VITAMIN D AND CALCIUM LEVELS IN ELDERLY PATIENTS PRESENTING WITH HIP FRAGILITY FRACTURES IN KNH

A dissertation submitted in partial fulfillment of the requirements of Master of Medicine Degree in Orthopaedic Surgery.

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DECLARATION

I hereby declare that this dissertation is my original work and has not been presented for a degree course in any other university elsewhere.

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This is to certify that the work identified below is the original work of the author. The research was carried out at The Kenyatta National Hospital.

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The researcher did not receive any financial benefits from this research.

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LIST OF ABBREVIATIONS

BMD	Bone Mineral Density
BMU	Bone Multicellular Unit
CLIA	Chemiluminescence immunoassay
CRP	C – Reactive Protein
DEXA	Dual-energy X-ray absorptiometry
IL	Interleukin
KNH	Kenyatta National Hospital
NRS	Numerical Rating Scale
PBM	Peak Bone Mass
PTH	Parathyroid Hormone
RA	Resection Arthroplasty
ROM	Range of Motion
THA	Total Hip Arthroplasty
THR	Total Hip Replacement
UON	University of Nairobi
VDR	Vitamin D receptor

OPERATIONAL DEFINITIONS

Elderly patient: A patient above 65 years of age

Fragility fracture: Fractures that occur as a result of a minimal trauma such as fall from standing height.

Type of hip fracture: Neck of femur fractures, intertrochanteric fractures and sub-trochanteric fractures.

Selected patient characteristics: Age and Gender

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ABSTRACT

BACKGROUND

Fragility fractures are associated with significantly reduced bone strength in elderly patients due to changes in bone mass, architecture and material characteristics. They are occasioned by low energy injuries in the elderly. Vitamin D deficiency has been identified as an independent risk factor for hip fragility fractures. It is associated with muscle weakness and poor muscle function among the elderly, with increased risk of falls, poor rehabilitation post injury and increased risk of re-fracture in these patients. Studies documenting vitamin D levels in Africa are few, and mainly from South Africa and West Africa. No study has been done in Africa specifically studying vitamin D in patients with hip fragility fractures.

OBJECTIVE: To determine the pattern of serum calcium and vitamin D among elderly patients presenting with hip fragility fractures at KNH.

METHODOLOGY: This was a hospital based descriptive cross-sectional Study carried out among elderly patients (>65yrs) presenting with hip fragility fractures at the Kenyatta National Hospital Accident and emergency and Orthopedic wards. The study duration was June – September 2019. Consecutive sampling was done until the desired sample of 65 was achieved. The patient's biodata, mechanism of injury, date and type of injury was documented. Upon admission, the serum calcium and hydroxyvitamin D levels were assayed and recorded.

DATA MANAGEMENT: Data was entered, coded and analyzed using Statistical Package for Social Sciences (SPSS)version 23. The primary outcomes were the serum level of 25 hydroxycholecalciferol and calcium. Means and standard deviations as well as Median and IQR

were reported for serum level of 25 hydroxycholecalciferol and calcium. Pearsons Chi Square test were done to test for association between serum vitamin D with selected patient characteristics.

RESULTS: The study recruited 65 participants**.** Majority were female (58.5%), and the participants mean age was 74.5 (SD = 8.9) years. The proportion of vitamin D deficiency was 48%, insufficiency 38% and normal Vitamin D was 14%. The mean serum Vitamin D was 21.5 (SD =7.7) ng/ml. The albumin adjusted serum calcium level was normal in 89.2% and low in only 10.8% of the participants. A Fisher's exact test was used to test the association between Calcium level and gender, and there was no statistical association between Calcium level and gender.

The most common type of hip fragility fractures was neck of femur (58.5%), followed by intertrochanteric (27.7%) then sub-trochanteric (13.8%). There was a statistically significant, though weak, negative correlation between age and serum vitamin D levels.

CONCLUSION: This study demonstrated a high prevalence of vitamin D deficiency and insufficiency among the elderly patients presenting with hip fragility fractures in KNH. Majority of the participants however had normal serum calcium levels.

CHAPTER ONE

INTRODUCTION

Fragility fractures are fractures that occur as a result of minimal trauma, such as a fall from a standing height or less, or in the absence of an obvious trauma. The probability to sustain a fragility fracture increases with age. Bone fragility is defined broadly as the susceptibility of bone to fracture. The biomechanical definition includes at least 3 components: strength, brittleness and work to failure (1). Bone fragility is the result of four changes in the cellular machinery responsible for attainment of peak bone strength during growth and its maintenance during adulthood; a reduction in bone formation with continued bone resorption in each basic multicellular unit (BMU) that remodels bone on its endosteal surface, increased remodeling rate and a reduction in periosteal bone formation (2).

Hip fragility fractures are associated with excess morbidity and mortality and therefore are of intense interest globally. They are the most frequently operated fracture type, have the highest postoperative fatality rate of surgically treated fractures, and have become a serious health resource issue due to the high cost of care required after injury. Moreover, many elderly patients who sustain hip fractures are unable to regain pre-fracture functional status and nearly one third of them die within the first year post injury (3).

Vitamin D deficiency is reported to be high among elderly patients in western countries with seasonal variations and it is reported to be higher in patients with hip fractures with different studies reporting vitamin D deficiency prevalence of between 55% - 92%. Elderly patients are at an increased risk of vitamin D deficiency because of risk factors such as suboptimal sunlight exposure and lower cutaneous vitamin D synthesis, reduced dietary intake, impaired intestinal

absorption and impaired hydroxylation in the liver and kidneys. Vitamin D deficiency is associated with increased muscle weakness and pain and this leads to a decrease in muscle strength, balance and function; increased bone turnover and a higher risk of falls and hip fractures in older adults. Some authors have associated vitamin D deficiency in patients with hip fractures with delayed fracture healing and a higher mortality (4–6). There has been no local study on the level of vitamin D and calcium in patients with hip fragility fractures. Results reported from the study will be informative to the orthopedic surgeons in the management of patients with varying levels of vitamin D and calcium presenting with fragility hip fractures.

CHAPTER TWO

LITERATURE REVIEW

2.1 Fragility hip fracture epidemiology

Hip fractures are among the most common fractures among the elderly globally and are of intense interest because they are associated with high cost of care, morbidity and mortality. The life time risk of developing hip fractures approaches 15% among the elderly Caucasian women aged over 50 years (7). In the western countries, they are associated with serious consequences such as significant impairment of survival, a high prevalence of prolonged disability and an increased likelihood of institutionalization (4,8).

