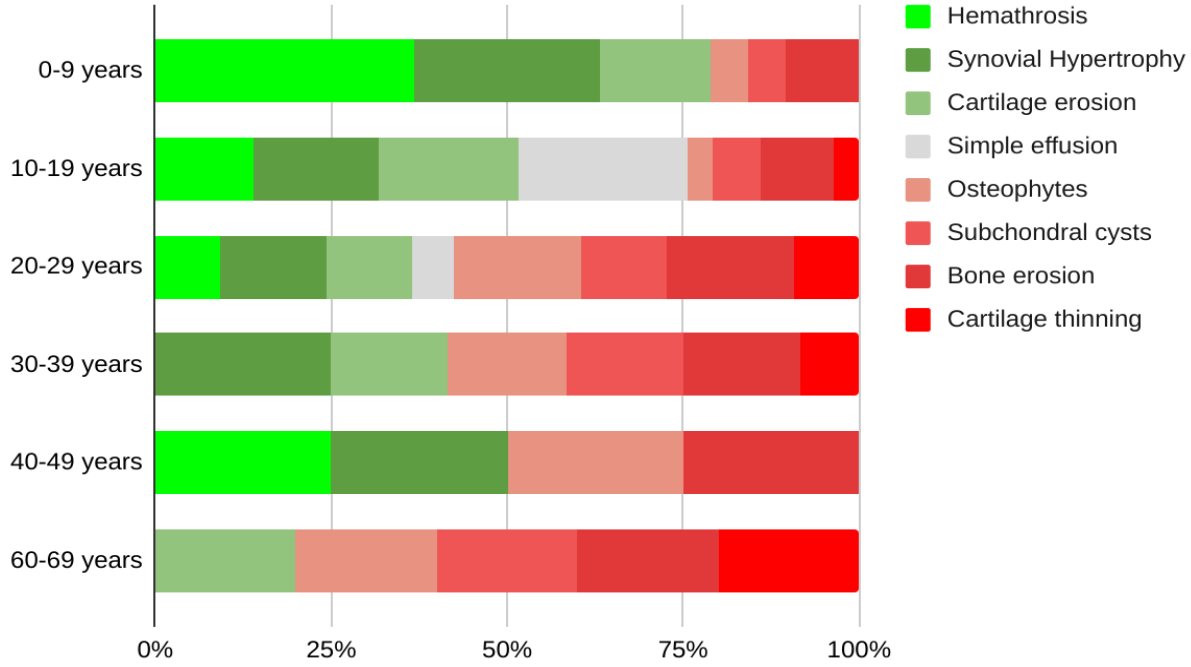
The ultrasound findings grouped according to the participants' age groups are presented in Tables 3.0 and figure 6.0. Bone involvement was less common among the younger participants as compared to the older patients.

Table 3.0.

	Finding	Percentage involvement of joints by the pathology					
		-9 years	0-19 years	0-29 years	0-39 years	0-49 years	0-69 years
	Hemarthrosis	7.5	0	2.86		00	
	Synovial Hypertrophy	2.5	5	1.48	5	00	
	Cartilage erosion	7.5	1.4	7.14	0		00
	Si						

	mple effusion		7.5	8.57			
	Osteophytes	2.5	2.5	5.71	0	00	00
	Subchondral cysts	2.5	5	7.14	0		00
	Bone erosion	5	7.5	5.71	0	00	00
	Cartilage thinning		2.5	2.86	5		00

Figure 6.0 showing ultrasound findings by age groups.



Ultrasound findings noted in participants with their corresponding clinical complaints are presented in table 6.0 and figure 7.0 below. NB; some patients had more than one complaint.

Table 6.0 Table showing the study Participants complaints versus the ultrasound findings.

Knee Pain		Knee swelling		Reduced Range Knee joint	
Synovial Hypertrophy	62%	Synovial Hypertrophy	73%	Hemarthrosis	72%
Bone erosions	49%	Hemarthrosis	57%	Synovial Hypertrophy	61%
Osteophytes	49%	Bone erosions	57%	Bone erosions	57%

Hemarthrosis	48%	Osteophytes	53%	Osteophytes	56%
Cartilage erosion	38%	Subchondral cysts	44%	Cartilage erosion	44%
Subchondral cysts	38%	Cartilage erosion	39%	Subchondral cysts	39%
Cartilage hyperechogenicity	31%	Cartilage hyperechogenicity	35%	Cartilage hyperechogenicity	28%
Cartilage thinning	21%	Tendinitis adjacent tendons	22%	Cartilage thinning	17%
Periarticular edema	14%	Simple effusion	13%	Periarticular edema	11%
Tendinitis adjacent tendons	14%	Periarticular edema	13%	Tendinitis adjacent tendons	11%
Simple effusion	13%	Cartilage thinning	13%	Simple effusion	6%
Synovial hyperemia	3%	Synovial hyperemia	4%	Medial meniscus tear	6%
Medial meniscus tear	3%	Medial meniscus tear	4%	Synovial hyperemia	0%
Lateral meniscus tear	0%	Lateral meniscus tear	0%	Lateral meniscus tear	0%
Anterior cruciate ligament tear	0%	Anterior cruciate ligament tear	0%	Anterior cruciate ligament tear	0%
Posterior cruciate ligament tear	0%	Posterior cruciate ligament tear	0%	Posterior cruciate ligament tear	0%

