University of Nairobi

PREVALENCE OF MUSCULOSKELETAL COMPLICATIONS AMONG HEMOPHILIA PATIENTS AS SEEN AT KENYATTA NATIONAL HOSPITAL

A STUDY SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN ORTHOPAEDIC SURGERY, UNIVERSITY OF NAIROBI

By

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H58/68341/2011

2019

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I declare that this dissertation is my original work under the guidance of my supervisors and has not been presented for a degree course in the University of Nairobi or any other university.

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This is to certify that the study was undertaken under my guidance and supervision and that this book is submitted with our approval as the University Supervisors.

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DEDICATION

I dedicate this work to God the almighty for his bountiful Graces, and my family for their continued support and encouragement.

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LIST OF ABBREVIATION

ADL – Activities of Daily Living

FVII - Factor VII

FIX - Factor IX

HTC - Hemophilia Treatment Center

KHA - Kenya Hemophilia Association

KNH - Kenyatta National Hospital

MRI - Magnetic Resonance Imaging

PLWH - Patient Living With Hemophilia

ROM - Range of Movement

SES - Social Economic Status

SPSS - Statistical Package for Social Sciences

WFH - World Federation of Hemophilia

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OPERATIONAL DEFINITIONS

1.	Hemophilia	A hereditary coagulopathy that is characterized by quantitative or qualitative deficiency of coagulation protein factors VIII and IX.
2.	Musculoskeletal complications	Conditions that develop in the muscles, bones, and joints as a result of repeated bleeding episodes within these structures. They include hemarthrosis, Muscle hematomas, Pseudotumors, Pathological fractures, and Peripheral nerve palsy.
3.	Aid to ambulation	Any device utilized in assisting a patient to move about as they carry out activities of daily living.
4.	Household income	Sum total of money received by economically active individuals in the family.

1 ABSTRACT

Background

Hemophilia is an X-linked heritable coagulopathy that is characterized by quantitative or qualitative deficiency of protein factors VIII and IX. Musculoskeletal manifestations are common in hemophilia patients, accounting for 70-80% of hemorrhages in severe hemophilia. These bleeds are usually of childhood onset, either as spontaneous or trauma induced hemorrhagic episodes, and may progressively lead to musculoskeletal complications with significant chronic disability, morbidity and reduced quality of life. This necessitates frequent need for restorative physical therapy and orthopedic surgical procedures. In Kenya 654 people are registered as living with Hemophilia with 81.8% having Hemophilia A and 18.2% Hemophilia B. However there is paucity of information in regard to the prevalence and pattern of musculoskeletal manifestations and complications in this population.

Study objective: To determine the prevalence and pattern of musculoskeletal complications in hemophilia patients visiting Kenyatta National Hospital.

Study Design: Descriptive Cross-sectional study.

Study Setting: Kenyatta National Hospital hematology outpatient clinics and Wards.

Materials and method: A sample of 37 hemophilic patients visiting KNH were recruited into the study. For each patient clinical history and examination was undertaken to establish presence or history of musculoskeletal complications i.e. Hemarthrosis, Arthropathy, Muscle hematoma, Pathological fracture, Pseudotumor, and Nerve palsy. Evaluation of affected joints was carried out based on the Gilbert Joint Scoring System. All the data was entered in the data collection sheet and later transferred to a secure database.

Statistical analysis: Data was analysed using Statistical Package for Social Sciences version 24. Descriptive statistics methods were utilized to analyze quantitative variables. Pearson's *r* correlation technique was used for empirical relationship between variables. Statistical significant p-value of 0.05 and 95% confidence level was used. Data was presented in tables and graphs.

Results: All 37 patients were males. 91.9% had Hemophilia A and 8.1% had Hemophilia B. The average age was 21.5 (SD=13.9) years with the youngest being 5 years old and the oldest 61 years old. The average age at the time of diagnosis was 2.7 (SD=2.8) years with 56.7% diagnosed within the first

year of life. 70.3% had severe hemophilia while 29.7% had moderate hemophilia. 97% of the patients presented with various orthopedic manifestations. 86.5% of the patients reported recurrent hemarthrosis, 75.7% had loss of Range of Motion in various joints, and 70.3% had fixed flexion joint contractures occurring in single or multiple joints. 67.3% reported history of muscle hematoma. One patient had a fracture and none were found to have peripheral nerve palsy or pseudotumor. There was a significant association between the reported hemophilia severity levels and the Global Joint Score (p value = 0.001) and between the frequency and severity of joint bleeds and Global Joint score (p value = 0.001). There was no significant relationship between the age at diagnosis of the patient and the Global Joint Score (p value = 0.575), and the household income level and the Global Joint Score (p value = 0.603).

Conclusion: The study demonstrated a wide prevalence of various orthopaedic complications in hemophilia patients visiting KNH. There was a significant association of severity of orthopaedic complications and the prevailing severity of disease. Therefore there is need for prophylactic factor replacement therapy and early involvement of orthopaedic surgeons in management and follow up of hemophilia patients.

2 BACKGROUND

2.1 INTRODUCTION

Hemophilia is a hereditary coagulopathy that is characterized by quantitative or qualitative deficiency of coagulation protein factors VIII and IX. Hemophilia A is as a result of Factor VIII deficiency and Hemophilia B as a deficiency in Factor IX. This deficiency predisposes to spontaneous or injury associated bleeds into soft tissues, joints, peritoneum, and brain [1].

It is an X-linked recessive disorder with females ordinarily presenting as asymptomatic carriers though they may rarely present with moderate to severe disease. As many as 30% of hemophilia cases arise from spontaneous mutations. In severe hemophilia A, a large inversion and translocation defect has been found affecting F8 gene while in hemophilia B, more than 2100 point mutations have been found affecting F9 gene [1, 2].

Worldwide the prevalence of the disorder is estimated to be 1/10,000 male births with Hemophilia A having a higher prevalence i.e. 80–85% of the total hemophilia population. World Hemophilic Federation's annual global surveys indicates that globally there are approximately 400,000 people living with hemophilia. According to the 2016 WFH Global Survey, Kenya has a total of 654 Kenyans registered as living with hemophilia, of which 535 have Hemophilia A and 119 have hemophilia B [3].

Severity of the disease is classified based on the serum levels of coagulation protein factors. In severe disease the clotting factor serum level is less than 1%, moderate form 1-4%, and mild form 5-25% of normal serum levels. The serum level of coagulation factors has a direct correlation with the regularity and severity of various bleeding episodes [2].

Musculoskeletal manifestations are common in hemophilia patients. Hemarthrosis is the commonest accounting for 45-70% of hemorrhages. When recurrent it predisposes to the development of chronic synovitis, joint flexion deformities, and hemophilic arthropathy [2]. Bleeding in the muscles, accounting for 10-25% of bleeds, predisposes to hematoma formation which if inadequately treated causes pressure effects to the adjacent neurovascular structures and may organize to form pseudotumors. Pseudotumors within bone predispose to pathological fractures [4, 5].

The principle for management of hemophilia patients involves reducing the incidence of bleeding episodes into joints and muscles. This is primarily achieved by replacement therapy with recombinant

clotting factor or with blood products. Prophylaxis with intravenous recombinant clotting factor concentrates is also key in preventing bleeds. Other prevention modalities include avoidance of contact sports, maintenance of a healthy body, and regular exercise to strengthen muscles [6].

In spite of these interventions musculoskeletal functional disability, as a result of recurrent bleeds, remain one of the most devastating problem and contribute heavily to the reduction in quality of life of hemophilia patients. Therefore there is need for continuous orthopedic interventions in the care of hemophilia [7].

Currently in Kenya there is no literature describing the prevalence and pattern of musculoskeletal manifestations of hemophilia patients. This data is salient in filling the knowledge gap on the level of musculoskeletal morbidity, and the effect on quality of life. The main purpose of this study is to determine the prevalence and pattern of musculoskeletal complications in this group of patients.

2.2 LITERATURE REVIEW

2.2.1 HISTORY OF HEMOPHILIA

The earliest recorded incidences of abnormal bleeding patterns were captured as from the 2nd century AD in Jewish rabbinical writings on laws and traditions. Various rulings were done then allowing baby boys with brothers who had previously died from bleeding after circumcision, to be exempted from that tradition. In the 10th century, Abu Khasim, an Arabian physician, is recorded describing families associated with male deaths from excessive bleeding after trauma. In an article published in 1803, John Conrad Otto, described a similar hereditary bleeding disorder that would primarily affect men and be traced back to their female ancestry. This hereditary disease would later be described as 'Hemophilia' by Dr. Schonlein and Friedrich Hopff at the University of Zurich. In 1947 Dr. Alfredo Pavlovsky described Hemophilia A and Hemophilia B. Between 1920 and 1960 several coagulation factors would be described by various scientists and given Roman letters as defined to date. Hemophilia has also been referred to as a "royal disease" since Queen Victoria of England (1837-1901) was believed to have been a carrier of hemophilia B and passed the disease to the ruling families of Russia, Spain, and Germany [8].

In 1979 Kenya Hemophilia Association was formed in response to several incidences of bleeding disorders and associated challenges in the management of these patients. KHA serves as the official Kenyan patient organization, recognized by World Federation of Hemophilia, and takes charge of representing the rights of all patients living with Hemophilia. It collects country-level data on the epidemiology of hemophilia, maintains the National Register, and coordinates the care of Hemophilia patients through Hemophilia Comprehensive Care Clinics at Kenyatta National Hospital, Moi Teaching and Referral Hospital Eldoret, Coast General Hospital, and recently Murang'a County Hospital. Other associations have also been formed to assist families with persons living with hemophilia e.g. Jose Memorial Hemophilia Society of Kenya.

2.2.2 EPIDEMIOLOGY

The worldwide prevalence of hemophilia is estimated to be about 1 in 5,000 live male births without any distinction of any race or geographical region. Hemophilia A prevalence is approximately 1 in 10,000 males, while Hemophilia B is approximately 1 in 35,000 males. Prevalence rates vary from country to country with lower prevalence rates being reported in lower income countries as compared to higher income. This is thought to be due to differences in Health budgetary allocations thus affecting resource availability in diagnosis and management of people living with hemophilia. Lower income

countries tend to focus most of their resources to public health issues affecting larger portions of the population [9]. Household Social Economic Status also tend to affect health seeking behavior since low SES household spending most of their income on food. Reported data from WFH Global Surveys show an overall worldwide progressive increase in prevalence of Hemophilia through the years though some countries are still recording low numbers of what is expected. The prevalence in Kenya is approximately 2.1/10,000 with 654 males having been identified and registered as people living with Hemophilia [3]. This accounts for only 14.5% of what is expected. However there is no record of whether the number accounts for deaths within that period.

Clinical presentation usually depend on the severity and chronicity of the disease, with the severity of disease having a direct correlation with the frequency and severity of bleed. In individuals with severe hemophilia, the first hemarthrosis commonly occur early in childhood [10]. In a 2002 study conducted in Western Cape, South Africa, 49 patients were evaluated of which 76% had Hemophilia A and 24% had Hemophilia B. 43% had severe form, 29% moderate, and 22% mild form. The mean age at diagnosis was 9 months in severe cases, 11 months in moderate cases, and 21 months in mild cases. They also found 73% of the patients to be on On-Demand replacement therapy and in the group 50% had functionally restricted joints. 20% were on periodic prophylaxis because of repeated bleeding episodes and in the group only 20% had restricted joint functionality. The remaining 7% were on continuous prophylaxis. Overall 43% of the study population were found to have joint functionality restriction. However the form and severity of the restriction was not characterized and no other forms of musculoskeletal complications were studied. This study also demonstrated the positive effect of periodic prophylaxis on joint functionality [11].