Fragility fractures are fractures that occur as a result of a minimal trauma, such as a fall from a standing height or less, or in the absence of an obvious trauma. Worldwide, about 200 million people are at risk of fragility fracture yearly. The incidence varies greatly in different regions and is higher in the USA and Scandinavia compared to the great Britain and central Europe (9). After the age of 50, the lifetime risk of having a hip fragility fracture is 33% for an American woman and 20% for a man. The incidence increases exponentially after the age of 65 (10). It is projected that the number of hip fractures occurring in the world each year will rise from 1.66 million in 1990 to 6.26 million by 2050 (11). The incidence of hip fractures is highest in Sweden and North America, with almost seven-fold lower rates in Southern European countries (3). About 330,000 fragility hip fractures occur yearly in the US and the number is estimated to raise to 550,000 by 2040 (10). In general therefore, these fractures are well documented in Europe, America and Asia largely as osteoporosis related fragility injuries (11).

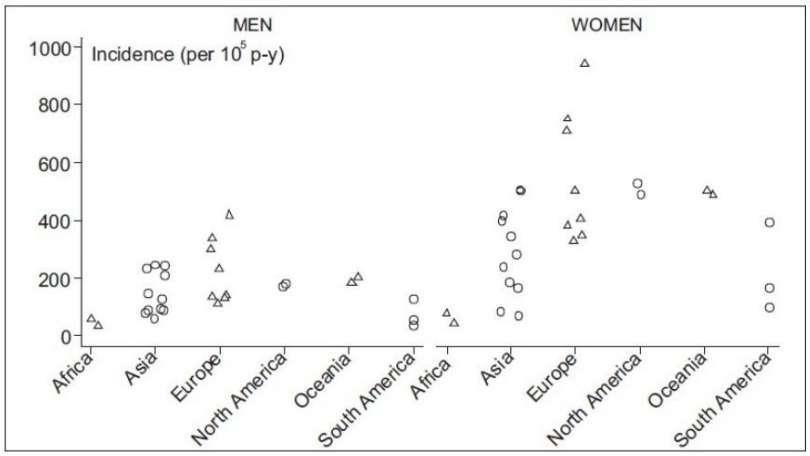

Figure 1: Hip fracture per 100000 person years in different continents: Adopted from Dhanwal DK et al. Indian Journal of orthopedics, 2011 Jan; 45(1):15-22.

Only a few papers are available documenting the incidence of hip fractures in Africa, though osteoporosis and fragility fractures are believed to be uncommon (11). Zabezi et al in a study conducted in Cameroon found an incidence of 52.1/100,000 in women and 43.7/100,000 among men above 35 years of age respectively (12). These fractures were more common in men than in women and among the men, most occurred before 50 years while in women they were more common after the age of 50. After 50 years, 90% the fractures in women and 83.3% in men were fragility fractures associated with falls (12). Adebajo et.al in their study in Nigeria found no evidence of age related increase in the rates of hip fractures in women (13).

In Kenya, the rate of post-menopausal hip fractures averaged 243 per 100 000 (14). The prevalence of osteoporosis in postmenopausal women is about 24.3% compared to 0.9 % in premenopausal women while that of osteopenia is 32% against 20.5% in Kenya (15) .

2.2 Causes of hip fragility fractures

Hip fragility fractures are caused by minimal trauma. Among the elderly, low energy axial trauma, with some rotation secondary to falls is known to cause these fractures. The falls maybe associated with slippery ground, uneven terrain, while others fall due to other unrelated medical conditions. Sustenance of fractures secondary to falls suggests bone fragility. Neither age-related osteoporosis nor the increasing incidence of falls with age sufficiently explain the exponential increase in the incidence of hip fractures among the aging (16). The most common risk factors for fragility fractures include; low body mass index, environmental risk, history of fragility fracture, early menopause, lack of vitamin D, endocrine disorders such as diabetes mellitus, excessive alcohol use and immobility (17).

2.3 Type of hip fractures

Hip fractures are subdivided into three subtypes as shown in the figure below(10,18):

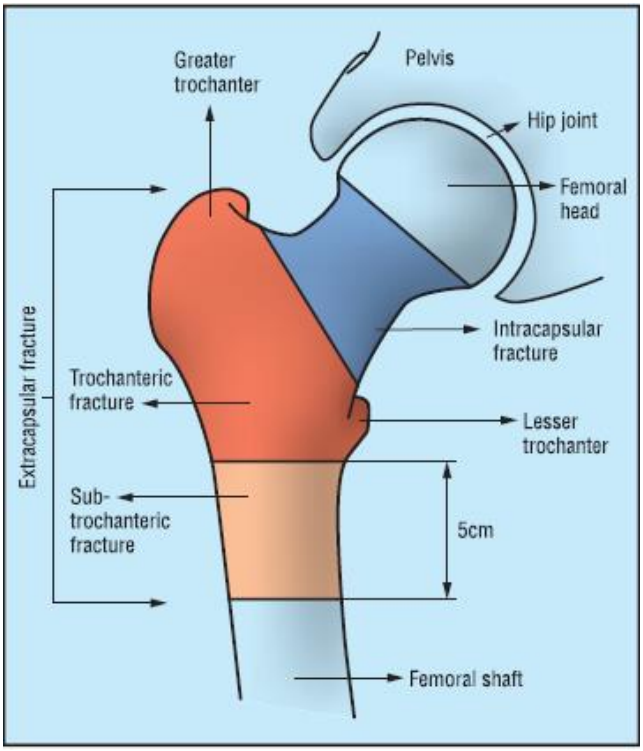

Figure 2: Hip fracture patterns adopted from Parker M, Johansen A. Hip fracture. BMJ. 2006

2.3.1 Intertrochanteric fractures

Intertrochanteric area of the femur is defined as the region from the extra-capsular femoral neck to the area just distal to the lesser trochanter (18,19). Almost 9 out of 10 of these fractures occur in patients who are older than 65 years with almost ¾ of them occurring in women (19).

2.3.2 Neck of femur fractures

Fractures through the intra-capsular femoral neck account for close to 50% of all hip fractures(20). Their incidence increases exponentially with age and are more common in females. These fractures are diagnosed from the AP pelvis and lateral radiographs though they are mainly diagnosed from the AP pelvis because of the challenge of obtaining the lateral radiograph due to pain (18,20).

2.3.3 Sub-trochanteric fractures.

These fractures occur in the proximal femur between the inferior aspect of the lesser trochanter to about 5 cm below it. In the elderly osteopenic population they result from low energy falls. They are less frequent than the neck of femur fractures and intertrochanteric fractures and constitute about 10-30% of hip fractures (18,21).