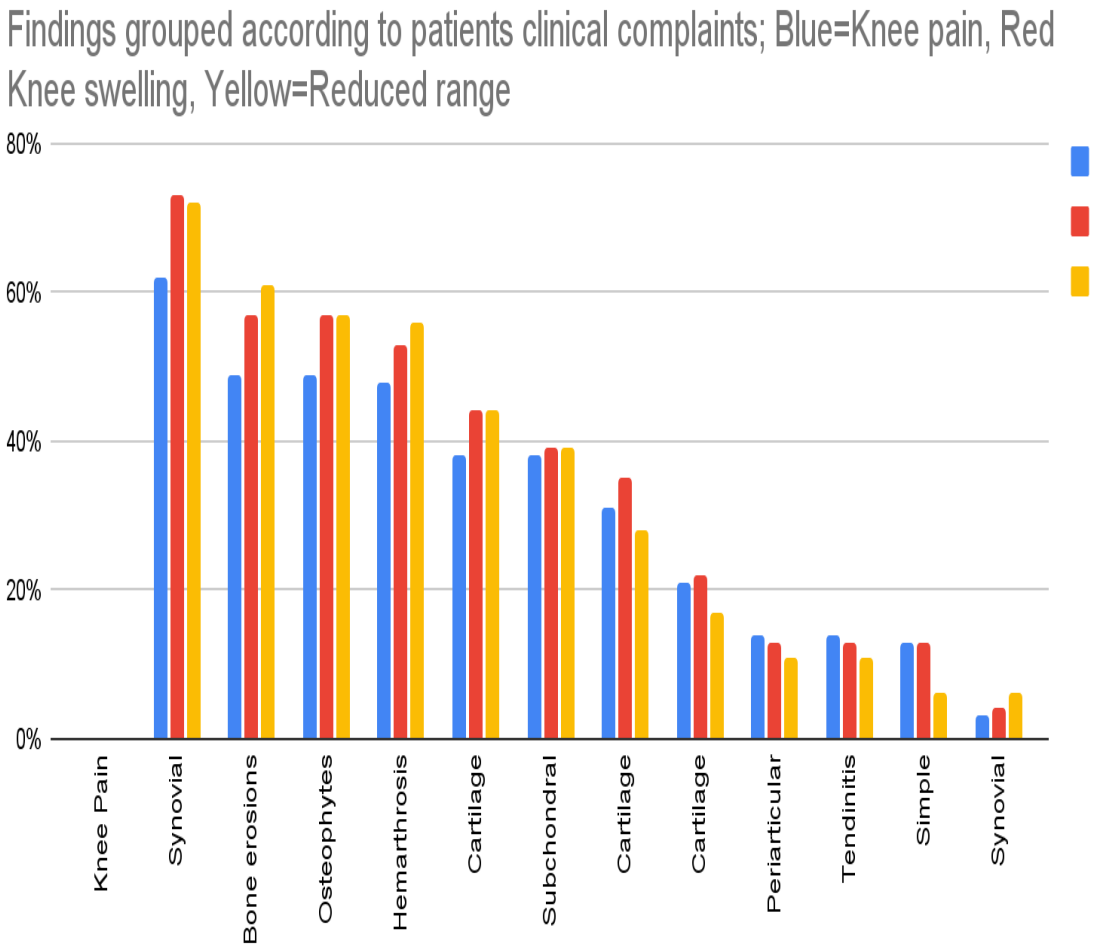


Figure 8.0 Sample image from ultrasound scanning during the study. Suprapatellar sagittal view (L1 anterior sagittal central view).