In 2014, S. Diop et al, in a cohort study of 140 patients analyzing the Senegalese 18 year experience in management of Hemophilia, established a prevalence rate of 2.3/10,000 male birth. Of the total study population 90.7% had Hemophilia A while 9.3% had Hemophilia B. Severe hemophilia accounted for 52.1%, moderate 24.2% and mild for 23.5% of hemophilia patients. They also demonstrated the mean age at diagnosis to be 4.9 years in severe hemophilia, 5.3 years in moderate form and 8 years in mild forms. This is still high as compared to developed countries which occur at an average of 1.6 years. On assessment of the musculoskeletal system they found that 36.5% had joint disabilities with more joint morbidity being recorded in those above 20 years [12].

In 2015, in a single center study involving 30 Egyptian boys (6-16years) with hemophilic arthropathy, Hayam et al found that 86.7% of the study population had hemophilia A and 13.3 % Hemophilia B. The mean age of first hemarthrosis in severe hemophilic patients was 2.22 ± 1 years with a range of 0.5 to 4.0 years. 50% of the studied hemophilic patients had severe hemophilia, 23.3% had moderate, and 26.7% had mild hemophilia. It was found that 73.3% of the cases were affecting the knee joint, 16.7% the ankle, 6.7 % the elbow, and 3.3% the shoulder joint. On clinical evaluation of the joints with Gilbert score, they found a significant inverse relationship between the global joint score and the level of serum factor. [13].

The prevalence of hemarthrosis is thought to be approximately 70-80% of all bleeds with the frequency varying from one joint to another. It is estimated that by the third decade of life approximately 85-90% of patients will develop chronic degenerative changes in at least one of the major joints [14, 15]. The most commonly affected joint is the knee joint, followed by the elbow, ankle, shoulder, wrist, and hip joints respectively (45%, 30%, 15%, 3%, 2%, and 2%) [2]. Similar result were found by Hayam et al in his study on thirty boys with hemophilic arthropathy, 73.3% of the cases were affecting the knee joint, 16.7% the ankle, 6.7 % the elbow, and 3.3% the shoulder joint [13]. However, in a multicenter study done in the UK, Stephensen et al found a change in the pattern of joint bleeds in adolescents and young adults whereby ankle joint bleeds were more common as compared to other joints. This was a self-reported cohort study of 100 patients whereby 42.7% of the bleeds were found to occur in the ankle joint, 20.7% in the elbow, 19.6% in the knee, 3.9% in the shoulder, 3.7% in the hip, and 2.4% in the wrist joint [16]. Aznar JA et al, in a 2009 study in Spain, demonstrated a similar pattern where the ankle joint was the most affected joint at 20%, the knee at 19%, the elbow at 17%, and the hip at 1.7% [17].

In severe Hemophilia, it is reported that 10–25% of all bleeds occur in muscles with the majority occurring in iliopsoas, quadriceps, and calf muscles in that order. They commonly occur after trauma but may also occur spontaneously. The clinical presentation is dependent on the severity of disease, the muscle involved, plus the muscle size and its fascial confines [18]. In 2010, Beyer et al conducted a cross sectional survey in five European countries where they found that most (approximately 71%) of muscle hematomas were associated with trauma. 55% were found to be occurring in iliopsoas muscle, 18 % in calf muscles, and 18% in thigh muscles [19]. On the other hand hemophilic

pseudotumors are rare complications and have been reported to occur in about 1–2 % of patients with severe hemophilia [20].

The incidence of osteoporosis and fractures has been demonstrated to be significantly higher in hemophiliacs when compared to the normal population. In 2007, in a case control study involving 50 patients, Nair AP et al demonstrated this after finding a significantly higher incidence of osteoporosis and fractures in adult patients with hemophilia as compared to controls (12% compared to 0%). There was significant osteoporosis at the Lumbar spine (50% of the patients), at intertrochanteric area (38% of the patients), and at hip (32% of the patients) [21]. Lee et al, in a cohort of 11 patients with fracture neck of femur, demonstrated that most of femoral neck fractures associated with hemophilia occur almost two decades earlier than in normal population [22].

Peripheral nerve palsies associated with hemophilia are not uncommon. They commonly result from compressive injuries by hematomas or pseudotumors. Most affected nerve is the femoral nerve then the median, ulnar, sciatic, and radial nerves respectively but it can also involve cervical roots, lumbar and sacral plexus [23]. In a study conducted in India, Saraf et al found that 15% of the 134 patients had different forms of nerve palsy. Majority of them involved the femoral nerve (75%) then the sciatic nerve (20%) and peroneal nerve (5%). Femoral nerve palsy was linked to iliac and inguinal hematoma, sciatic nerve palsy to gluteal hematoma, and peroneal nerve palsy to calf hematoma [24].

In 2007 Kar et al conducted a multicenter study in India and demonstrated that physical disability was widely prevalent in people living with hemophilia. 93.9% (139/148) of patients with severe hemophilia A had physical disability. Physical disability was measured by considering three parameters: general mobility status, functional ability, and joint range-of-motion. The severity of disability had a significant correlation with the patient's family income level indicating that presence and severity of disability would be more prevalent in the low income families [25].

Due to the efforts made in establishing Hemophilia comprehensive care centers and availing factor concentrates, the quality of life and life expectancy of hemophiliacs has progressively improved. For instance, in Belgium, about 44% of persons with hemophilia are more than 45 years old while in Kenya about 13% are more than 45 years old [3].

2.2.3 PATHOPHYSIOLOGY

Hemostatic process

The clotting process occurs in four phases; platelet plug formation, the coagulation cascade, termination of clotting process, and removal of the clot by fibrinolysis. The coagulation cascade ensures formation of a stable fibrin clot at injury sites. It is characterized by the sequential activation of a series of inactive precursor proteins to active enzymes, resulting in significant stepwise response amplification. This occurs in either the intrinsic pathway or the extrinsic pathway. Both are initiated by different independent mechanisms with intrinsic pathway being initiated by exposure to a platelet surface or a foreign surface, while the extrinsic pathway is initiated by tissue factor exposed at the injury site. Convergence occurs on the activation of factor X. Prothrombin is then converted to Thrombin by activated Factor X. This is followed by Thrombin converting fibrinogen to a fibrin clot [Guyton & Hall Textbook of Medical Physiology 11th Edition].

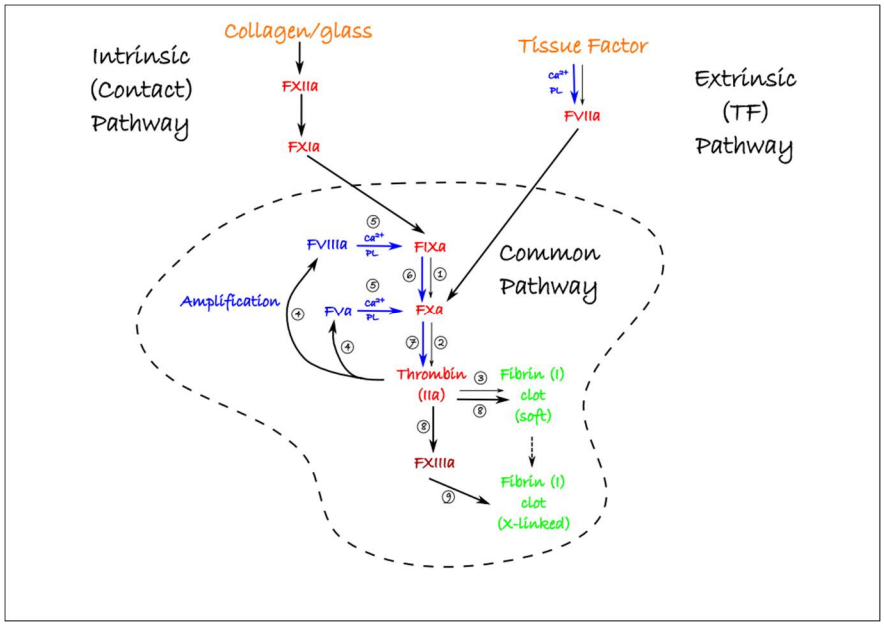


Figure 1: Coagulation pathways (adapted from http://www.nataliescasebook.com/tag/blood-coagulation)

In the intrinsic pathway Factor VIII is key in activation of Factor X, this enzyme that pivotal in the conversion of fibrinogen to fibrin. Therefore, the deficiency or lack of Factor VIII will significantly affect the quantity or quality of the formed clot and may result in bleeding. It is thought that joints and muscles lack tissue factor thus have a significantly higher chance of intra-articular bleeding in hemophilia [26].

Arthropathy

Hemarthrosis leads to changes in three joint structures; synovial tissue, cartilage, and bone. In the synovial tissue it brings inflammatory changes, in the cartilage degenerative changes, and changes to the subchondral bone.

One of the function of synovial tissue is to remove waste products, including blood, by the action of tissue macrophages. However removal of large amounts of blood will trigger an inflammatory process resulting into hypertrophy and hyperplasia of synovial cells and increased vascularization of the sub-intima. Progressively the inflammation cause fibrosis of the synovial tissue. At the same time hemosiderin, which accumulates within the synovial tissue and cartilage, trigger another additive inflammatory response through production of tumour necrosis factor (TNFα) and interleukins (IL-1, and IL-6). Iron has been shown to also have a proliferative effect on synovial cells. It induces expression of the pro-oncogene MYC (c-myc), which is known to cause hyperplasia of synovial tissue, and expression of mdm2 gene (that may bind to the tumour-suppressor p53) thereby inhibiting apoptosis of synovial tissue. Thus the synovium becomes more sensitive to microtrauma due to the increased likelihood of being impinged between the articular surfaces and causing further bleeding [27].

Articular cartilage damage arises from direct exposure to blood and through synovium-associated inflammation. In vitro studies with human articular cartilage have shown that exposure of articular cartilage to blood leads to inhibition of the proteoglycan synthesis rate in the cartilage matrix. This inhibition can last up to 10 weeks after exposure even to small amounts of blood. The prolonged effects are due to chondrocyte-associated apoptosis. It is hypothesized that the apoptosis is induced by hydroxyl radicals which are formed by the reaction of catalytic iron and H_2O_2. H_2O_2 is produced by chondrocytes as an effect of the pro-inflammatory cytokines produced by activated macrophages. Therefore recurrent joint bleeds provoke an arthropathy with both inflammatory and degenerative joint disease characteristics [28].

There is also effect on the subchondral bone. In children recurrent hemarthrosis will cause enlargement of the epiphysis and growth disturbance. It will also contribute to formation of osteophytes, bone erosions, osteoporosis, and subchondral cysts [28]. It is thought that the reason why most of the bleeding occur in the ankle, knee, and elbow joints is because these joints have convex-concave surface

articulations. These may face significant constraints during rotation thus increasing the chance of impingement of the enlarged synovium [26].