2.3.4 Distribution in fragility fractures

Intertrochanteric fractures have been documented to comprise about half of all fragility hip fractures (22). This finding has been reported in studies done in India and Asia (23). Tsabasvi et al in their study in Tanzania on fragility fractures in patients aged 50 years and above reported that most fractures were intertrochanteric at 55.8% (n 96) followed by neck of femur fractures at 28.5% (n 49), sub trochanteric at 9.9% (n 17) and 5.8% had mixed intertrochanteric and sub trochanteric (24).

2.4 Diagnosis of hip fractures

Hip fractures are diagnosed on the basis of clinical findings and AP pelvis radiographs. Lateral view radiograph of the hip can also be done to better delineate the displacement of the fracture. An AP radiograph obtained with the hip internally rotated 15-20 degrees provides the optimal image of the femoral neck (7).

2.5 Anatomy of the Hip

The hip encompasses the neck of the femur and the per-trochanteric region. This area is largely composed of cancellous bone. The trabecular in the neck region are arranged in both tension and compression groups (Figure 2). The wards triangle is enclosed by the trabecular arrangement in this region. The calcar femorale is a dense bone ridge in the posteromedial aspect of the junction between the neck and the lesser trochanter (Figure 3). The calcar is vertical in orientation, and the ridge projects laterally toward the greater trochanter.

The interior of the neck and trochanteric region of the femur exhibits a spongy configuration and represents spongy (cancellous) bone. It consists of numerous interconnecting bony trabeculae separated by a labyrinth of interconnecting marrow spaces (25). The three-dimensional orientation of bony trabeculae is not random but is correlated with the magnitude and directionality of hip joint loads (forces acting on the hip joint and transmitted on the head of the femur). The outer portion of the bone has a solid structure and represents compact (dense) bone (25).

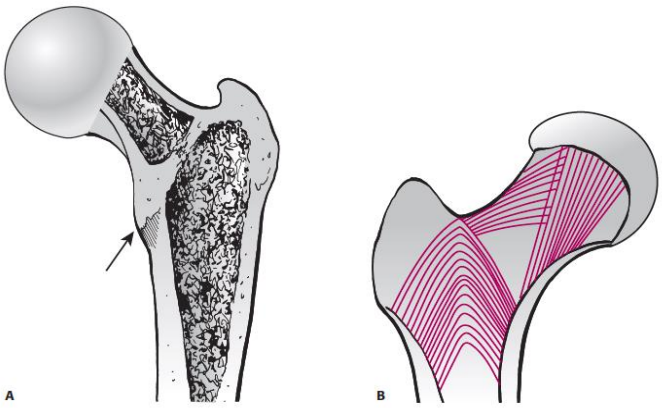

Figure 3: Showing the anatomy of the trochanteric region. In image A, the arrow shows the calcar femorale or the Adams Arch. Fractures that destroy this part are classified as unstable.

2.6 Bone strength and peak bone mass

Bone strength depends on bone mass, geometry and composition, material properties and microstructure. Bone mass accounts for 50%-70% of the bone strength. It depends on the bone size/ volume and density of the mineral content. Generally, larger bones are stronger than smaller bones because strength increases by the radius of the involved bone raised to the power of 4. Material properties like mineral content and protein content and quality also affect bone strength. Peak bone mass (PBM), is defined as the amount of bone tissue present at the end of skeletal maturation. It is an important independent determinant of bone fragility. It is considered that an increase in PBM by 1 SD reduces the fracture risk by 50%. Differences in the rate of bone growth during puberty account for the difference in PBM between females and males (26,27).

Bone mineral mass accumulation from infancy to post-puberty is a complex process involving genetics, endocrine, mechanical and nutritional factors. PBM is attained in the axial skeleton and in the proximal femur by the end of the second decade and thereafter an increase in mass and

strength is essentially due to increment in bone size. Bone mass in older adults is influenced by the peak bone mass achieved by age 18-25 less the amount of bone that was subsequently lost (28).

Aging and some skeletal diseases like osteoporosis and osteogenesis imperfecta reduce bone strength thereby producing skeletal failure due to under normal or non-traumatic conditions. Bone loading has been shown to determine bone strength and remodeling. Bone tissue is mechanosensitive and the cells associated with bone respond to mechanical stimuli by altering turnover to increase or reduce the amount of tissue present, which then alters both architecture and material properties. The structure of bone therefore represents the integration of the loading history experienced throughout the individual's lifetime (2).

The structural behavior of bone is governed chiefly by bone mass/ density, microarchitecture i.e. the geometrical and spatial distribution and connectivity of trabeculae and lastly by tissue material properties. Alteration in any of these components could compromise the integrity of the bone structure and its ability to bear loads. This alteration can occur due to aging, sex and disease (2).

2.7 Bone modeling and remodeling

Bone modeling is defined as deposition of new bone without prior bone resorption. Bone remodeling on the other hand is characterized by appearance of focally and temporary distinct regions of resorption followed by bone formation in the basic multicellular units (BMUs) (29).

Bone remodeling is a highly regulated succession of events involving osteoclastic bone resorption and osteoblastic bone formation. This interaction occurs within a spatial unit called the basic multicellular unit (BMU) in cortical bone and bone structural unit in trabecular bone. Bone loss occurs with age due disequilibrium between these processes. The cellular mechanism underlying the decreased bone formation is still controversial. Some authors have suggested decreased

osteoblast recruitment, decreased life span and a decreased capacity to synthesize collagen as possible mechanisms. Moreover, age related bone loss is associated with an increase in the amount of bone resorbed (30,31). The remodeling imbalance leads to disordered skeletal architecture and thus leads to increased fracture risk (28).

A high remodeling rate contributes to bone fragility by reducing the time available for secondary mineralization. Bone is removed and replaced with new, les densely mineralized bone, which reduces its material stiffness. High bone remodeling itself also alters collagen composition by impairing isomerization , maturation and crosslinking (29).

2.8 Factors affecting bone remodeling

Bone remodeling is influenced by both local and systemic factors as well as environmental factors. Osteocytes detect changes in the levels of hormones that affect their activity and survival rate. These hormones include oestrogens and glucocorticoids. Systemic hormones are brought to the BMU by means of blood capillaries and cells release local factors in an autocrine/ paracrine mode. This can influence the activation frequency, which is determined by the number of BMUs at a given point in time, in addition to influencing the balance of cells within each BMU (31).