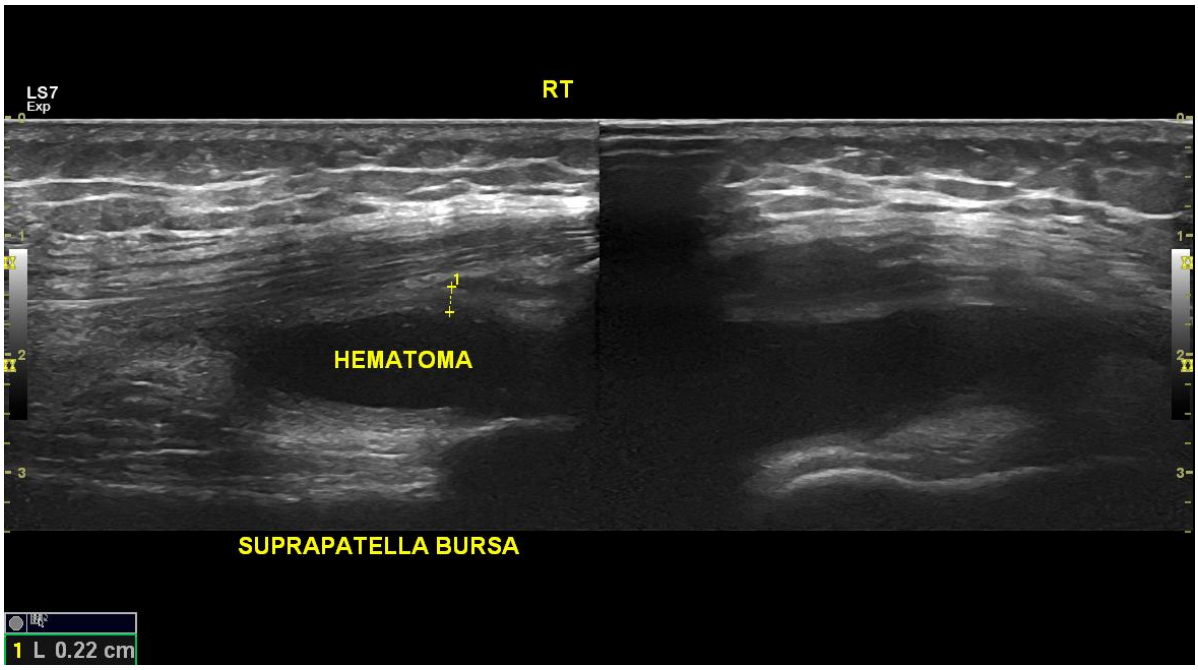


Figure 9.0 Sample image from ultrasound scanning during the study. Lateral (L3 lateral coronal) and Medial coronal (L2 Medial coronal).

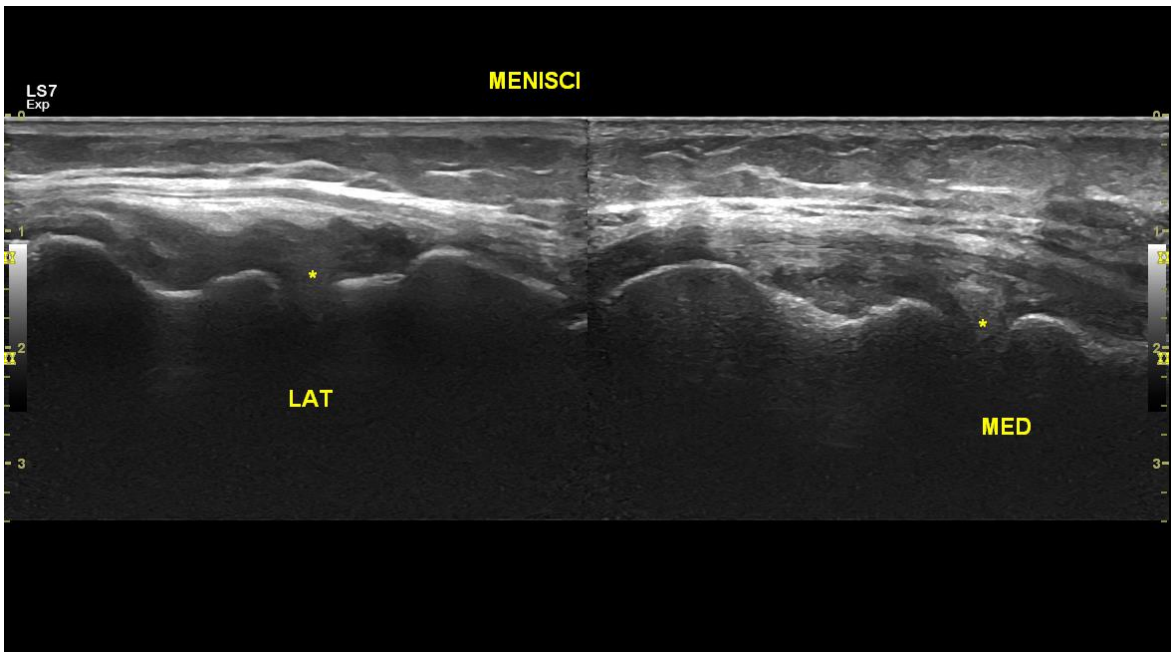


Figure 10.0 Sample image from ultrasound scanning during the study. Medial coronal (L2 Medial coronal).