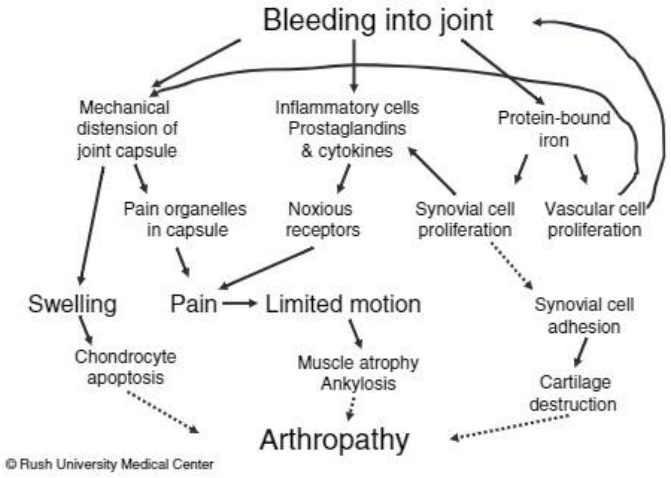


Figure 2: General scheme of the pathogenesis of hemophilic arthropathy (adapted from Lafeber et al, 2008)

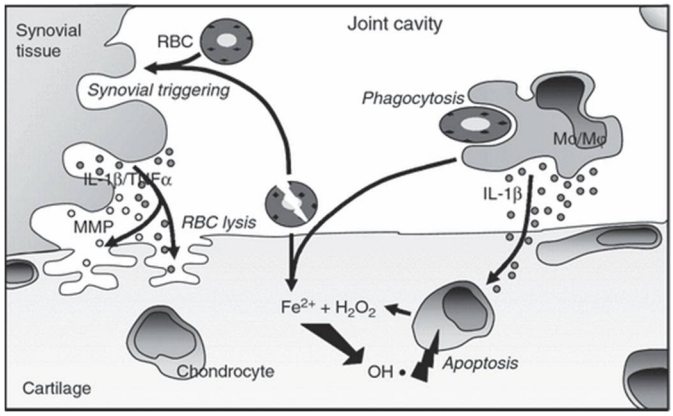


Figure 3: Mechanism of blood induced arthropathy (adapted from Jansen et al, 2008)

Muscle hematoma and other complications

Muscle hematomas typically occur as a result of trauma [19]. In the lower limb the commonly affected muscles are iliopsoas, quadriceps, and gastrocnemius-soleus muscles respectively while in the upper limb the deltoid and forearm flexors [26]. When a bleed occurs in muscle, an intact muscle fascia restricts expansion of the hematoma. A tender swelling in the muscle develops and progressively protective spasm will result. This will then cause severe pain, flexion of the adjacent joint, and reduction in the range of movement. As it expands the hematoma will strip off the neurovascular bundles causing muscle fiber ischemia. Eventually muscle necrosis will occur. The expanding

hematoma also causes excessive pressure to the surrounding tissues. In the process of healing the injured muscle, fibrous scar tissue replaces muscle fibers, eventually affecting overall muscle contractility and flexibility. This will result to shortening thus risk of contracture formation. Without spontaneous resolution or effective treatment several complications may occur: excessive blood loss, compartment syndrome, irreversible damage to muscles, muscle necrosis, Volkmann's ischaemic contractures, infection, myositis ossificans, nerve compression, and formation of hemophilia pseudotumours. [29]. Clinical presentation varies with the size, location, and duration of the hematoma. Large hematomas are associated with increased risk of complications while the most critical sites are those that have a risk of compromising neurovascular function. For instance iliopsoas muscle bleed will compromise the femoral nerve, gastrocnemius muscle will cause tibial nerve injury leading to equinous foot deformity, or forearm flexor muscles injury will cause Volkmann's ischemic contracture [29]. Beyer et al demonstrates this in a survey whereby, on comparison of different anatomical localizations of muscle hematomas, the responding surgeons classified iliopsoas (55%), calf (18%) and thigh (18%) bleeds as the most serious. Similarly they found that 71% were associated with trauma and would present as contusions or strains [19].

Pseudotumors result from progressive sub-periosteal or soft tissue hemorrhage resulting into pressure necrosis of bone and pressure to the surrounding structures. They usually present as painless slowly expanding mass. There are three types of pseudotumors; Type I which occurs in the soft tissue, Type II occur in the sub-periosteal region, while Type III occur in bone. Type III is further classified either as proximal type (occurring in long bones and pelvis) or as distal type (occurring in small bones). The resultant bone lesion compromise bone morphology and predispose the bone to pathological fractures [20, 30].

Osteoporosis and pathological fractures are also associated with hemophilia. It is thought that due to bleeds and arthropathy patients with hemophilia have a high likelihood of prolonged immobilization and limitation in weight bearing activities which affect bone mineralization. This puts them at risk of developing disuse osteoporosis and the complications therein. Osteoporosis can occur both in the axial and appendicular skeleton but commonly occur in the spine, hip and the intertrochanteric region [31].

Hemophilia patients are also at increased risk of fractures due to poor musculature, hemophilic changes in the bone, and osteoporosis [22]. Peripheral nerve palsies are as a consequence of; compressive

injury by hematomas and pseudotumors, scarring around nerves, or vasa nervorum compressive injuries [24].

2.2.4 CLINICAL EVALUATION

When conducting clinical evaluation of patients with hemophilia it is important to routinely perform a complete clinical assessment (history and examination) of the musculoskeletal system. This evaluation is useful in making diagnosis of acute or chronic musculoskeletal conditions and in making treatment plans. It involves clinical evaluation of pain, bleeds, joints, muscle tone, gait, motion, and functional level of disability [26].

Several clinical scores have been developed for use in the musculoskeletal evaluation of hemophilia patients. The most widely used joint scoring systems are the WFH Physical Examination Score (Gilbert Score) and the Hemophilia Joint Health Score (HJHS).

i. The WFH Physical Examination Score (Gilbert Score) was developed by Gilbert MS and the Orthopedic Advisory Committee of the WFH for use in clinical evaluation of joints [2]. It involves evaluation of 6 index joints (ankles, knees, and elbows), while scoring them based on four parameters; pain, bleeding, physical examination, and radiological features. Physical examinations assesses the following key functional and structural features: joint swelling, atrophy of the muscles, axial deformity, presence of crepitus on motion, limitation of joint Range Of Motion, presence of flexion contractures, and instability of the joint (Figure 4). The score range varies with the parameter assessed: from score of Zero to 3 for Pain, 3 for Bleeding, 12 for Physical examination, and 13 for radiological examination [32]. It is more reliable in evaluation of patients with extensive arthropathy, since it allows the possibility of having a systematic clinical examination and shows adequate ability to discriminate between known groups of patients. However one of its primary shortcoming is that it is less reliable and sensitive to smaller changes in early joint disease [33].

Physical finding	Score	Scoring key
Swelling	0 or 2 + (S)	0 = none 2 = present (S) if chronic synovitis is present
Muscle atrophy	0–1	0 = ⩽ 1 cm 1 = present
		Axial deformity: measured on knee and ankle only
Knee	0–2	0 = 0–7° valgus 1 = 8–15° valgus or 0–5° varus 2 = > 15° valgus or > 5° varus
Ankle	0–2	0 = No deformity 1 = < 10° valgus or < 5° varus 2 = > 10° valgus or > 5° varus
Crepitance on motion	0–1	0 = none 1 = present
Range of motion	0–2	0 = loss of < 10% of total full range of motion (FROM) 1 = loss of 10–33 1/3% of total FROM 2 = loss of > 33 1/3% of total FROM
Flexion contracture	0 or 2	0 = < 15% fixed flexion contracture 2 = ⩾ 15% fixed flexion contracture at hip or knee or equinus at ankle
Instability	0–2	0 = none 1 = present but neither interferes with function nor requires bracing 2 = instability that creates a functional deficit or requires bracing
Total	0–12 0–10	Ankle or Knee Elbow

Figure 4: WFH Physical Examination Score [32]

ii. The Hemophilia Joint Health Score (HJHS) was developed to address the shortcomings of WFH examination score. It is used to measure joint impairment and monitor joint change over time and assess efficacy of treatment regimen in children with mild joint impairment receiving prophylactic or on demand therapy. It was originally developed for patients aged 4-18 years but has also been found useful in the adult population [34].

2.2.5 RADIOLOGICAL EVALUATION

The conventional imaging modalities used in evaluation and diagnosis of any musculoskeletal complications are radiography, sonography, Computed Tomography, and Magnetic Resonance Imaging. Radiography is the standard for diagnosis of moderate to severe hemophilic arthropathy, in therapeutic planning, and in follow up of the progression of arthropathy [35]. On the other hand MRI is the most accurate modality for assessing musculoskeletal complications since by offering multi-tissue imaging it is able to reveal most musculoskeletal lesions. It is particularly useful for identifying early lesions, enabling early and aggressive management strategies [36]. Ultrasonography, which is a radiation-free modality, is useful in the assessment of soft tissue swellings. It is also useful in minimally invasive procedures such as joint aspirations or injections. Thus it has a big role as a complementary modality in the evaluation and management of haemophilic arthropathy [37].

2.2.6 MANAGEMENT OF COMPLICATIONS

The principle of management of hemophilia patients involves reducing the incidence of bleeding episodes and thus associated complications. This is primarily achieved by replacement therapy with recombinant clotting factor or with blood products [6]. In early management of acute bleeding there is need to combine immediate factor replacement therapy with adjunct modalities i.e. the RICE (Rest, Ice, Compression, and Elevation) regime and, in certain cases, joint aspiration. The recommended dose for intravenous on-demand Factor VIII replacement therapy is 25-40 IU/kg and in severe cases up to 50 IU/kg. It is recommended that factor is administered within 2 hours of bleeding onset and repeated every 12 hours. Treatment should continue until FVIII plasma level of 80 - 100% for major bleeds and 40 - 60% for minor bleeds is achieved or until resolution of pain and recovery of function. Cryoprecipitate and Fresh Frozen Plasma have also been used where factor concentrates are unavailable [38].

Primary and secondary prophylaxis with clotting factor concentrates has been shown to be efficacious in prevention of bleeds and in preservation of normal musculoskeletal function. It is recommended as part of the standard care and should be started as early as possible [39].

Physiotherapy plays a key role in preservation of joint movement and function. It is also useful in joint rehabilitation as it ensures restoration and maintenance of muscle strength and joint ROM. Muscle strengthening program should start with isometric contractions then concentric exercises. Specific individualized course of exercises should be designed and carried out in a stepwise fashion [40].

Synovectomy is recommended when joint bleeding and chronic synovitis are poorly controlled with prophylaxis. It is useful in prevention of progression of hemophilic arthropathy to end-stage arthropathy. Three methods of synovectomy are available i.e. chemical synovectomy (Rifampicin or Oxytetracycline), radiosynovectomy (yttrium, dysprosium, rhenium, or phosphorus), and surgical synovectomy (open or arthroscopic) [41].

Surgical orthopaedic procedures that may be performed in the management of hemophilia patients include open or arthroscopic synovectomy, arthrocentesis, fasciotomy for compartment syndrome, tendon lengthening, alignment osteotomies, nerve releases, arthroscopic joint debridement joint arthrodesis, joint arthroplasty, resection or percutaneous treatment of pseudotumours, and osteosynthesis of fractures.

A multidisciplinary approach, between hematologists, orthopaedic surgeons, rehabilitation physicians and physiotherapists, is essential in ensuring surgical success. These surgeries should be carried out where there is adequate availability of replacement therapy, experienced surgeons, and a supportive HTC that is capable of managing and adapting to optimum replacement therapy [42].

CONCLUSION

1. Musculoskeletal complications are common in people living with hemophilia. There are no local studies that have evaluated the prevalence and pattern of musculoskeletal complications.
2. After hemarthrosis, intra-articular hemosiderin and iron play a central role in bringing inflammatory changes to synovial tissue, degenerative changes to intra-articular cartilage and subchondral bone. Delay in resolution or an expanding muscle hematoma is associated with various other musculoskeletal complications e.g. pseudotumors, nerve palsies.
3. Factor replacement therapy reduces incidences of bleeding thus effective in preservation of normal musculoskeletal function. Factor replacement therapy is expensive.
4. Early detection and intervention of musculoskeletal complications is a priority in care of hemophilia patients necessitating early involvement of orthopedic specialists in clinical evaluation and management.