Local growth factors, cytokines and prostaglandins also function to either enhance or inhibit osteoclast formation and function. Osteoclast activity is promoted by IL-1, IL-3, IL-6, IL-11 Tumour necrosis factor and granulocyte macrophage colony stimulating factor among others. On the other hand, IL-4, IL-10, IL-18 and interferon inhibit development of osteoclasts. Members of the BMP family, Wnt family, hedgehog family and growth factors such as insulin-like growth factor also modulate various steps in osteoblastogenesis. In addition, prostaglandins are also involved in the process of bone remodeling and repair and target both the osteoblasts and osteoclasts (31).

The main systemic factors are hormones that are key in bone remodeling include the following:

Parathyroid hormone: It is an 84 – amino acid peptide that is responsible for the short term regulation of calcium homeostasis. It secretion from the parathyroid gland is controlled by the extracellular levels of calcium. It works to increase renal tubular absorption of calcium and also stimulates renal synthesis of 1,25 vitamin D3 (31).

1, 25-Dihydroxyvitamin D3: Secreted in response to low calcium levels, it major target tissues are bone, kidneys and the intestine. In bone, it stimulates the activity of osteoclasts increasing bone resorption. It increases calcium absorption in the intestine by stimulating the synthesis of calbindins. These proteins then bind to calcium and transport it against its concentration gradient. A similar mechanism is also found in the renal calcium reabsorption (31).

Sex steroids: Decline in estrogen is associated with progressive loss of trabecular bone structure. In oestrogen deficiency, bone formation is unable to match the increased bone resorption. Oestrogen deficiency is associated with an increase in intensity of bone remodeling through an increase in the lifespan of osteoclasts and reduced lifespan of osteoblasts (29).

Mechanical factors have also been shown to influence bone remodeling. Osteocytes act as mechanosensors that signal the need for bone remodeling in line with functional loading according to Wolf's law. They are thought to recognize changes in the interstitial flow rate within the canaliculi system that occur upon functional loading of the bone. They are connected to osteoblasts and bone lining cells therefore the demand to establish a new BMU is transmitted to the bone surface(31). Absence of muscular activity, rest and weightlessness has deleterious effects on bone. Trabeculae tend to align with maximum stresses. Mechanical stress also influences collagen alignment as new bone is formed (26).

2.9 Effect of aging on bone fragility

Bone fragility can be defined broadly as the susceptibility of bone to fracture. The biomechanical definition of bone fragility includes at least 3 components: strength, brittleness and work to failure(1). Bone fragility results from a reduction in bone mass and bone density. Therefore, disorders of collagen, mineral content composition and distribution and disorders of bone remodeling can lead to bone fragility (29). Aging affects bone mass, architecture and material properties. Bone mass decreases with age after peak bone mass has been achieved in both men and women. By 80 years of age, BMD decreases by 13-18% in men and by 15-54% in women. Recent studies on femoral heads of patients with hip fractutres undergoing THR have demonstrated significantly increased mineral to matrix ratio compared to femoral heads of patients without fractures suggesting that compositional failures may precede the fracture (32).

Changes in the cellular machinery responsible for attainment of peak bone strength during growth and its maintenance during adulthood; a reduction in bone formation with continued bone resorption in each basic multicellular unit (BMU) that remodels bone on its endosteal surface, increased remodeling rate and a reduction in periosteal bone formation can influence bone fragility (1).

2.10 Pathophysiology of fragility

Bone stiffness (resistance to deformation) and strength (maximum stress to failure) determine its ability to carry large loads, while toughness, or ductility, determine its ability to absorb the energy from impact loads. Bone strength is determined by the amount of mineral content. Alteration in collagen structure may also contribute to increased brittleness due to the shift in its cross-linking profile, which not only stiffens the organic matrix, but also affects the morphology of the mineral component. As one ages, sex-related differences in the distribution (geometry and morphology)

become more pronounced, and these differences are believed to contribute to increased fracture incidence in the extremely elderly population. Age-dependent changes were associated with increases in cortical porosity, non-enzymatic collagen cross-links, and absolute collagen content.

Repetitive loading of bone leads to development of cracks, initially at the sub-micron level, but eventually these cracks become visible, and if they are not repaired by the bone remodeling process, they can lead to failure. It has been hypothesized that the initial cause of the cracks is either disruption of bone mineral crystallites, bond interference at the mineral organic interface, disruption of collagen fibrils, or some combination of all three. Disruption of the structure of the bone cells that are embedded in mineral also can contribute. With age, the extent of these micro-damage increases exponentially as the micro-crack densities and lengths also increase. The inability to repair the cracks and their increasing propagation with age likely contribute to the reduced toughness of both cortical and trabecular bone (33).

Changes in bone morphology with age also influence fragility. Bones remodel to facilitate their mechanical functions i.e. being strong enough to withstand large forces while being streamlined enough to minimize energy demands. During early life, the cross-sectional geometry of long bones undergoes cortical drift, where it begins with a more uniform outer wall thickness and progresses to an ellipsoidal shape. This occurs when formation is decreased and resorption increased on the endosteal surface, while bone is deposited on the periosteal surface. It leads to an increase in bone diameter and cortical thinning where endosteal resorption is greater than formation. Cortical drift occurs rapidly during pre-pubertal growth and levels off after closure of the epiphyseal plate. It increases again in the elderly, often resulting in weaker bone with a wider diameter and significantly thinner cortices (33).

Changes in bone cells also occur with aging. About 60 to 80% of osteoblasts that are recruited to a resorption pit die by apoptosis within 200 days. Some become small, quiescent bone-lining cells along inactive surfaces. The remaining osteoblasts are surrounded by mineral and extend long processes (dendrites), which allow signaling and nutrition to pass from cell to cell through canaliculi. These are called osteocytes and make up about 90% of the cells in bone. Their lifespan is about 1 to 50 years and they function as mechanoreceptors.

Osteoclasts are of hematopoietic origin, and they are multinucleated giant cells responsible for removing bone (resorption) following signals from osteoblasts and osteocytes. The osteoblasts, osteoclasts, and osteocytes have a limited lifespan, which is controlled by the number of replication cycles and external factors. Aging is associated with the development of an inability to respond to forces. This leads to increased susceptibility to mechanical damage, increased apoptosis, and alterations in intracellular signaling, and an impaired regulation of gene expression.

The amount of bone deposited with each cycle of remodeling decreases with age. This is likely due to a reduction in the number of cell precursors of osteoblasts, a reduction in the number of stem cells from which these precursors are derived, or a reduction in the lifespan of osteoblasts. Osteocyte apoptosis also has been noted to increase with tissue age, and this contributes to bone weakening independent of BMD (33).