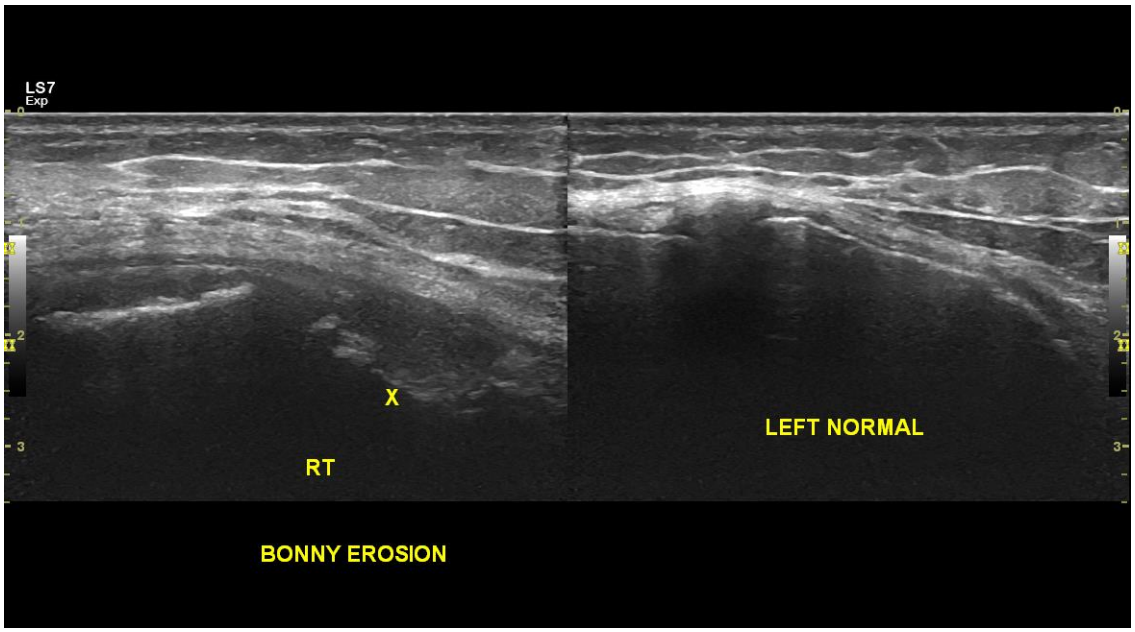


Figure 11.0 Sample image from ultrasound scanning during the study. Posterior medial sagittal (L2 posterior sagittal medial) and Posterior lateral sagittal (L2 posterior sagittal lateral) showing normal area of popliteal fossa between the medial head of the gastrocnemius muscle and semimembranosus tendon, the location where baker's cyst would be found. The second image shows the normal lateral meniscus..

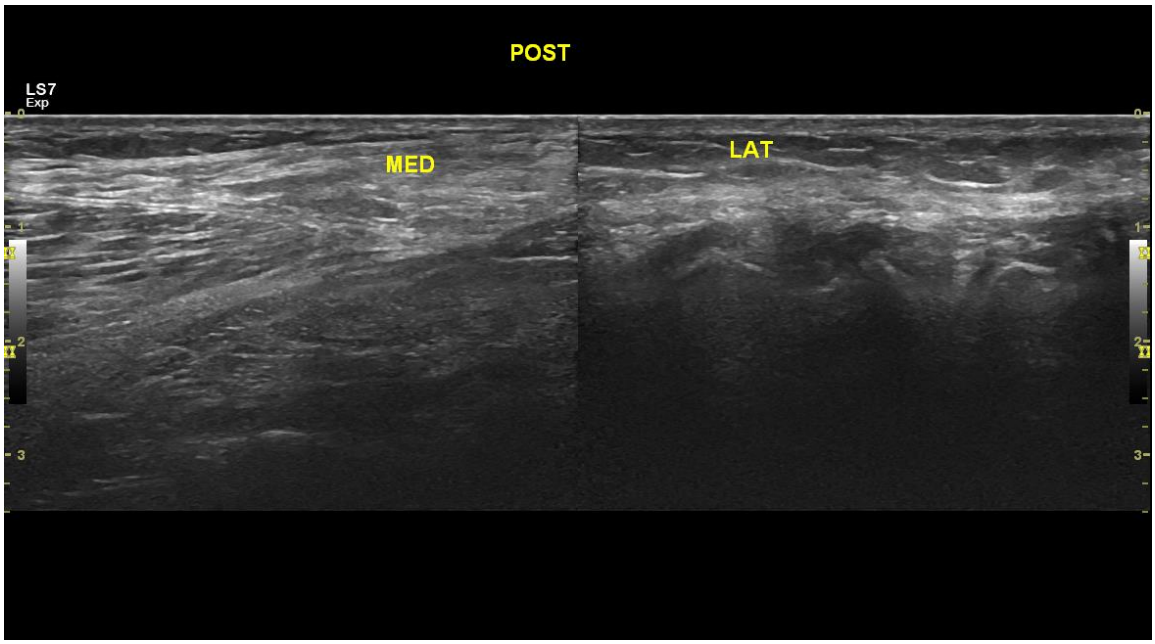


Figure 12.0 Sample images from ultrasound scanning during the study. Suprapatellar sagittal view (L1 anterior sagittal central view) and L2 at joint line showing hematoma in the suprapatellar recess and thinning of the femoral trochlea cartilage.