2.3 STUDY JUSTIFICATION

Early detection and intervention for musculoskeletal disability is a priority in care of hemophilia patients. In order to optimize effectiveness of available treatment guidelines, a strategic plan for comprehensive management of hemophilia patients and resource allocation needs to start with mastery of local disease patterns. However in our local setup there are no local epidemiological studies carried out to establish the burden of these musculoskeletal complications. At the same time orthopedic specialists usually get involved in the management of hemophilia patients quite late in the disease process.

This study aims at determining the prevalence, and pattern of musculoskeletal complications in hemophilia patients visiting Kenyatta National Hospital. This information will be useful in establishing need for orthopaedic care in clinical management of hemophilia patients, act as a baseline for follow up, and guide further orthopedic interventions for patients involved in the study. The study outcome will be useful in increasing awareness among clinicians and help in policy formulation towards clinical management of hemophilia patients especially when focusing on orthopedic interventions.

2.4 STUDY QUESTION

What is the prevalence and pattern of musculoskeletal complications seen in hemophilia patients visiting Kenyatta National Hospital?

2.5 STUDY OBJECTIVES

2.5.1 Main objective

To study the prevalence and pattern of musculoskeletal complications as seen in hemophilia patients visiting Kenyatta National Hospital.

2.5.2 Specific objectives

i. To establish the frequency of musculoskeletal complications in hemophilia patients.

ii. To describe the pattern of musculoskeletal complications in hemophilia patients.

iii. To evaluate factors associated with development of musculoskeletal complications in hemophilia patients.

3 METHODOLOGY

3.1 STUDY DESIGN

Descriptive Cross-sectional study

3.2 STUDY SITE

The study was conducted at Kenyatta National Hospital. This is a tertiary, referral and teaching hospital, located in Upper Hill area, within the Nairobi City metropolis. It is a multispecialty hospital receiving patients from the country and the larger Eastern Africa region. It hosts the main Hemophilia Comprehensive Care Clinic in the country. Patients were recruited from the following areas:

i. Medical and Pediatric hematology outpatient clinics
ii. Hemophilia Treatment Center
iii. Inpatient Medical Wards, Pediatric wards, and Surgery wards
iv. Accident and Emergency unit

3.3 STUDY POPULATION

The study population included all hemophilia patients visiting KNH in the various outpatient clinics and those admitted in the aforementioned inpatient wards.

3.3.1 Inclusion criteria:

All hemophilia patients with an already determined hemophilia type and who consented or had their parent/guardian assent to participate in the study were included.

3.3.2 Exclusion criteria

i. Those who are unable or were unwilling to give consent or assent
ii. Those who had other forms of arthropathy

3.4 SAMPLING AND SAMPLE SIZE ESTIMATION

The study sample size was determined using the Yamane (1967:886) formula at a precision level of 5% and 95% confidence interval (Israel, 2013) as shown below. As per this formula, the target population over the study period was estimated as 40 patients. This was based on the

average number of hemophilia patients who visited the weekly KNH hematology clinic over a period of three months.

$$n = {}^{N}/_{1 + N\sigma^2}$$

Where,

n is the desired sample size

N is the target population (40)

σ is the level of precision (5%)

$$n = {}^{40}/_{1 + 40 * 0.05^2} = 36.36 \approx 37$$

Sampling procedure: All patients who visited KNH and met the inclusion criteria were recruited into the study until the required sample size was obtained.

3.5 ETHICAL CONSIDERATION

Approval to conduct the study was sought from the Kenyatta National Hospital and University of Nairobi Ethics and Research Committee (KNH/UoN-ERC). All participants and/or their guardian were given an elaborate description of the study before giving informed consent or assent by signing the consent form. Participation in this study was voluntary and those who declined were not prejudiced in any way. Recruitment followed upon signing of the consent form. Privacy was maintained during history taking and clinical examination. All costs pertaining to the study were borne by the principal investigator. Any patient noted to have an acute illness was referred to the Accident and Emergency department for commencement of acute care. Confidentiality was maintained.

3.6 DATA COLLECTION

Recruitment of Research Assistant

The principal investigator recruited and trained a research assistant. She was an undergraduate student in her 6th year of study and was trained over a period of two days on the recruitment

and consenting procedure, clinical assessment of all parameters, computation of various scores, and data entry into the data collection sheet.

Recruitment and Consenting Procedure

In the various study areas patients known to have hemophilia were identified and approached by the principal investigator or the assistant. A patient and or the parent/guardian was taken through the purpose of the study and the contents of the consent form. The patient was recruited into the study only after signing the consent form.

Data collection procedure

All data was collected on a structured Data Collection Sheet.

Upon recruitment each patient was allocated a unique serial number, history taking and clinical examination followed. This was conducted in the clinical areas and privacy was maintained. The findings were then recorded as per the data collection sheet. A guideline was used for data entry. The following data was collected in the order indicated:

1. Patient data was collected by enquiring about their; Age, Age at first diagnosis, Site of first bleed, Sex, Hemophilia type, Mode of treatment, and approximate household monthly income.
2. History or presence of any pain and swelling in joints, muscles, and bone was enquired and later physical examination of the specific sites carried out.
3. History or presence of any loss of sensation or muscle weakness in the limbs was enquired and later a motor and sensory examination was carried out to rule out nerve palsy.
4. History of use of any ambulation aid was enquired. If a participant utilized an ambulation aid of any form the following letters were added at the end of the evaluation:
    i. B for Brace or Orthosis
    ii. C for Cane
    iii. CR for Crutches
    iv. WC for Wheelchair
5. Joint Pain was characterized as mild, moderate, or severe and given a score of 0-3:

    0: No pain: No functional deficit. No analgesic use (except with acute hemarthrosis)

1: Mild pain: Does not interfere with occupation nor with activities of daily living (ADL). May require occasional non-narcotic analgesic

2: Moderate pain: Partial or occasional interference with occupation or ADL. Use of non-narcotic medications. May require occasional narcotics

3: Severe pain: Interferes with occupation or ADL. Requires frequent use of non-narcotic and narcotic medications

6. Joint Bleeding was measured by the number of minor and major hemarthrosis episodes encountered in the previous year and given a score of 0-3:

   0 = None

   1 = No major, 1-3 minor

   2 = 1-2 major or 4-6 minor

   3 = 3 or more major or 7 or more minor

   Minor bleed was characterized by; Mild pain, Minimal swelling, Minimal restrictions of motion, Resolves within 24hrs of treatment

   Major bleed was characterized by: Pain, Effusion, Limitation of motion, Failure to respond within 24hrs

7. Joint Physical examination was based on the additive score of 0-12 with a score of 0 being a normal joint and a score of 12 being for the most affected joint. Assessment started with the knee joint, ankle joint, and then elbow joint. The following parameters were assessed; joint swelling, muscle atrophy, knee and ankle axial deformity, crepitation on motion, range of motion, flexion contracture, and joint instability.

   Joint swelling was assessed by inspecting around the joint considering that the swelling could have been due to effusion, synovial thickening, periarticular soft tissue mass, bony enlargement or a deformity. Thereafter muscle atrophy was assessed by measuring the circumference around the thigh, leg, arm, or forearm 15cm above or below the joint line and compared with the other limb. Non-Radiographic goniometric measurement of knee and ankle alignment was utilised. Patients were asked to adduct the legs till there was contact between the legs. Three points were considered; proximally the midpoint of ASIS and pubic tubercle, midpoint the centre of the knee along the joint line, and distally the mid-ankle point. Varus or valgus was recorded to the nearest degree. Ankle axial deformity was measured as a deviation from a reference line, a line from mid

popliteal fossa (mid knee joint) and the midpoint between the medial and lateral malleoli extending to the heel.

Range of motion of joints was measured by goniometry and presence of any fixed flexion deformity was noted. Normal Range of movement was considered to be; 0 to 135° of knee flexion, 0 to 20° of ankle dorsiflexion, 0 to 40° of ankle plantarflexion, and 0 to 140° elbow flexion. Crepitation on motion was assessed by palpation of the joint during passive and active movements. Joint stability was assessed by performing; Knee MCL and LCL stress tests, Knee anterior and posterior Drawer's tests, Ankle anterior Drawer's test, and Elbow varus and valgus stress tests.

8. Global Pain Score, Global Bleeding Score, Global Joint Score, and total number of affected joints was computed and recorded.

The findings were then explained to the patient or the guardian, and they were advised on any options available to manage the noted complications. A KNH interdepartmental referral form was filled referring a patient with noted complication to the relevant specialist clinic. In patients found to have need for urgent care, e.g. an acute bleed, they were immediately referred to the Kenyatta National Hospital HTC or the Accident and Emergency department.

3.7 STATISTICAL DATA ANALYSIS

Data from the collection sheets was entered and stored into a secure database. With the help of a statistician, statistical analysis was performed using Statistical Package for Social Sciences version 24 (SPSS v24). Demographic data of the patients was analyzed and presented as frequencies and proportions for categorical data, means with standard deviations as well medians with interquartile range were calculated for continuous data. The musculoskeletal complications and patterns in hemophilia patients were analyzed and presented as frequencies and proportions. Factors associated with the development of musculoskeletal complications were analyzed by correlations of variables using the Pearson's *r* Correlation technique. A p-value <0.05 was considered significant and 95% confidence level was used.

Data presentation

Data was represented in graphical analytic techniques i.e. tables and graphs. Discussions of the results and outcome was compared with similar studies. Conclusions were made and recommendations made for clinical protocol formulation.

3.8 STUDY LIMITATIONS

The following limitations were encountered:

a) Selection bias. Being a hospital setting most of the patients had come to sort treatment for acute bleeds or were on follow up at the outpatient clinic. These are patients who were at an increased chance of having developed complications associated to hemophilia.
b) Reporting of previous bleeding episodes was dependent on patient's description since there were no previous clinical records.
c) Reporting of history or presence of muscle hematoma and pseudotumors was dependent on patient's recall of a previous radiological diagnosis.