Changes in the bone protein also occur with age. Collagen (mainly type I) and approximately 5% non-collagenous proteins form the bone matrix. Collagen provides the flexibility (toughness) to the bone structure, which provides resistance to impact loading and serves as a template for the oriented deposition of mineral crystals. Protein production reduces with aging (33).

2.11 Hormonal changes with aging.

Aging is associated with a decline in a variety of hormones including hormones involved in the regulation of bone metabolism like estrogens, androgens, growth hormones and vitamin D. Estrogen deficiency in postmenopausal women is associated with accelerated bone loss with women losing between 1/3 to ½ of their bone mass within up to 10 years of their menopause. Spontaneous and stimulated growth hormone secretion as well as insulin-like growth factor 1 also decrease with advance in age. Elderly subjects are frequently deficient in vitamin D. The deficiency is attributed to lack of sunlight exposure, inadequate dietary intake, medications that may impair vitamin D metabolism and medical conditions that may impair vitamin D metabolism. Vitamin D deficiency can lead to secondary hyperparathyroidism leading to increased bone turnover and bone loss, muscle weakness and pain (31).

2.12 Sex and Disease

The incidence of fragility fractures is generally higher in women. For both sexes, volume fraction and density in human cancellous bone declines steadily throughout life (32). Histophometry studies have shown that sex has minimal impact in this decline. For men, decreased bone volume results from progressive thinning of trabeculae while maintaining the trabeculae network. In women on the other hand, bone volume reduction results mainly from loss of trabeculae (which leads to increased trabeculae separation) while thickness of the remaining trabeculae is maintained (1,32,34).

Disruption in bone metabolism by disease e.g osteoporosis or osteogenesis imperfect can compromise structural integrity and the ability of the bone to bear loads. Osteoporosis is marked by reduced bone density and a deteriorated architecture which reduces bone strength and increases likelihood of fractures. At 50 years, white women have been shown to have a 40% lifetime risk

and white men a 13% lifetime risk of sustaining a hip, forearm or spine fracture due to osteoporosis (32,34).

2.13 Vitamin D

Vitamin D, first identified as a vitamin early in the 20th century, is now recognized as a pro-hormone. Vitamin D, also known as calciferol, comprises a group of fat-soluble seco-sterols. The two major forms are vitamin D_2 and vitamin D_3. Vitamin D_2 (ergocalciferol) is largely human-made and added to foods, whereas vitamin D_3 (cholecalciferol) is synthesized in the skin of humans from 7-dehydrocholesterol and is also consumed in the diet via the intake of animal-based foods (35). There are a few naturally occurring food sources of vitamin D. These include fatty fish, fish liver oil, and egg yolk. Some foods are, however, fortified with vitamin D. In some countries like Canada, fortification of some foods like milk and margarine with vitamin D is mandatory (36). Calcitriol (1, 25 dihyroxyvitamin D3) which is the active form of vitamin D has a half-life of about 15 hours while calcidiol (25 hydroxyvitamin) has a half-life of about 15 days (6,35). Wearing a sunscreen with a sun protection factor of 30 reduces vitamin D synthesis in the skin by more than 95%. People with a dark skin tone have a natural sun protection and require at least 3-5 times longer exposure to the sun to make the same amount of vitamin D as people with a white skin tone (37).

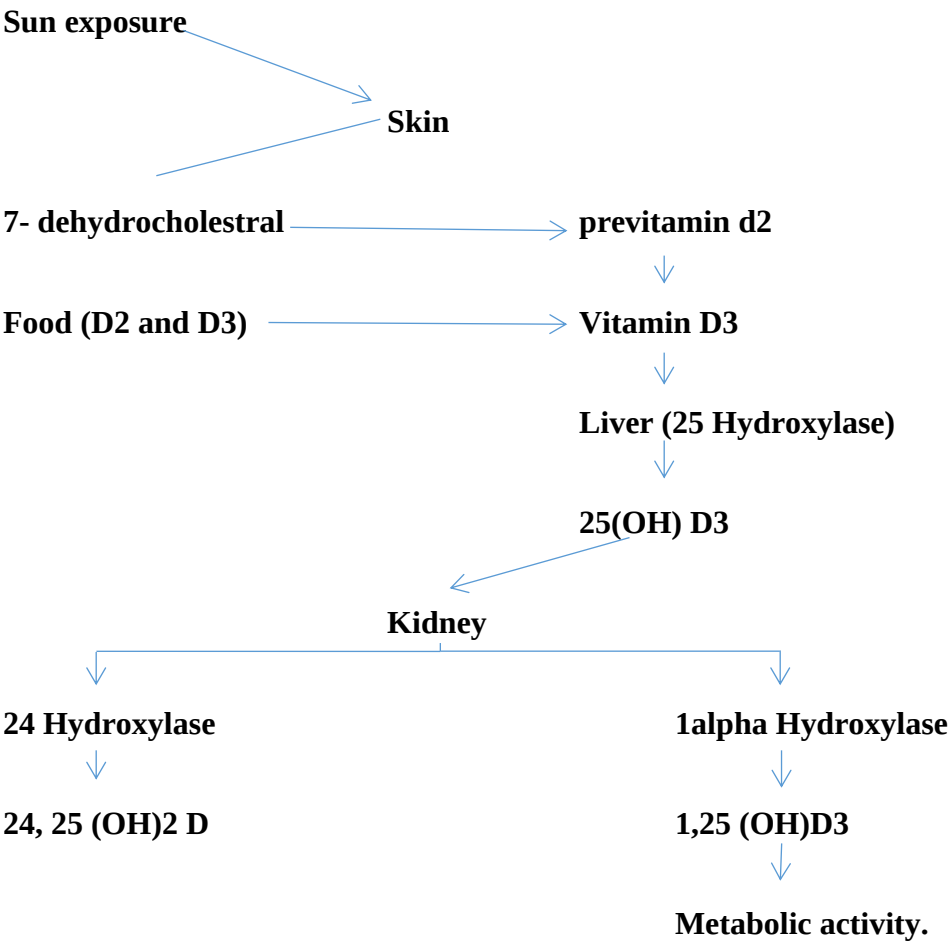

Figure 4: Overview of Vitamin D synthesis, intake and activation

2.14 Mechanism of action of Vitamin D

Effects of 1, 25-VD are mediated through the VDR, a member of the nuclear receptor superfamily that includes receptors for steroids (androgen, progesterone, glucocorticoid and estrogen) as well as for thyroid hormone and retinoids. 1, 25-VD passively diffuses into target cells, binds to VDR in the cell membrane or nucleus of various cell types and activates target genes containing one or more vitamin D response elements (VDREs) within their promoters. Target genes include: osteocalcin, osteopontin, calbindin, 24-hydroxylase, and p21 (6). At the nuclear level, the activation of VDR induces heterodimerization between the active VDR and the retinoic receptor

(RXR). This leads to the activation of the vitamin D response element (VDRE), a complex of genes coding for the "genomic effects" of vitamin D (5,38). This regulates the expression of more than 900 genes, thus affecting a myriad of signaling cascades in the body (38).