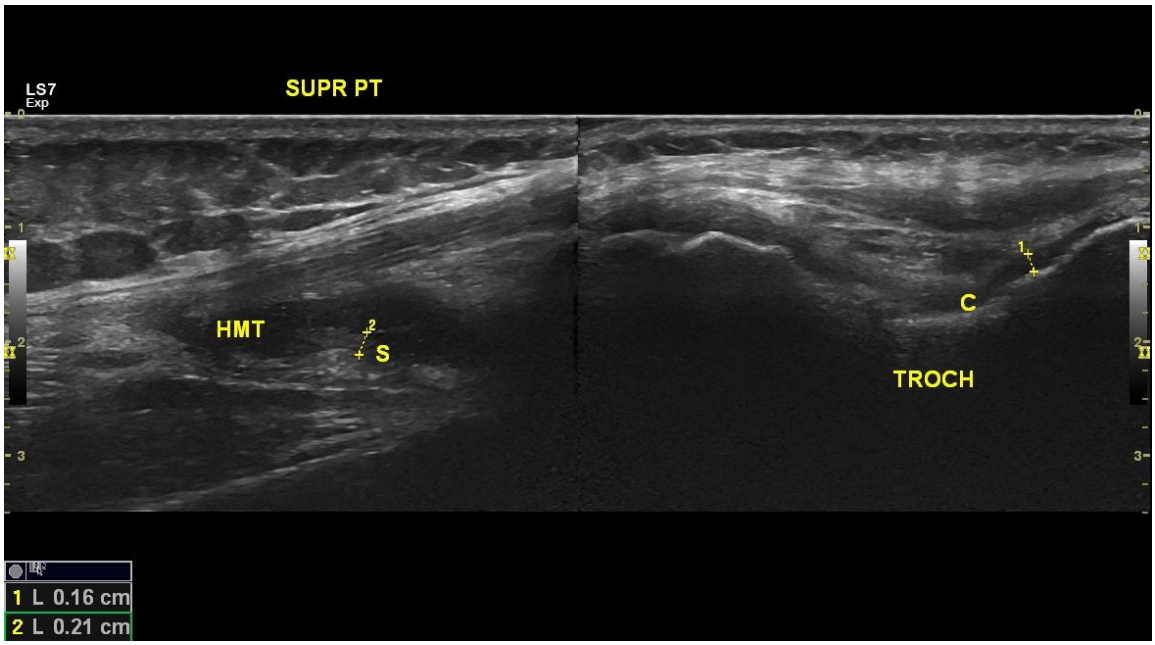


Figure 13.0 Sample images from ultrasound scanning during the study. Medial coronal (L2 Medial coronal) and
Lateral (L3 lateral coronal) showing bonny erosion and osteophytes.

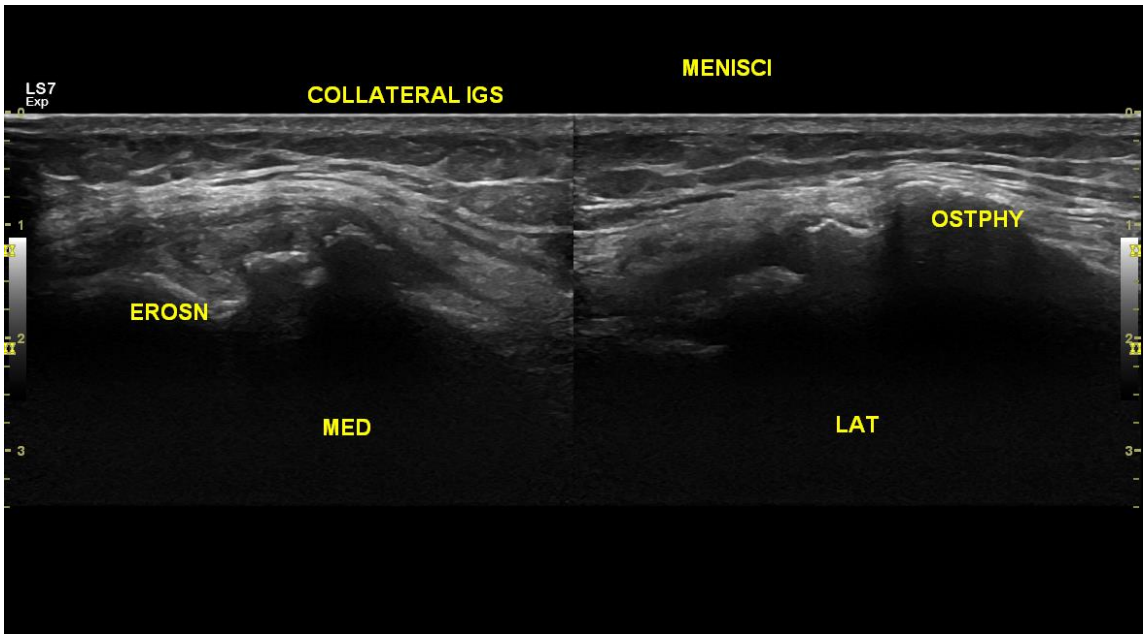


Figure 14.0 Sample images from ultrasound scanning during the study showing rice bodies within the suprapatellar bursa.

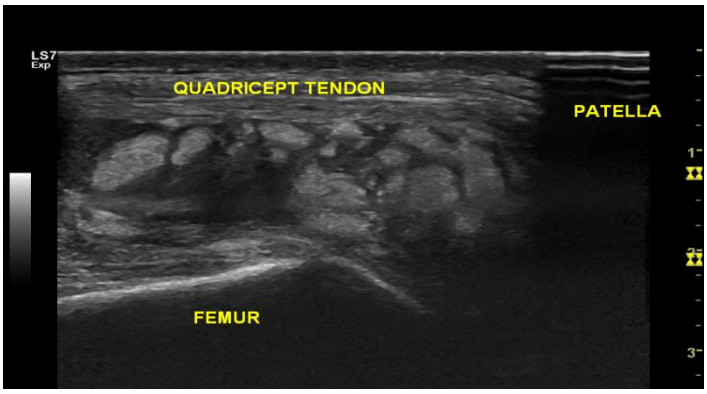


Figure 15.0 Sample images from the ultrasound scanning during the study showing bony erosions and sub-chondral cysts.