3.9 DISSEMINATION AND UTILITY

The outcome of this study was presented at the Orthopedics Surgery department and will be disseminated to:

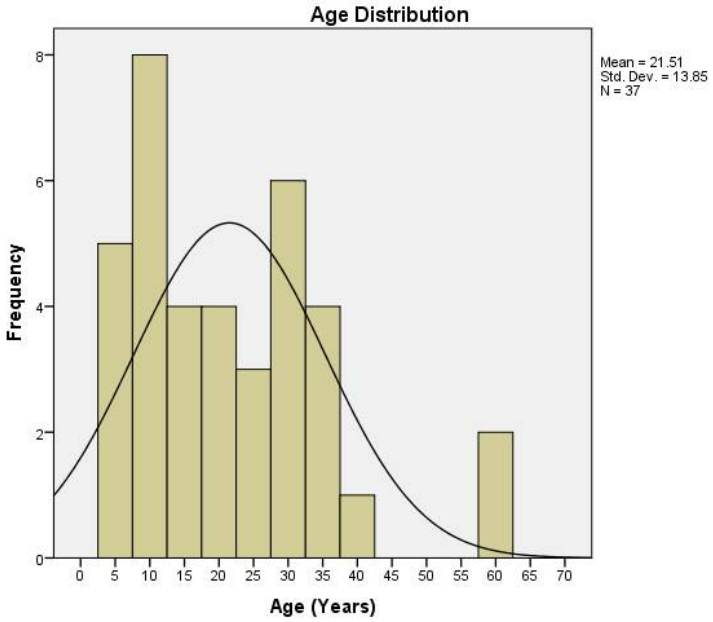
a) The department of Orthopedic Surgery, University of Nairobi
b) The University of Nairobi Library
c) Publication in a peer reviewed Journal and for presentation in scientific conferences

4 RESULTS

4.1 SOCIAL DEMOGRAPHIC CHARACTERISTICS

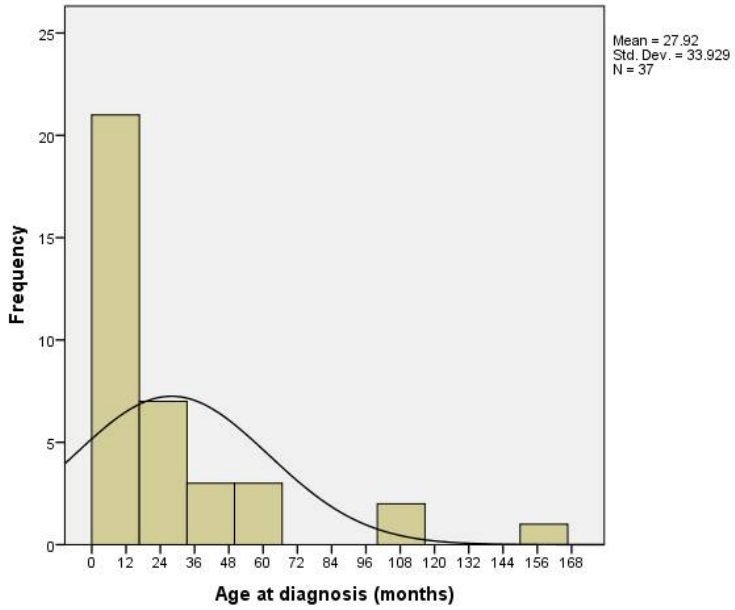
Thirty seven participants were included in the study. All participants were male.

Figure 5. Distribution of Hemophilia Patients according to age



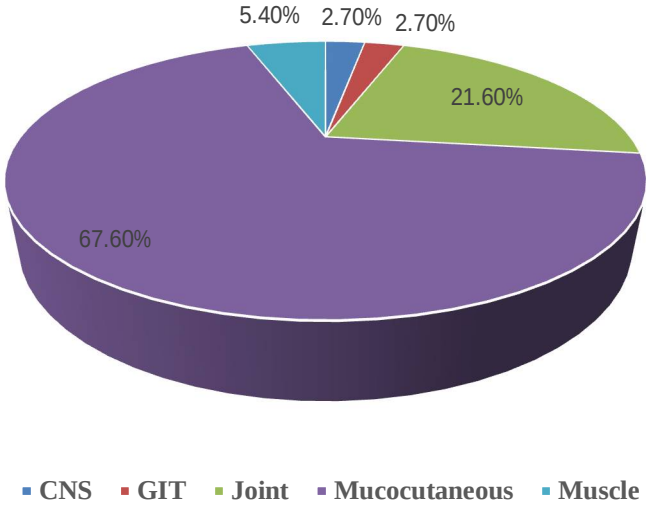
The mean age was 21.5 (SD=13.9) years, while the median age was 19 (IQR=21) years. The youngest patient was 5 years while the oldest was 61 years of age.

Figure 6: Distribution of Age at diagnosis



The mean age at the time of diagnosis was 27.9 (SD=33.9) months, while the median age was 16 (IQR=22) months. 56.7% of the patients were diagnosed at the age of 1year within a range of 1 month to 13years.

Figure 7: Distribution of sites of bleed at diagnosis



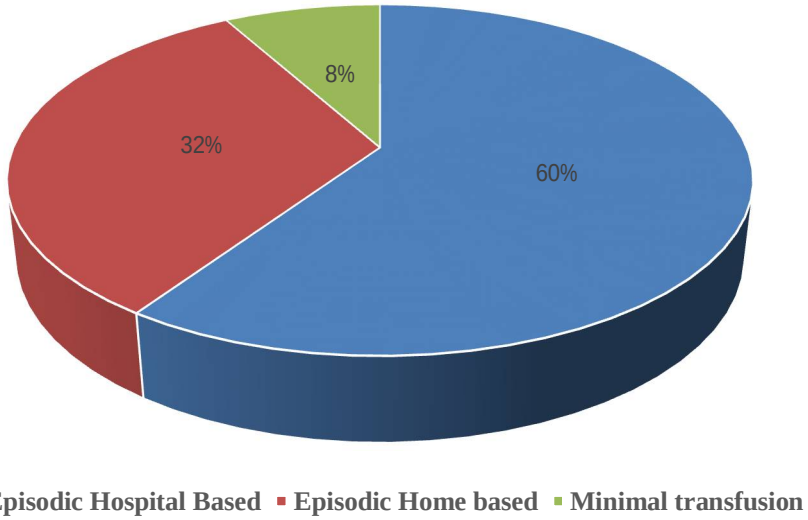
At the time of diagnosis 67.6% presented with mucocutaneous bleeds, 21.6% with joint bleeds, 5.4% with muscle bleeds, 2.7% with GIT bleed and 2.7% with CNS bleed.

Table 1: Distribution of Hemophilia type and severity

	MODERATE HEMOPHILIA	SEVERE HEMOPHILIA	TOTAL
HEMOPHILIA A	8 (23.5%)	26 (76.5%)	34 (91.9%)
HEMOPHILIA B	3 (100%)	0	3 (8.1%)
TOTAL	11(29.7%)	26 (70.3%)	37

Out of the 37 patients, 34 patients (91.9%) had Hemophilia A and 3 patients (8.1%) had Hemophilia B. 70.3% were reported to have severe hemophilia while 29.7% had moderate hemophilia.

Figure 8: Distribution of mode of treatment



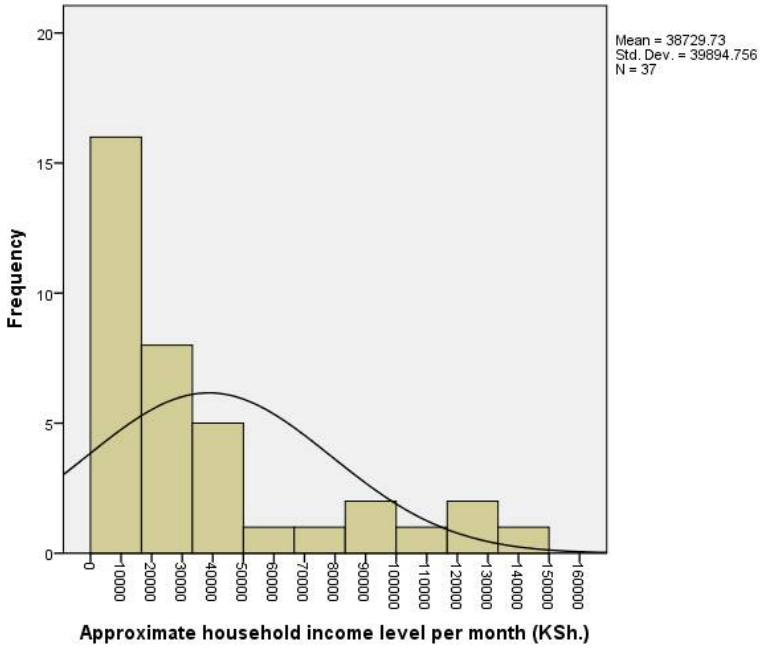
All patients were on On-Demand replacement therapy with either Recombinant Factor VIII or Factor IX. 32.4% of the patients had on several occasions been allowed to have home-based infusion of factor concentrates. 8.1% were on minimal factor transfusion therapy. The factor was provided at no cost to the patient except for hospital service charges.

Table 2: Distribution of approximate monthly household income levels

Approx Monthly income (KSh)	Frequency	Percent
Less than 10,000	5	13.5
10,000-30,000	19	51.4
30,001-60,000	6	16.2
60,001-90,000	1	2.7
Above 90,000	6	16.2
Total	**37**	**100.0**

A majority of the patients (64.9%) came from households with a total monthly income of less than KSh 30,000. 18.9% had a monthly income level of between KSh 30,000 and 90,000 and 16.2% above KSh 90,000.

Figure 9: Distribution of the monthly household income levels

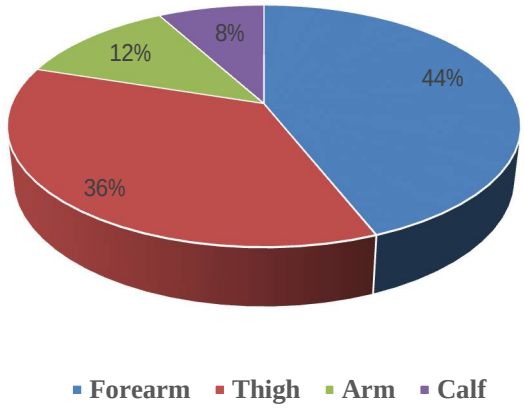


The mean monthly income was KSh 38,730 (SD 39,895), median income was 20,000 (IQR 40,000) the lowest income being KSh 5,000 and the highest income level at KSh 150, 000.

4.2 MUSCULOSKELETAL COMPLICATIONS

4.2.1 Muscle hematoma

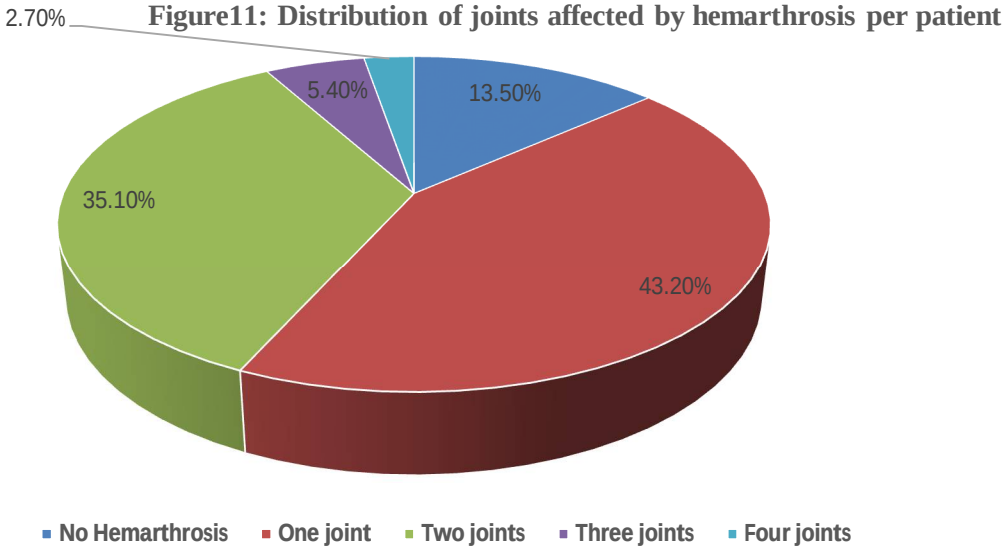
Figure 10: Distribution of Muscle hematoma sites



From the study 67.6% of the patients reported history of muscle hematoma. 44% of the muscle hematomas occurred in forearm muscles, 36% in thigh muscles, 12% in arm muscles, and 8% in calf muscles. None had an active muscle bleed at the time of examination.