2.15 Effects of vitamin D in muscles

The VDR is also expressed in muscles and effects of vitamin D in muscles occur through two mechanisms: VDR acts as a nuclear receptor which mediates the so-called genomic effects; VDR also acts via nonnuclear receptor mediating non-genomic actions. Genomic effects of VDR include the increase in calcium handling by enhancing the activities of the calcium binding protein (calbindin-D9K) in cell sarcoplasm, muscle cell differentiation and proliferation through effects on insulin growth factor expression which in turn induces skeletal muscle hypertrophy. The non-genomic actions are not well understood. 1,25 vitamin D appears to bind a membrane receptor which activates a transduction signal inducing MAP kinase (MAPK) and phospholipase C (PLC) pathways, which in turn lead to a rapid influx of calcium into the cell (5).

Many authors have explored the relationship between vitamin D levels and muscle function and strength. Most of the observational studies report a significant association between hypovitaminosis D and muscle dysfunction in all categories of ages, except in very old individuals. On the contrary, vitamin D levels greater than 50 nmol/L are associated with the lowest probability of muscle dysfunction (5). Vitamin D receptors are also located on the fast twitch muscles which are the first to respond in a fall. Low vitamin D concentration is associated with increased of falls in older adults (37).

Risk of falling increases due to muscle weakness that is commonly associated with slower reflex response. Low muscle strength has also been shown to increase the risk of fragility fracture because

of its long term negative impact on bone density. Lack of muscle strength and bulk has been shown to influence fracture development upon a fall onto the hip region due to lack of adequate shock absorber (3,39).

2.16 Vitamin D Deficiency and Hip Fracture risk

Vitamin D deficiency is associated with increased muscle weakness and pain and this leads to a decrease in muscle strength, balance and function; increased bone turnover and a higher risk of falls and hip fractures in older adults (4,8). Elderly patients are at an increased risk of vitamin D deficiency because of risk factors such as suboptimal sunlight exposure and lower cutaneous vitamin D synthesis, reduced dietary intake, impaired intestinal absorption and impaired hydroxylation in the liver and kidneys (4,40).

Studies in the west have shown vitamin D deficiency to be common among the elderly especially during periods of spring due to decreased cutaneous synthesis during the winter months. In their study, Cauley et. al found that the adjusted odds ratio for a hip fracture per 10ng/ml decrease in serum 25 vitamin D to be 1.3 times. Fracture risk in vitamin D deficiency has been shown to be independent of the bone density in similar studies that included measurement of BMD (4,41).

In a study in Singapore involving 412 patients with acute hip fractures, vitamin D deficiency was found in 57.5%, insufficiency in 34.5% and sufficiency in 8% of the patients (41). Todd et.al had observed a high mortality in post-menopausal women with vitamin D deficiency (42). In a case control study in Chinese population, Fu et al. in 2015 reported a positive correlation between low serum 25 hydroxycholecalciferal and hip fractures among postmenopausal women (43). Furthermore, general hypovitaminosis D in adults with acute hip fractures in a Japanese population have been documented.

Among patients with fragility fractures, previous studies have shown vitamin D deficiency prevalence rates of between 55%-91.6% (8,11,41,44,45).

The fracture risk in various levels of vitamin D has been explored before in osteoporosis. However, many authors have disagreed on the optimum serum 25 (OH) D levels associated with increased fracture risk. In 2010, Melhus et al found that a serum 25(OH) D below 40nmol/l suggested an increased fracture risk. Cauley et al in 2008 had reported that 25(OH) D ranges between 60-70 nmol/l were associated with the lowest risk of fracture. Van Schoolar in 2008 found that serum 25 (OH) D less than or equal to 30 nmol/l were associated with the greatest fracture risk (4,46,47).

Previous similar studies have shown geographical, seasonal and gender variations in the levels of vitamin D and calcium level patterns among elderly patients with hip fractures. Half the elderly patients with hip fractures in the United States were reported to have hypovitaminosis D compared to ¾ in India and only 21.6% in Italy (11,43). Patients with lower vitamin D levels have been demonstrated to have a higher risk of hip fracture independent of the number of falls, physical function, frailty and sex steroid hormone levels (4). Various authors have recommended a serum vitamin D level of 75 nmol/l as adequate to maintain bone metabolism and levels below 50 nmol/l as predictive for fracture occurrence. However, there is still no consensus on the utility of vitamin D utility in predicting fracture occurrence (43).

Other studies have explored the utility of vitamin D and calcium supplementation in preventing hip fractures. Lips et al found out that a daily vitamin D supplement of 800 IU/ day reduced the relative risk of getting hip fracture by between 26%- 29% (40,48). Daily doses of less than 400 IU were found to be of no benefit in reducing the fracture risk (37). Current recommendation for

vitamin D supplementation in people with osteoporosis or substantial risk of osteoporosis is 800 – 1200 IU of vitamin D3 if dietary intake and sunlight exposure are not adequate (10).

Elderly people are also known to have varying ambulation status depending on comorbid conditions, nutrition status and age. Vitamin D deficiency is now known to cause muscle weakness. Studies have shown that performance speed and muscle strength can be greatly improved by vitamin D supplementation in patients with vitamin D deficiency (40,48).

There are however reports that have not associated hypovitaminosis D with hip fractures (49,50).

2.17 Assessment of Vitamin D levels

The most reliable assessment of vitamin D status is the measurement of plasma 25-hydroxyvitamin D concentration. Quantitation of serum 25(OH) D provides a clinically useful assessment of an individual's vitamin D status mainly because, first the half-life of 25(OH) D is about 3 weeks. This serves as rather better indicator for both the vitamin D obtained from ultraviolet irradiation and from dietary sources over longer periods (51–53). Secondly, the liver production of 25(OH) D is not significantly regulated and is primarily dependent on substrate concentration. Measurement of serum 25(OH)D therefore provides the best estimate of the patient's vitamin D status (51,54,55).