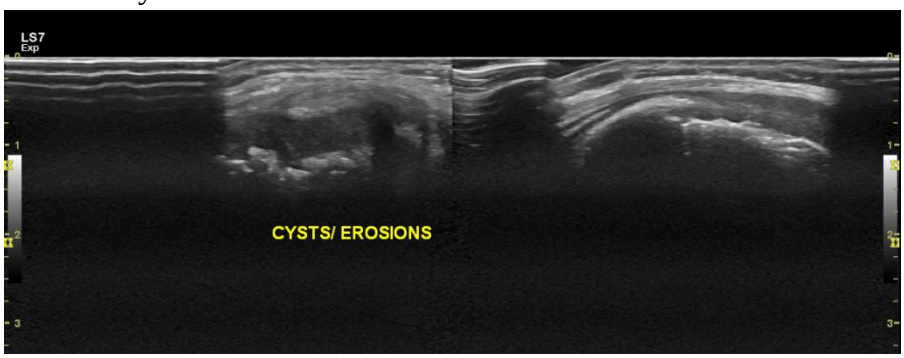
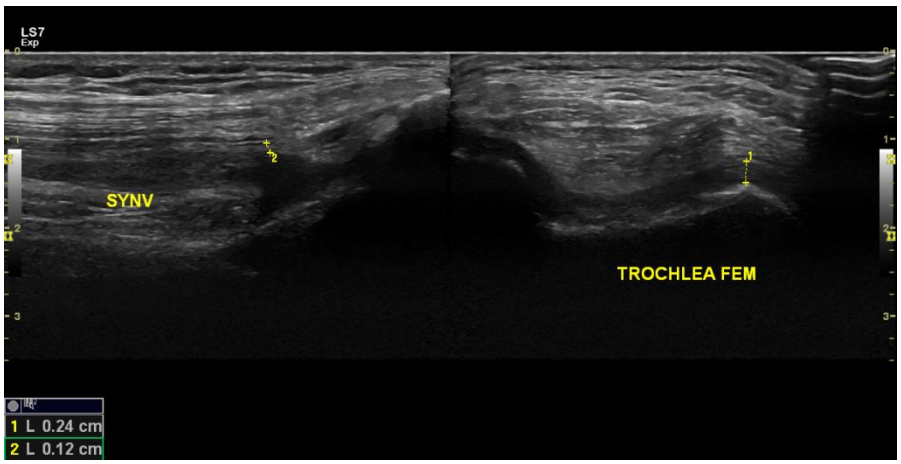


Figure 16.0 Sample image from ultrasound scanning during the study showing articular cartilage

hyper echogenicity.



CHAPTER 4 DISCUSSION AND CONCLUSION

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.

Our 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. (7) in Spain noted hemarthrosis in 13 out of 35 joints studied, a 37% prevalence. It is noted that the study by Ceponis et al. 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 PLWH, and thus highlighting the severe burden hemophilia places on the patients as reported earlier in the study by Lorio et al. (3) 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 followup 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. (7) 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. (40) 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.

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 (38, 39).

Our study showed cartilage thinning was more prevalent in the elderly patients as compared to younger patients. , similar to findings by Kerr, R. (2) 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 out 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.

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.

During the scanning process, the soft tissues that are superficial were more readily detected and the soft tissues that lie deeper anatomically were not identified in most cases. For instance, the medial and lateral collateral ligaments, the medial and lateral menisci, the synovium and the patella ligaments were identified in 100% of the participants. This is similar to the findings in other studies using ultrasound for imaging of the knee joint (36) where the superficial structures were noted to be easily visualized. However, the anterior and posterior cruciate ligaments were not visualized in any of the patients scanned in our study, unlike in similar study by Lee et al. where the anterior cruciate and posterior cruciate were visualized to varying extents (36). The non visualization of the cruciate ligaments in this study was due to the Universal Simplified Protocol (USP) technique that was adopted for our study. The USP technique does not involve scanning in the central knee and popliteal region where the sonographic window for visualization of the cruciate ligaments exists. Instead, it involves 5

standard views customized to optimize the detection of more knee structures within the shortest time in clinical setup. (26) In addition, the pathological state of the scanned knees, especially pain and swelling, limited maneuverability of the knees thus limiting the proper sonographic window.

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 (37).

In conclusion, 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

1. 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.
2. The study, being clinic based, has limited generalizability to the general population.

RECOMMENDATIONS

3. 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 followup of patients with hemophilia is recommended.

4. 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.
5. Updating of local hemophilia patient followup 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.
6. A randomized controlled trial to be done in the future to compare the outcomes of early versus late clinical intervention in the identified knee pathologies with the aim of preventing the progressive loss of joint function among hemophilia patients in Kenya.
7. Establishing or improving the psychosocial support systems for patients living with hemophilia in view of the debilitating lifelong lifestyle adjustments they have to make while living with hemophilia.

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Appendices

APPENDIX 1 PARTICIPANT CONSENT INFORMATION.

Study Title: The utility of knee ultrasound in patients with hemophilia who present with knee pain or swelling at the hemophilia clinic in Kenyatta national hospital

Background of the study;

Hemophilia is a bleeding disease and the patients with this condition usually bleed into several regions of their body usually without any triggering accident. Knee joints are among the commonest places for such internal bleeding.

To diagnose the effects of this condition on joints, an expensive MRI scan is currently utilized. Sometimes X Rays are used. MRI is expensive and not readily available. X Rays involve ionizing radiation dose to the patient. Ultrasound has been proposed to be used instead. This is because it is safer, more easily available, cheaper, and does not involve any ionizing radiation.

Broad Objective of the study;

You are requested to take part in this study to ascertain the usefulness of ultrasound scanning of the knee joint in patients with hemophilia. The study aims to find out if ultrasound is able to identify the different changes in the knee joint that is caused by hemophilia in the local setting.25

This study has approval of The Kenyatta National Hospital-University of Nairobi Ethics and Research Committee protocol Number;

_____

Study Procedure;

What is ultrasound of the knee joint?

This is an imaging method that uses a special type of sound waves to show the pictures of the body and is able to show images of tissues deep inside the body.

The purpose of such imaging is to show any changes in the knee joint that is caused by hemophilia. These changes are common in people with hemophilia.