4.2.2 Hemarthrosis and Arthropathy

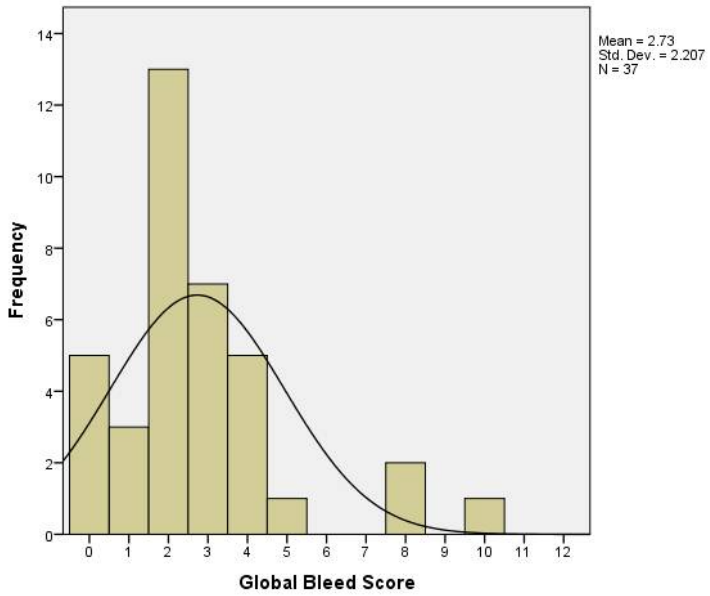
Figure11: Distribution of joints affected by hemarthrosis per patient



Of the study patients 86.5% presented with a history of hemarthrosis in different joints within the previous 12 months. The knee joint was the most affected by bleeds at 67.5%, elbow joint at 17.5%,

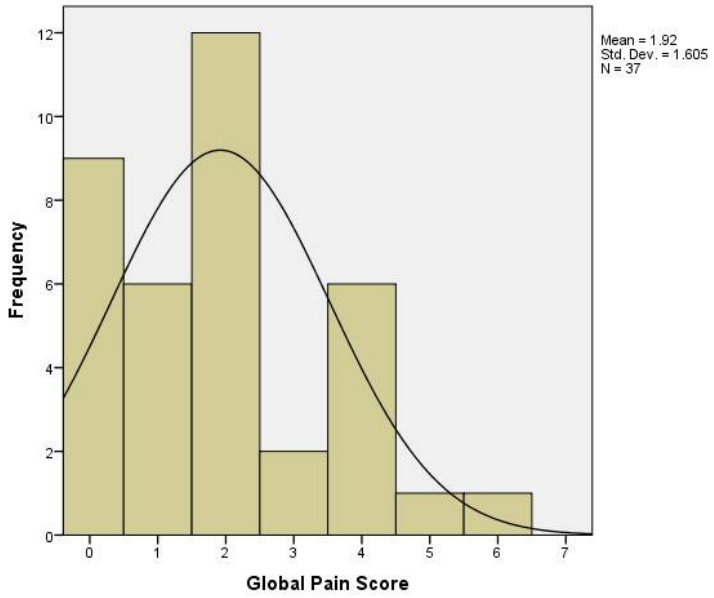
and the ankle joint at 15% of the patients. The highest number of joints affected in one individual were four out of a total of six joints (2.7%), three joints in 5.4%, two joints in 35.1%, one joint in 43.2%, while 13.5% of the patients did not have any affected joint.

Figure 12: Distribution of the Global Bleed Score



The mean Bleed Score was 2.73 (SD=2.21) per patient with a maximum possible score of 18. The most frequent score was 2 which was recorded in 35.1% of the patients. 13.5% of the patients scored 0 and only one patient (2.7%) scored the highest score of 10.

Figure 13: Distribution of the Global Pain Score



24.3% of the patients reported no interference with Activities of Daily Living due to joint pain and did not use analgesics except in instances of hemarthrosis. The commonly painful joint was the knee joint i.e. in 66.7% of the patients, followed by the elbow joint in 18.2% of the patients, and then the ankle joint in 15.1% of the patients. The mean Pain Score for the six main joints was 1.92 (SD = 1.605) per patient with the highest possible score being 18. The most frequent score was 2, which was recorded in 32.4% of the patients, within a range of a score of 0 and 6.

Table 3: Number of Joints affected as per the physical examination findings

Physical Examination Finding	Right Knee	Left Knee	Right Ankle	Left Ankle	Right Elbow	Left Elbow
Swelling						
Absent	21	24	35	36	34	35
Present	16	13	2	1	3	2
Muscle Atrophy						
Absent	25	31	35	37	36	36
Present	12	6	2	0	1	1
Angular deformity						
Knee: 0-7° valgus	31	32	-	-	-	-
Knee: 8-15° valgus or 0-5° varus	6	5	-	-	-	-
Knee: >15° valgus or >5° varus	0	0	-	-	-	-
Ankle: No deformity	-	-	35	37	-	-
Ankle: Up to 10° valgus or up to 5° varus	-	-	2	0	-	-
Ankle: >10° valgus or >5° varus	-	-	0	0	-	-
Crepitus on motion						
Absent	37	37	37	37	37	37
Present	0	0	0	0	0	0
Range of motion						
Loss of <10% of total full range of motion	20	25	34	35	30	34
Loss of 10-33 1/3% of total FROM	8	4	2	0	2	3
Loss of >33 1/3% of total FROM	9	8	1	2	5	0
Fixed Flexion Contractures						
<15° FFC or none	21	27	36	36	32	34
=>15° FFC	16	10	1	1	5	3
Instability						
None	37	37	37	37	37	37
Noted on examination but neither interferes with function nor requires bracing	0	0	0	0	0	0
Instability that creates a functional deficit or requires bracing	0	0	0	0	0	0

On clinical evaluation of the joints:

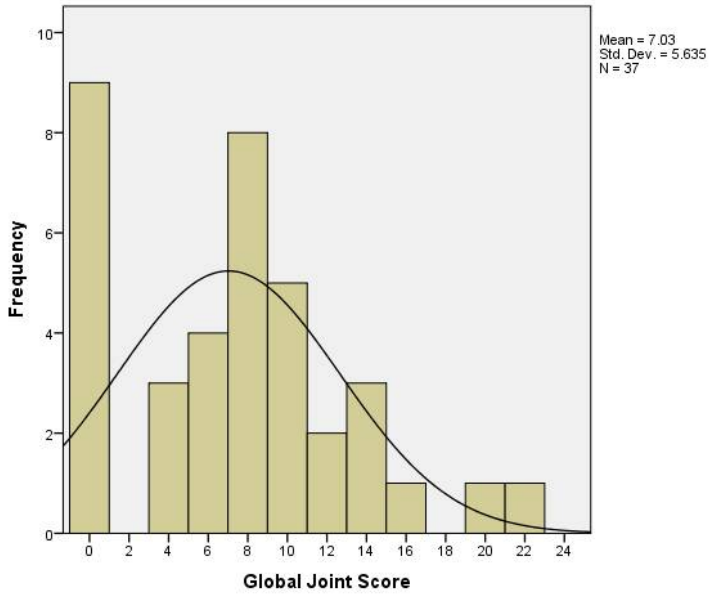
- None had intra-articular crepitation and joint ligament instability
- 64.9% of the patients had knee swelling, 5.4% had elbow swelling, and 2.7% had ankle swelling.
- 59.5% of the patients had muscle atrophy in various muscle compartments. Quadriceps muscle group had the highest rate of atrophy (48.6%).

- 24.3% of the patients had Valgus knee deformity of 8-15° valgus and 5.4% had Valgus ankle deformity of up to 10° valgus.
- 75.7% of the patients had a total loss of Range of Motion of more than 10% in at least one of the joints. The knee joint was the most affected joint with 67.6% of the patients having reduced Range of Motion.
- 70.3% of the patients had fixed flexion joint contractures of >15° involving one or more joints in one patient. A majority (88.5%) of these patients had knee fixed flexion contractures.

Table 4: Number of patients affected as per physical examination findings

Physical Examination Finding	Knee (n = 37)	Ankle (n = 37)	Elbow (n = 37)
Swelling			
Absent	11	35	34
Present	26	2	3
Muscle Atrophy			
Absent	19	35	36
Present	18	2	1
Angular deformity			
Knee: 0-7° valgus	28	-	-
Knee: 8-15° valgus or 0-5° varus	9	-	-
Knee: >15° valgus or >5° varus	0	-	-
Ankle: No deformity	-	35	-
Ankle: Up to 10° valgus or 5° varus	-	2	-
Ankle: >10° valgus or >5° varus	-	0	-
Crepitus on motion			
Absent	37	37	37
Present	0	0	0
Range of motion			
Loss of <10% of total full range of motion	12	32	30
Loss of 10-33 1/3% of total FROM	8	2	1
Loss of >33 1/3% of total FROM	17	3	6
Fixed Flexion Contractures			
<15° FFC or none	14	36	32
=>15° FFC	23	1	5
Instability			
None	37	37	37
Noted on examination but neither interferes with function nor requires bracing	0	0	0
Instability that creates a functional deficit or requires bracing	0	0	0

Figure 14: Distribution of Global Joint Scores



The mean Global Joint Score was 7.03 (SD=5.64) per patient out of a maximum possible score of 72. Only one patient (2.7%) scored the highest score of 22 while 24.3% of the patients had normal examination findings i.e. a score of 0. The least affected joint was the left ankle joint in 5.4% of the patients while the most affected joint was the right knee in 45.9% of the patients.

4.2.3 Other Complications

One patient had a tibial diaphyseal fracture after a trivial fall and was on non-operative management with an above knee full cast. There was no patient with history or presence of pseudotumors or peripheral nerve palsy.

4.3 FACTORS ASSOCIATED WITH MUSCULOSKELETAL COMPLICATIONS

Pearson *r* correlation technique was utilised to measure the degree of the relationship between variables:

a) There was a significant relationship between the frequency of hemarthrosis (Bleed Score) and the severity of structural and functional status of joints (Global Joint Score) (p value = 0.001)

b) There was a significant relationship between the frequency of hemarthrosis (Bleed Score) and severity of disease (p value = 0.012)

c) There was a significant association between the severity of disease and the severity of structural and functional status of joints (Global Joint Score) (p value = 0.001).

d) There was no significant relationship between the age at diagnosis of the patient and the severity of structural and functional status of joints (Global Joint Score) (p value = 0.575).

e) A statistically significant relationship was established between the monthly income level and home-based infusion treatment method (p value = 0.039). However there was no significant relationship between the household monthly income level and the severity of structural and functional status of joints (Global Joint Score) (p value = 0.603).

f) All patients were on On-Demand treatment mode with factor concentrates thus the association between prophylactic treatment and severity of the functional status of the join could not be established.

5 DISCUSSION

This study provides descriptive information about the orthopaedic manifestations i.e. Hemarthrosis, Arthropathy, Muscle hematoma, Pathological fracture, Pseudotumor, and Nerve palsy, in hemophilia patients visiting Kenyatta National Hospital within the study period. The most frequently encountered was Hemophilia A at 91.9% while Hemophilia B was at 8.1% of the study population. This is similar to the findings by Diop et al who found 90.7% of the study population to have had Hemophilia A while Hemophilia B was 9.3% [12]. It differs slightly from Hayam et al findings of 86.7% for hemophilia A and 13.3% for Hemophilia B, and Kenyan data from 2016 WFH Global Survey where 81.8% had Hemophilia A and 18.2% of the patients had Hemophilia B though these were statistics from all over the country [3, 13].