The methods utilized in assessment of vitamin D levels vary widely depending on the manufacturer. There has been an upsurge in the methods of analyzing vitamin D in the recent past but this has been associated with a high inter and intra user variability depending on the machine and type of analysis. The accepted gold standard is the liquid chromatography isotope dilution tandem mass spectrometry (LC-IDMS/MS) (54,56–58). A variety of immunoassays are also used to determine the concentration of total vitamin D and its other metabolites. These immunoassays are more variable than the LC-MS/MS because they rely on antibodies that may differ in their

recognition of both the vitamin D2 and D3 metabolites. DiaSorin LIASON offers CLIA method which measures total 25-hydroxyvitamin D and other metabolites in human serum through a two-step procedure. First, 25(OH)D2 is dissociated from its binding protein and binds to the specific solid phase antibody. Vitamin D isoluminal tracer is then added to initiate the chemiluminiscent reaction. The light signal is then detected by a photomultiplier and this measurement is inversely proportional to the concentration of 25-hydroxyvitamin D (58,59).

2.17.1 Suggested vitamin D levels

Vitamin D deficiency has been defined as a 25(OH) D below 20 ng/ml (50 nmol/l). Insufficiency is defined by a 25(OH)D of between 21-29 ng/ml (52.5-72.5 nmol/l) while sufficiency is defined by 25(OH)D levels of above 30 ng/ml (75 nmol/l) (35,40,54).

2.18 Calcium in hip fractures

Calcium is bone protective based on its key structural role in bone and metabolic balance (60,61). Of total body calcium, 99% is found in bone and teeth as calcium hydroxyapatite. The remaining 1% is found in the extracellular fluid where 50% of it is free while 40% is highly bound to proteins (80% to albumin and 20% to globulins) and 10% exists as diffusible inorganic and organic anions e.g. bicarbonates and citrates (62).

The main sources of calcium are foods and supplements. Dietary sources are mainly dairy products such as milk, cheese and yoghurt. Supplements exist as fortified foods or medical supplements(63). Its metabolism is regulated by vitamin D and parathyroid hormone. Calcium is absorbed by active transport (transcellularly) and by passive diffusion (paracellularly) across the intestinal mucosa. Active transport of calcium is dependent on the action of calcitriol and the intestinal vitamin D receptor (VDR). This transcellular mechanism is activated by calcitriol and accounts for most of

the absorption of calcium at low and moderate intake levels. Transcellular transport occurs primarily in the duodenum where the VDR is expressed in the highest concentration. With aging and after menopause, fractional calcium absorption has been reported to decline on average by 0.21 percent per year after 40 years of age. Other authors have also reported decreased absorption with age (62,64).

The vitamin D metabolic system forms the basis of the calcium homeostatic mechanism in mammals. Total calcium concentration in serum is tightly regulated to remain between 8.5 and 10.5 mg/dL (2.12 and 2.62 mmol/L). If this level deviates slightly, the calcium sensing receptor of the parathyroid gland signals the secretion of PTH. PTH then acts to increase calcium levels by stimulating 1, 25 vitamin D secretion from the kidneys thereby increasing absorption in the intestines and reabsorption in the kidneys (64,65).

2.18.1 Reference ranges for serum calcium

The serum calcium levels (both free and total) are characterized by high physiologic variation depending on age, sex, physiologic state and even season. Therefore, separate reference ranges have been established based on both sex and age as shown below:

Parameter	Age (yrs)	Reference ranges (mg/dl)
Serum calcium in males	17-18	9.5- 10.4
	19- 21	9.3- 10.3
	22 and above	8.9- 10.1
Serum calcium in females		
	15- 18	9.1- 10.3
	19 and above	8.9- 10.1

Figure 5: Total serum calcium reference ranges in males and females by age group.

Hypo-albuminemia is a common cause of pseudo-hypocalcemia. Therefore calcium levels are corrected for albumin levels using the following equations (60,62,66):

Corrected Calcium = Measured Total Calcium -0.8(4.0- serum albumin)

(mg/dl) (mg/dl) (g/dl)

The corrected total calcium concentration is normally 8.5 – 10.2 mg/dl (62).

Corrected Ca = Measured total Ca + [40 - serum albumin (g/L)] X 0.02

(mmol/l) (mmol/l) (g/L)

Calcium is maintained within a fairly narrow range from 8.5 to 10.5 mg/dl (4.3 to 5.3 mEq/L or 2.2 to 2.7 mmol/L). Normal values and reference ranges may vary among laboratories as much as 0.5 mg/dl (62).

Low calcium has been postulated as one of the causes of osteoporosis which led to the promotion of calcium supplementation as one of the methods in controlling fragility fractures (67,68). However, there are controversies as to whether calcium supplementation prevents fragility fractures. Some studies have shown that long term supplementation of calcium is fracture protective (69,70). While other studies have not demonstrated a significant reduction in the risk of hip fracture secondary to calcium supplementation (71).

Nevertheless, low serum calcium levels have been associated with low bone mineral density and an increased risk of trochanteric fractures (61,72). In their study, Li et.al focused on individuals who were in vegetative state, with low BMD and found out that they had concomitant low serum calcium levels (72). None of the studies carried out a calcium survey on a normal group of patient who had suffered trochanteric fractures. It is therefore of interest to quantify the serum levels of calcium in otherwise normal individuals, immediately after sustaining hip fractures and analyze their relationship.

2.19 Conclusion of literature review

Fragility hip fractures are the most common osteoporotic fracture. They are associated with high morbidity and mortality burden and huge cost of treatment. Vitamin D deficiency is reported to be high in patients with fragility hip fractures, and low vitamin D has been shown to be a risk factor for development of these fractures. Low calcium has been documented as a cause of secondary osteoporosis. Current recommendation is to supplement vitamin D and calcium in people with osteoporosis or substantial risk of osteoporosis if dietary intake and sunlight exposure are not adequate.

2.20 Justification

Life expectancy is rising globally and the number of elderly individuals is increasing. Several physiological, mechanical and disease states contribute to bone and muscle strength which influence individual's risk of sustaining fragility fracture. Serum vitamin D and PTH are key regulators of bone remodeling while calcium has a key structural role in bone and metabolic balance.

Elderly patients are at an increased risk of vitamin D and calcium deficiency due to decreased sunlight exposure, low cutaneous synthesis, reduced dietary intake, impaired intestinal absorption and hydroxylation in the liver and kidneys. Observational studies have documented a significant association between hypovitaminosis D and muscle dysfunction across all age groups. Sufficient serum vitamin D levels (>50mmol/l) are associated with the lowest possibility of muscle dysfunction. Elderly patients receiving high dose vitamin D and calcium supplements not only develop improvements in bone density but also develop improved balance and are less likely to suffer falls.