Does ultrasound have side effects or discomfort? No. The sound waves used are safe and do not cause any side effects. No discomfort is experienced during scanning.

What exactly will be done to me if I accept to participate in this study?

You will come to the hemophilia clinic at Kenyatta Hospital and your knee joints will be scanned by ultrasound. During this process, the knee joints will not be injured in any way since the scanning gadget is placed lightly on the skin. No blood samples are collected. No pricking is necessary.

This will be done by a qualified doctor. This takes less than 20 minutes to complete.

Voluntariness of participation; Each participant participates in the study out of their own will.

Will I have to pay? No payment will be required.

What will happen after the study? If any disease is noted in your knee during this study, you will be informed and advised on how to get medical attention.

What will happen to the images taken of my knees? Your name will not be recorded. That means no one will be able to relate you with the images. The information, including the images obtained will be kept confidential.

The images will be analyzed by experts to see if the technique is able to assess the knee joint well.

What benefits will I get for participating in this study? You will receive free testing through the ultrasound scanning of both of your knees. The condition of your knees will be explained to you. If any condition requiring medical attention is detected, you will be advised on what to do to get medical attention.

The results of the study will assist many patients who have hemophilia by improving their diagnosis and treatment in Kenya.

Rights of withdrawal: As a participant, you will have the right to withdraw your consent of participation at any time of your choice, without any negative consequence on your part.

Whom can I contact to answer any other question I may have about the study? You can contact Dr Dennis +0723731344 email obuondennis@gmail.com or KNH-UON ERC Secretary Contact telephone numbers 2726300 ext. 44102, email **uonknh_erc@uonbi.ac.ke**

APPENDIX 2.0 CONSENT FORM (STATEMENT OF CONSENT)

Form Number_____

I have read carefully the study information sheet or it has been read to me. I have understood the purpose of the study. I have had my questions about the study answered in a language that I understand. I understand that my participation is voluntary.

I do understand that I can withdraw my consent to participate in this study at any stage after agreeing to take part.

I understand that all the information I will give to this study, including the images of my knee that will be obtained, will be kept confidential.

I agree to take part in this study. (Tick appropriately).

Yes _____ No_____

I agree that images of my knees can be obtained by ultrasound scanning for the study.

Yes _____ No_____

Researcher's statement

I, the undersigned, have fully informed and explained all the necessary details of this study to the above-named participant. I believe the participant has now understood, is willingly and has freely given his/her consent.

Principal Investigator's Name: **Dr. Obuon Dennis Odiwuor** Contact +254723731344

Supervisors' names;

1. **Dr. Callen Kwamboka Onyambu**, Senior Lecturer, Department of Diagnostic Imaging and Radiation Medicine, University of Nairobi. Contact; +254721539987
2. **Dr. Christine Amo Mamai,** Senior Radiologist, Kenyatta National Hospital. Contact +254722939063

For more information contact Dr Dennis. 0723731344 email Obuondennis@gmail.com or KNH-UON ERC Secretary Contact telephone numbers 2726300 ext. 44102, email **uonknh_erc@uonbi.ac.ke**

APPENDIX 3.0 PATIENT CONSENT IN KISWAHILI

KIBALI CHA MGONJWA

NAMBARI YA FOMU___

Maelezo kuhusu Utafiti huu

Utafiti huu inafanywa na Dactari Obuon Dennis. Utafiti huu inachunguza jinsi ambavyo picha ya Ultrasound inaweza kutumika kupima magoti ya wagonjwa wanaougua Hemophilia. Wagonjwa wanaougua Hemophilia wanakuwa na matatizo ya viungo mbalimbali hasa magoti.

Maelezo ya jinsi utafiti utakavyofanywa

Utafiti huu itatumia kipimo cha picha ya ultrasound kuchunguza magoti yako. Ultrasound haina madhara yoyote kwa mwili. Pia, hakuna malipo yoyote utakayotozwa unapopimwa magoti katika utafiti huu.

Mimi, Dactari Obuon Dennis, nitakupima magoti kwenya utafiti huu. Kwa hivyo, naomba ruhusa yako ili nikupime magoti kutumia picha ya ultrasound, na pia kutumia majibu yatakayotokea kwenya utafiti huu.

Jinsi majibu yatakayowekwa siri

Majibu yako yatawekwa siri na jina lako halitaandikwa popote unapopimwa, ila nambari ya fomu pekee ndiyo itakayotumika.

Uhuru ya kujiondoa kutoka kwenye utafiti

Kwa sababu unashiriki kwenye utafiti huu kwa hiari yako, uko huru kushitisha kibali chako wakati wowote ukitaka kufanya hivyo.

Iwapo unakubaliana na hayo, tafadhali weka sahihi yako hapa;

Sahihi_____Tarehe_____.

Mimi, Dactari Obuon Dennis, Nakiri kwamba nimeeleza mgonjwa kuhusu utafiti huu na kwamba mgonjwa amekubali kwa hiari kushiriki kwenye utafiti huu.

Sahihi_____Tarehe_____

Iwapo kuna swali ama unahitaji maelezo zaidi, tafadhali wasiliana na;.