The average age for this study was 21.5 years with the youngest patient being 5 years and the oldest 61 years (Fig. 5). This could be a reflection of the increasing life expectancy of Hemophilia patients due to the improved efforts in provision of factor concentrates. According to the WFH Survey of 2016 about 13% of Kenyans living with Hemophilia are more than 45 years of age [2].

The average age at the time of diagnosis was 2.7 years with a range of 1 month to 13 years. The majority (27%) were diagnosed within the first year of life and 91.9% within the first 5years of life [Fig.6]. This is similar to the findings by Hayam et al where the average age at diagnosis was 2.2 years with a range of 6months to 4 years [13]. This finding could be attributed to the increasing literacy levels among the population and the efforts to sensitize all health care workers towards diagnosing and referring patients with bleeding tendencies to the appropriate centres. However this is still high as compared to the developed countries whose average age at diagnosis is 1.6 years [2].

A majority (70.3%) of the patients in this study reported severe hemophilia while the rest reported moderate haemophilia [Table 1]. There was a significant association between the reported severity of disease and the Global Joint Score. It was noted that patients with severe Hemophilia had higher joint scores as compared to those with moderate severity. There was also an association between frequency of joint bleeds and Global Joint score, with increasing frequency and severity of joint bleeds being associated with reduced structural and functional joint health status. This is similar to Hayam et al study that found association between higher global joint scores and reducing serum factor levels [13].

From the study 67.6% of the patients reported history of muscle hematoma. However none had an active muscle bleed at the time of evaluation. Most of them (44%) occurred in forearm muscles, 36% in thigh muscles, 12% in arm muscles, and 8% in calf muscles [Fig.10]. This is different from the findings of Beyer et al who demonstrated 55% to be occurring in iliopsoas muscle, 18% in calf muscles, and 18% in thigh muscles [20].

Of the study patients 86.5% presented with a history of hemarthrosis in different joints within the previous 12 months. The most commonly affected joint was the knee joint, followed by the elbow joint, then the ankle joint (67.5%, 17.5%, and 15% respectively) [Fig.11]. The distribution of hemarthrosis is similar to pattern described by the WFH survey that indicates the prevalence of hemarthrosis to be approximately 70-80% and the most commonly affected joint to be the knee, elbow, and then the ankle joints (45%, 30%, 15% respectively) [2]. However Hayam et al found a slightly different frequency with the knee joint to be the most frequently affected joint (73.3%) followed by the ankle joint (16.7%) while the elbow joint was at 6.7% [13]. Stephensen et al and Aznar JA et al demonstrated different patterns where the ankle joint was the most affected joint followed by the knee and elbow joints [16, 17]. It also demonstrates the increased risk of bleeding in convex-concave surface articulations which have significant constraints during rotation thus predisposing them to synovial impingement and bleeding [26].

From the study 83.8% of the patients had one or more joints affected. The highest number of joints that were affected in one individual were four out of a total of six joints (2.7%), three joints in 5.4%, two joints in 32.4% and one joint in 40.5% of the patients [Fig.11]. This correlates to the tendency of most haemophilia patients having repeated hemarthrosis of one particular joint (Target joint).

Clinical evaluation of the joints demonstrated a high prevalence of musculoskeletal complications that would require the intervention of an orthopaedic team in their management. For instance 70.3% of the patients had fixed flexion joint contractures of >15° involving one or more joints in one patient [Table3]. This calls for early intervention by physiotherapy, use of orthoses, casting, and bracing of affected joints, and by orthopaedic surgeons in managing the contractures by either tendon lengthening, extension osteotomies or use of external fixations where indicated. 75.7% of the patients had a total loss of Range of Motion of more than 10% in at least one of the joints and 59.5% of the patients had muscle atrophy in various muscle compartments [Table4]. These call for continuous preventive joint and muscles rehabilitation modalities in preserving joint movement and function after bleeding

episodes. Therefore there is need for provision of physiotherapy services in management of hemophilia arthropathy.

Only one patient had a fracture. There was no patient with peripheral nerve palsy. This is unlike the findings in India by Saraf et al where 15% of the patients had different forms of nerve palsy [24]. This may have been as a result of a small sample size and there may be need to evaluate all patients to establish the prevalence of nerve palsies. Of the study patients none presented with a pseudotumor. This could have been influenced by the fact that this was a clinical evaluation based study and did not include radiological evaluation.

Overall thirty six out of the thirty seven evaluated patients (97.3%), were found to have had one or several musculoskeletal complications.

The study also found no correlation between the household income and severity of musculoskeletal complications though the level of income influenced the probability of the patient being allowed to do home-based factor concentrate infusions. This could be due to the tendency of high income individuals being associated with higher education levels, need for convenience, and positive influence on health seeking behaviour. However the study was considering total income while in reality the amount of money apportioned to health within a household is influenced by many factors e.g. size of family. The findings are unlike the ones demonstrated by Kar et al in a multicentre study conducted in India where they found an inverse correlation between a patient's family income level and severity of physical disability in patients living with Hemophilia [25].

All patients were on On-Demand replacement therapy for hemophilia associated bleeds with either recombinant Factor VIII or Factor IX [Fig.8]. No patient was on prophylactic treatment which was as a result of prudent measures put in place for the utility of the factor donations to Kenyatta National Hospital. This could not allow determination of any correlation between prophylactic therapy and the associated positive effect on joint functionality as demonstrated in other studies [9, 11, 26, 39].

5.1 CONCLUSION

In conclusion this study demonstrated a high (97.3%) prevalence of various orthopaedic manifestations in hemophilia patients seen at Kenyatta National Hospital. Most patients had Hemophilia A (91.9%) with a majority (70.3%) reporting severe disease. The average age was 21.5 years while the average

age at the time of diagnosis was 2.7 years. The most frequently encountered musculoskeletal complication was hemarthrosis (86.5%) followed by muscle hematoma (67.3%) with only one patient found to have had a pathological fracture and none with a nerve palsy or psuedotumor. All patients were on On-Demand replacement therapy and were dependent on donations from well-wishers. Therefore the study demonstrated the need for early involvement of orthopaedic team in management and follow up of hemophilia patients. It also highlighted the association of severity of orthopaedic complications and the prevailing serum factor levels. This is an indication of the need for incorporating prophylactic treatment regimens in the management of hemophilia patients seen at Kenyatta National Hospital.

5.2 RECOMMENDATIONS:

1. Increase resource allocation to allow prophylactic factor concentrate administration.
2. Improve Orthopaedics care to haemophilia patients. There is need for a timely concerted effort towards clinical evaluation, radiological evaluation, and management of orthopaedic manifestations to improve the quality of life for patients living with hemophilia. Several protocols and tools can be designed to assist clinicians and other health care providers in offering standardised orthopaedic care to hemophilia patients.

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7 APPENDICES

7.1 APPENDIX 1: CONSENT FORMS

Consent to Participate in a Research Study

RESEARCH TITLE: PREVALENCE OF MUSCULOSKELETAL COMPLICATIONS AMONG HEMOPHILIA PATIENTS AS SEEN AT KENYATTA NATIONAL HOSPITAL

Principal investigator:

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Supervisors:

1. DR. EDWARD MUTHIKE GAKUYA, Consultant Orthopedic Surgeon, Department of Orthopedics Surgery, University of Nairobi
2. DR. JOHN KINGORI, Consultant Orthopedic Surgeon, Department of Orthopedics Surgery, University of Nairobi

Introduction: I would like to let you know that I am conducting a study on bone and muscle complications in persons living with Hemophilia under the supervision of the above Consultant Orthopaedic surgeons. The purpose of this form is to provide you with information about this study so that you are able to decide whether to participate or not. Your participation is on voluntary basis thus you may withdraw without providing any reasons. Kindly be at liberty to ask any questions regarding this study to myself, my supervisors, or the Chairman Ethics and Research Committee through the provided contacts. Once you decide to participate in the study, I would request you to sign as provided at the end of the form.

Purpose of the study: The purpose of this evaluation is to find out if as a person living with Hemophilia, you may have developed complications affecting bones and muscles as a result of continued bleeding in joints and muscles. This information will be useful in making a treatment plan for you and other Hemophilia patients, and in formulating policies that will help in improving care of people living with Hemophilia. It is a study that will involve all Hemophilia patients visiting Kenyatta National Hospital.

Expectations of the participant: Once you agree to participate in the study the investigator will ask you several questions regarding your condition and then examine your joints to establish if continued bleeding has had an effect on the structure and function of the joint. All findings will be recorded on the study's Data Collection Sheet.

Confidentiality: We will do everything to ensure that the information collected is kept confidential and will only be used for the purpose of this study. For the purpose of record keeping and data analysis, we will use a code number as an identifier. At no time will we use your name. All data collection sheets will be in the principal investigator's custody under lock and key while digital data will be secured in a password-protected database.

Withdrawal: You may unconditionally withdraw from the study at any given time.

Benefits: As a participant you will benefit by having a free clinical evaluation and advice on how to proceed with the management of any complication thereof. The information obtained will contribute to the knowledge of the prevalence and burden of musculoskeletal complications and will also be helpful in formulating orthopaedic care management policies for persons living with hemophilia.

Risks and discomforts: There is risk of loss of privacy and the discomfort of having to wait for a little longer for the investigator to carry out the clinical evaluation.

Costs: All costs associated to the study will be borne by the principal investigator. You will not be required to bear any costs towards this study.

Statement of Consent for Adults

I certify that I have read this form and the purpose of this study and my role in it has been fully explained to me. I do understand confidentiality will be maintained and my identity will not be disclosed. That this is a voluntary study and I may withdraw at any given time if I so wish. I hereby willingly agree to participate in it.

Participant's name_____ Signature (thumbprint) _____
Date _____

Statement of Assent for minors

I certify that I am the parent/guardian to _____and have read this form and the purpose of this study and the role of my child in it has been fully explained to me. I do understand confidentiality will be maintained and his/her identity will not be disclosed. That this is a voluntary study and I may withdraw at any given time if I so wish. I hereby willingly agree to participate in it.

Parent/Guardian name_____ Signature (thumbprint)_____
Date _____

Investigator statement

I confirm that I have clearly explained to the participant about the study and the participant has consented to participate voluntarily without any coercion or undue pressure.

Investigator's Signature…… Date ……

For further enquiries, please contact the principal investigator, supervisors or;

Chairperson Kenyatta National Hospital/University of Nairobi Ethics and Research Committee
College of Health Sciences
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Ridhaa ya kushiriki Katika Utafiti

UTAFITI KUHUSU: MATATIZO YA MISULI NA MIFUPA YANAYOBAINIKA MIONGONI MWA WAGONJWA WA HEMOFILIA WANAOKWENDA KWA MATIBABU KATIKA HOSPITALI YA KITAIFA YA KENYATTA (KNH)

Mtafiti Mkuu:

DKT. EDWARD NGUYO MAINA, Idara ya Matibabu ya Mifupa, Chuo Kikuu cha Nairobi
Namba ya simu: 0721 810 302, Barua pepe: enguyo@gmail.com

Wasimamizi wa utafiti:

1. Dkt. EDWARD MUTHIKE GAKUYA, Daktari Mshauri wa upasuaji wa mifupa, Idara ya Matibabu ya Mifupa, Chuo Kikuu cha Nairobi
2. Dkt. JOHN KINGORI, Daktari Mshauri wa upasuaji wa mifupa, Idara ya Matibabu ya Mifupa, Chuo Kikuu cha Nairobi

Utangulizi: Ningependa kukujulisha kwamba ninafanya utafiti kuhusu matatizo ya mifupa na misuli yanayowakabili watu wanaougua ugonjwa wa damu kutoganda yaani hemofilia. Ninasimamiwa na kupewa muungozo katika utafiti huu na madaktari wawili washauri niliowataje hapo juu. Kusudi la fomu hii ni kukupa maelezo kamili kuhusu utafiti huu ili kukuwezesha kuamua kama utashiriki au la. Kwa hivyo kushiriki kwako ni kwa hiari na una uhuru wa kuamua kutoshiriki bila kutoa sababu. Tafadhali, jisikie huru kuniuliza mimi, wasimamizi wangu ama Mwenyeketi wa Maadili na Kamati ya Utafiti maswali yoyote uliyonayo kuhusu utafiti huu kupitia anwani nilizotoa hapo mwisho wa fomu hii. Endapo utaamua kushiriki katika utafiti huu, ninakuomba utie saini katika nafasi iliyotengwa katika mwisho wa fomu hii.

Kusudi la utafiti: Kusudi la utafiti huu ni kutaka kujua, wewe kama mtu anayeugua ugonjwa wa damu kutoganda yaani hemofilia, je umepatwa na matatizo ya mifupa na misuli yanayosababishwa na kutokwa na damu bila kuacha kwenye viungo na misuli? Maelezo haya yatakuwa muhimu katika kupanga matibabu yako na yale ya wagonjwa wengine wanaougua hemofilia, na pia maelezo hayo yatasaidia katika utungaji sera ambazo zitasaidia katika kuwatunza watu wanaoishi na ugonjwa wa hemofilia. Utafiti huu utawahusisha wagonjwa wote wanaozuru Hospitali ya Kitaifa ya Kenyatta (KNH) ilikupata matibabu.

Matarajio kwa mhusika katika utafiti huu: Endapo utakubali kushiriki katika utafiti huu, mtafiti atakuuliza maswali kadhaa kuhusu hali yako na kutazama viungo vyako ili kuthibitisha kama kutokwa na damu bila kuacha kumeathiri muundo na utenda kazi wa viungo vya mwili wako. Matokeo yote yatanakiliwa kwenye karatasi ya ukusanyaji wa takwimu.

Uhifadhi wa siri wa taarifa utakayotoa: Tutafanya kila kitu kuhakikisha kwamba maelezo yanayotolewa yanahifadhiwa kwa uangalifu na kwa siri na kutumika kwa kusudi la utafiti huu pekee. Kwa kusudi la kuweka rekodi na kufanya ufafanuzi wa maelezo, tutatumia nambari ya msimbo ama kodi namba kama kitambulishi. Hakuna wakati jina lako litatajwa au kutumika katika utafiti huu. karatasi zote ya ukusanyaji wa takwimu zitahifadhiwa kwa kufungiwa kwa kufuli na ufunguo na mtafiti mkuu na maelezo ya kidijitali yatalindwa kwa kutumia nenosiri (password).

Kujiondoa katika utafiti: Una ruhusa ya kujiondoa katika utafiti huu wakati wowote unapohisi hutaki kuendelea kushiriki.

Faida na hatari: Kama mshiriki katika utafiti huu, utafaidika kwa kupata, bila malipo, ukaguzi wa kiafya na ushauri wa jinsi ya kuendelea na matibabu kwa matatizo yoyote yatakayogunduliwa katika utafiti huu. Maelezo yatakayopatikana yatachangia katika ufahamu wa kuweko kwa matatizo ya misuli na mifupa na mzigo utokanoa na ugonjwa huo, na pia yatasaidia katika utunzi wa sera za matibabu ya mifupa na pia sera za kuwatunza watu wanaoishi na ugonjwa wa hemofilia. Hatari iliyopo ni kupungua kwa usiri na pia usumbufu wa kungoja kwa muda mrefu ili mtafita afanye ukaguzi wake wa kimatibabu.

Gharama: Gharama zote kuhusiana na utafiti huu zitasimamiwa na mtafiti mkuu. Hutahitajika kugharamia chochote kuhusiana na utafiti huu.

Taarifa ya kukubali kwa watu wazima

Nathibitisha kuwa nimeyasoma maelezo yaliyotolewa kwenye fomu hii na nimeelezewa kikamilifu kusudi la utafiti huu na kuhusu mchango wangu. Ninaelewa kwamba maelezo nitakayotoa yatahifadhiwa kwa siri na jina langu halitatambulishwa. Naelewa pia kwamba kuhusika kwangu katika utafiti huu ni kwa hiari na naweza kujiondoa wakati wowote nitakapopenda kufanya hivyo. Kwa hivyo nakubali kwa hiari kushiriki katika utafiti huu.

Jina la mshiriki _____ Saini (kidole gumba) _____

Tarehe _____

Taarifa ya kukubali kwa watoto

Nathibitisha kwamba mimi ni mzazi/mlezi wa _____ na nimeyasoma maelezo yaliyotolewa katika fomu hii na nimeelezewa kikamilifu kusudi la utafiti huu na kuhusu mchango wa mtoto wangu. Ninaelewa kwamba maelezo yatakayotolewa yatahifadhiwa kwa siri na jina lake halitatambulishwa. Naelewa pia kwamba kuhusika katika utafiti huu ni kwa hiari na naweza kujiondoa wakati wowote nitakapopenda kufanya hivyo. Kwa hivyo nakubali kwa hiari kushiriki katika utafiti huu.

Jina la Mzazi/Mlezi_____Saini (kidole gumba) _____

Tarehe _____

Taarifa ya mtafiti

Nathibitisha kwamba nimemuelezea kwa uwazi mshiriki wa utafiti huu na amekubali kushiriki kwa hiari bila kushurutishwa ama kulazimishwa.

Saini ya mtafiti …… Tarehe ……

Kwa maelezo zaidi, tafadhali wasiliana na mtafiti mkuu, wasimamizi ama;

> Mwenyekiti wa Kamati ya Maadili na Utafiti ya Hospitali ya Kitaifa ya Kenyatta na Chuo Kikuu cha Nairobi, S.L.P. 19676-00202, Nairobi, Simu: +254202726300-9 Ext 44355

7.2 APPENDIX 2: DATA COLLECTION SHEET

Enquire from the patient the following details, tick where appropriate, then clinically evaluate the joints and score as per attached guidelines

PATIENT DETAILS							**DATE**		
Unique ID NO		Age		Sex		Age at diagnosis		Site of bleed at diagnosis	
Hemophilia Type		Factor level				Mode of Treatment			
Approximate Household Income Level per Month (KSh)									
History or presence of Muscle Hematoma						Yes	No	SITE	
History or presence of Pseudotumor						Yes	No	SITE	
History or presence of Pathological fracture						Yes	No	SITE	
History or presence of Peripheral Nerve palsy						Yes	No	SITE	
Require an aid for ambulation						Yes	No	Type	

JOINT EVALUATION		**SCORE**						
		RT Knee	LT Knee	RT Ankle	LT Ankle	RT Elbow	LT Elbow	
1	Pain							
2	Bleeding							
PHYSICAL EXAMINATION								
1	Swelling							
2	Muscle atrophy							
3	Angular deformity							
4	Crepitus on motion							
5	Range Of Motion							
6	Flexion contracture							
7	Instability							
	GLOBAL JOINT SCORE							
	GLOBAL PAIN SCORE							
	GLOBAL BLEED SCORE							
TOTAL NUMBER OF AFFECTED JOINTS								

7.3 APPENDIX 3: GUIDELINES TO FILLING THE DATA COLLECTION SHEET

MODE OF TREATMENT(fill in the following letters) **O** = No, or minimal transfusion therapy **E** = Episodic transfusion for most of all bleeding episodes **M** = Maintenance or prophylactic therapy **(H)** = Added after E or M indicates that the patient is on a homeself-transfusion program	**AID TO AMBULATION** (fill in the following letters) B = Brace or orthosis C = Cane CR = Crutches WC = Wheelchair
PAIN **0: No pain** No functional deficit No analgesic use (except with acute hemarthrosis) **1: Mild pain** Does not interfere with occupation nor with activities of daily living (ADL) May require occasional non-narcotic analgesic **2: Moderate pain** Partial or occasional interference with occupation or ADL Use of non-narcotic medications May require occasional narcotics **3: Severe pain** Interferes with occupation or ADL Requires frequent use of non-narcotic and narcotic medications	**BLEEDING** This is measured by the number of minor and major hemarthrosis per year. 0 = None 1 = No major, 1-3 minor 2 = 1-2 major or 4-6 minor 3 = 3 or more major or 7 or more minor Description Minor: Mild pain, Minimal swelling, Minimal restrictions of motion, Resolves within 24hrs of treatment Major: Pain, Effusion, Limitation of motion, Failure to respond within 24hrs
PHYSICAL EXAMINATION Swelling Absent = 0 Present = 2 Add (S) if chronic synovitis is present Muscle atrophy Absent = 0 Present = 1 Angular deformity (for knee or ankle only) Knee: 0-7° valgus = 0 Knee: 8-15° valgus or 0-5° varus = 1 Knee: >15° valgus or >5° varus = 2 Ankle: No deformity = 0 Ankle: Up to 10° valgus or up to 5° varus = 1 Ankle: >10° valgus or >5° varus = 2 Intra-articular crepitation Absent = 0 Present = 1	ROM (%) Total full ROM loss: <10% = 0 Total full ROM loss: 10-30% = 1 Total full ROM loss: >30% = 2 Flexion contracture (for hip, knee, or ankle) <15° FFC = 0 >15° FFC = 2 Instability Absent = 0 Present, but functions are not affected = 1 Present, but functions are limited = 2

7.4 APPENDIX 4: WFH PHYSICAL EXAMINATION (GILBERT) SCORE

Physical finding	Score	Scoring key
Swelling	0 or 2 + (S)	0 = none
		2 = present (S) if chronic synovitis is present
Muscle atrophy	0–1	0 = ⩽ 1 cm
		1 = present
		Axial deformity: measured on knee and ankle only
Knee	0–2	0 = 0–7° valgus
		1 = 8–15° valgus or 0–5° varus
		2 = > 15° valgus or > 5° varus
Ankle	0–2	0 = No deformity
		1 = < 10° valgus or < 5° varus
		2 = > 10° valgus or > 5° varus
Crepitance on motion	0–1	0 = none
		1 = present
Range of motion	0–2	0 = loss of < 10% of total full range of motion (FROM)
		1 = loss of 10–33 1/3% of total FROM
		2 = loss of > 33 1/3% of total FROM
Flexion contracture	0 or 2	0 = < 15% fixed flexion contracture
		2 = ⩾ 15% fixed flexion contracture at hip or knee or equinus at ankle
Instability	0–2	0 = none
		1 = present but neither interferes with function nor requires bracing
		2 = instability that creates a functional deficit or requires bracing
Total	0–12	Ankle or Knee
	0–10	Elbow

7.5 APPENDIX 5: BUDGET AND IMPLEMENTATION TIMETABLE

Budget

	ITEM	COST (KSh)
1.	KNH/ERC Research fee	2,000
2.	Statistician fee	30,000
3.	Stationery, Printing, Binding	10,000
4.	Research Assistant Fee	15,000
6.	Contingency	13,000
	TOTAL	70,000

Implementation timetable

Activity	Jun– Dec 2018	Jan 2019	Feb-Apr 2019	May 2019	June 2019	July 2019	Aug-Sept 2019
Proposal development							
Proposal presentation							
Submission for ethical approval							
Data collection and Analysis							
Dissertation writing and presentation							