Mchunguzi Mkuu wa Utafiti huu: **Daktari. Obuon Dennis Odiwuor**

Nambari ya simu +254723731344 Barua pepe;Obuondennis@gmail.com

Msimamizi Mkuu wa Utafiti huu;

1. **Daktari. Callen Kwamboka Onyambu**, Idara ya Radiology, Chuo Kikuu cha Nairobi. Nambari ya simu; +254721539987

2. **Daktari. Christine Amo Mamai,** Daktari katika Idara ya Radiology, Kenyatta National Hospital. Nambari ya simu +254722939063

3. **Jopo la usimamizi wa uchunguzi ya kisayansi la Hospitali kuu ya Kenyatta na Chuo Kikuu ch Nairobi.** Sanduku la posta 20723-00200. Nambari ya simu 020-2726300 Ext 44102. Barua pepe;**uonknh_erc@uonbi.ac.ke**

APPENDIX 4 DATA COLLECTION FORM

THE UTILITY OF KNEE ULTRASOUND IN PATIENTS WITH HEMOPHILIA WHO PRESENT WITH KNEE PAIN OR SWELLING AT THE HEMOPHILIA CLINIC IN KENYATTA NATIONAL HOSPITAL

Patient Study Number	

Patient Demographic data;

atient Age		
Sex;	01. Male	02. Female
ccupati on	01. Self employed 02. Formally employed 03. Not employed	
atient's signs and sympto ms	01. Knee joint pain 02. Knee joint swelling 03. Knee joint; reduced range of motion 04. Knee joint; Redness and warmth around the joint	

nee Ultraso und finding

Synovium	01 Normal	02 Hypertrophied	03 Hyperemic
Simple Joint effusion	1 Absent	02 Present	
Hemarthrosis	1 Absent	02 Present	
Periarticular skin edema	1 Absent	02 Present	

	Articular Cartilage erosion	1 Absent	02 Present
	Articular Cartilage thinning	1 Absent	02 Present
	Articular Cartilage Hyperechogenicity	1 Absent	02 Present
	Medial meniscus Tear	1 Absent	02 Present
	Lateral meniscus Tear	1 Absent	02 Present
	Anterior Cruciate ligament Tear	1 Absent	02 Present
	Posterior Cruciate ligament Tear	1 Absent	02 Present
	Bone erosion	1 Absent	02 Present
	Subchondral Cyst	1 Absent	02 Present
	Osteophytes	1 Absent	02 Present
	Tendinitis of adjacent tendons	1 Absent	02 Present

Resubmission P604/11/2020

RECEIVED
27 JAN 2021

THE UTILITY OF KNEE ULTRASOUND IN PATIENTS WITH HEMOPHILIA WHO PRESENT WITH KNEE PAIN OR SWELLING AT THE HEMOPHILIA CLINIC IN KENYATTA NATIONAL HOSPITAL

DR. OBUON DENNIS ODIWUOR
H58/7459/2017

DISSERTATION SUBMITTED AS A PART FULFILLMENT OF MASTER OF MEDICINE DEGREE IN DIAGNOSTIC IMAGING AND RADIATION MEDICINE, UNIVERSITY OF NAIROBI

January 2020

KENYATTA NATIONAL HOSPITAL
14 JAN 2021

Cover Letter: Second submission of Proposal to KNH-UON ERC.

I have carefully studied the corrections suggested by the ERC and I have made the following corrections to my proposal.

Comment from ERC	Error	Correction made	Page number of the correction
1. Title page-Include your student registration Number.	Missing student registration number	Student registration number has been Inserted.	Page 1
2.Take note that the abstract is not complete without subsection on ; • **Data management** • **Expected main outcome measure(s)**		Data management subsection added. Expected main outcome measure included.	Page 12 Page 12
3. Pay attention to the remarkable grammatical and typographical errors throughout the text.			

Error	Correction(s) made	Page
…hemophiliac clinic	…hemophilia clinic	11
…Currently, improved life expectancy has been observed due to improved health care for PLWH (3)	…Currently, improved life expectancy has been observed due to improved health care for PLWH. (3) (full stop added)	13
…, Subchondral cysts, premature physeal closure,…	…, subchondral cysts, premature physeal closure… Capital S replaced with small s.	17
Tibiofemoral	tibio-femoral	20
Patellofemoral	Patello-femoral	20
Skin- Appears hypo echoic thin layer.	**Skin**- Appears as hyper echoic thin layer.	21

KENYATTA NATIONAL HOSPITAL
APPROVED
15 FEB 2021
KNH/UoN-ERC

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15th February 2021

Dr. Obuon Dennis Odiwuor
Reg. No.H58/7459/2017
Dept. of Diagnostic Imaging and Rad. Medicine
School of Medicine
College of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL * APPROVED 15 FEB 2021 KNH/UoN-ERC P. O. BOX 20723 - 00202 NAIROBI *

Dear Dr. Odiwuor

RESEARCH PROPOSAL – THE UTILITY OF KNEE ULTRASOUND IN PATIENTS WITH HEMOPHILIA WHO PRESENT WITH KNEE PAIN OR SWELLING AT THE HEMOPHILIA CLINIC IN KENYATTA NATIONAL HOSPITAL (P604/11/2020)

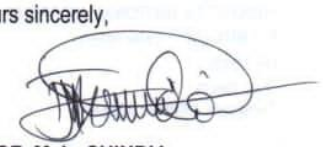
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 15th February 2021 – 14th February 2022.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
g. Submission of an *executive summary* report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

For more details consult the KNH- UoN ERC website**http://www.erc.uonbi.ac.ke**

Yours sincerely,



PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

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The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Diagnostic Imaging and Rad. Medicine, UoN
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