Previous studies have shown geographical, seasonal and gender variations in the levels of vitamin D and calcium among the elderly patients with hip fractures. No study has been carried out on vitamin D and calcium level in patients with hip fragility fractures in Kenya or Africa. This study therefore aimed to bridge the knowledge gap on vitamin D and calcium level patterns in our setting. The knowledge shall be useful in the management of elderly patients with or at risk of hip fragility fractures.

2.21 Problem statement

Vitamin D and calcium deficiency is common in the elderly. Vitamin D deficiency has also been documented as an independent risk factor for sustenance of fragility fractures. The levels of vitamin D and calcium have not been studied locally in patients with hip fragility fractures. This study therefore aimed to determine the level of serum calcium and vitamin D among elderly patients presenting with fragility hip fractures at KNH and to correlate these levels with patients' selected characteristics such as type of hip fracture, age and gender.

2.22 Research question

What are the levels of serum calcium and vitamin D level among elderly patients with hip fragility fractures at Kenyatta National Hospital?

2.23 Objectives

2.23.1 Broad objective

To determine the levels of serum calcium and vitamin D distribution among patients with hip fragility fractures at KNH.

2.23.2 Specific objectives

1. To determine the serum calcium and vitamin D levels among elderly patients with hip fragility fractures at KNH.
2. To describe the types of hip fractures at Kenyatta National Hospital.
3. To correlate the serum calcium and vitamin D levels with selected patient characteristics including type of hip fracture, age and gender.

CHAPTER 3:

METHODOLOGY

3.1 Study design

This was a hospital based descriptive cross-sectional study.

3.1 Study site

This study was carried out at the Kenyatta National Hospital Accident and Emergency department and orthopedic wards. The analysis of Calcium and Vitamin D was done at the Pathologists Lancet Kenya laboratory Nairobi.

KNH is a metropolitan, tertiary, referral and teaching hospital situated at Upper Hill area along Hospital Road about 5km from Nairobi city centre. It has a 2000 bed capacity and is one of the two main referral hospitals in Kenya, also serving the greater East and Central African region. Pathologists Lancet Kenya laboratory in Nairobi is a franchise of Lancet group of laboratories originally founded in South Africa about 65 years ago and has been in operation in Kenya since 2009. They offer specialist pathology services by providing vital diagnostic, monitoring and screening testing from routine to specialized and esoteric tests.

3.2 Study period

This study was conducted between the month of June 2019 and September 2019.

3.3 Study population

The participants comprised of elderly (>65 years) patients with hip fragility fractures seen at KNH Accident and Emergency department and orthopedic wards.

3.3.2 Case definition for hip fracture

A hip fragility fracture was defined as a hip fracture occurring as a result of minimal trauma such as a fall from a standing height or less, or in the absence of an obvious trauma.

A hip fracture type was defined as femoral neck fractures, intertrochanteric fractures or sub trochanteric fractures.

3.3.3 Inclusion criteria

- Patients aged ≥65 years with a hip fracture and seen at KNH within the study period.
- Patients who give written informed consent.

3.3.4 Exclusion Criteria

- A hip fracture due to metastatic bone disease.
- Hip fractures resulting from high energy.

3.4 Sample size calculation

The primary outcome of this study was the level of serum Vitamin D and calcium among elderly patients with hip fractures. The outcome was expressed in terms of mean level of vitamin D in the study population. The sample size was therefore calculated using the formula for estimation of population mean (Charan & Biswas, 2013) (73).

$$\boldsymbol{n \geq \frac{Z^2_{\alpha/2}.\sigma^2}{d^2}}$$

Where; n is the minimum sample size required?

$Z_{\alpha/2}$ is the standard normal critical value at α-level of significance ($\alpha = 0.05$; $Z_{\alpha/2} = 1.96$)

σ is the standard deviation of Vitamin D in the population ($\sigma = 4ng/ml$based on the standard reference range for people defined as having insufficient level of vitamin D (21-29 ng/ml))

d is the desired margin of error (d=1 ng/ml)

Based on this formula, the required minimum sample size was n=63 patients

3.5 Sampling method and recruitment

Consecutive sampling method was used to recruit patients into the study until the desired sample size was achieved. The principal investigator and one research assistant went through the daily admission/patient register at the A &E and orthopedic wards to identify all eligible patients seen/admitted on each day. The patients' file and radiographs were then retrieved for further scrutiny to select patients with hip fragility fractures. The nature and purpose of the study was explained to the patients who met the inclusion criteria after which a written informed consent was obtained from those who accepted to participate in the study. Patients who decline to consent were excluded.

3.6 Data collection procedure

3.7.1 Clinical methods

Permission to access clinical information from the participants' records was sought from the participant, thereafter a diagnosis of hip fragility fracture was made by the principal investigator (PI) based on the mechanism of injury. The type of hip fracture was observed on the radiograph by the principal investigator and an orthopedics consultant and documented in a study proforma. Data on the mechanism of injury and the demographic characteristics of the participant such as age, sex, marital status, history of smoking and alcohol consumption was also recorded on the

study proforma. Each study proforma was assigned a unique study serial number and no identifying features of participants were used to ensure confidentiality. All data gathered was securely stored and was only accessible to the relevant personnel. All databases were secured with password-protected access systems.

3.7.2 Laboratory methods

Using aseptic technique 5 milliliter blood volumes was drawn from the ante-cubital fossa from each study participant after application of tourniquet on the arm. The blood was collected into a plain (red cap) vacutainer and used for the assay of serum calcium, Vitamin D and albumin. The samples were labeled with unique serial numbers assigned to the patient to maintain privacy and confidentiality. They were then delivered to the Lancet Kenya limited, Upper hill Nairobi for processing. Serum vitamin D concentrations were determined by the LIAISON® 25-OH Vitamin D assay technique. This is an automated chemiluminescent immunoassay (CLIA) method that is rapid, accurate and precise. This method is well validated according to the National Committee for Clinical Laboratory Standards (NCCLS) protocols(74). Analysis of calcium and albumin level was done using the COBAS INTEGRA 400/800 machine, which is an automated biochemistry analyzer. All samples were analyzed within 30 minutes of collection, where not possible the samples were stored in ice or refrigerated for up to 48 hours (62,67). Disposal of all used samples was done as per the Lancets protocols and standard operating procedures on disposal of biomedical waste.

Study flow chart

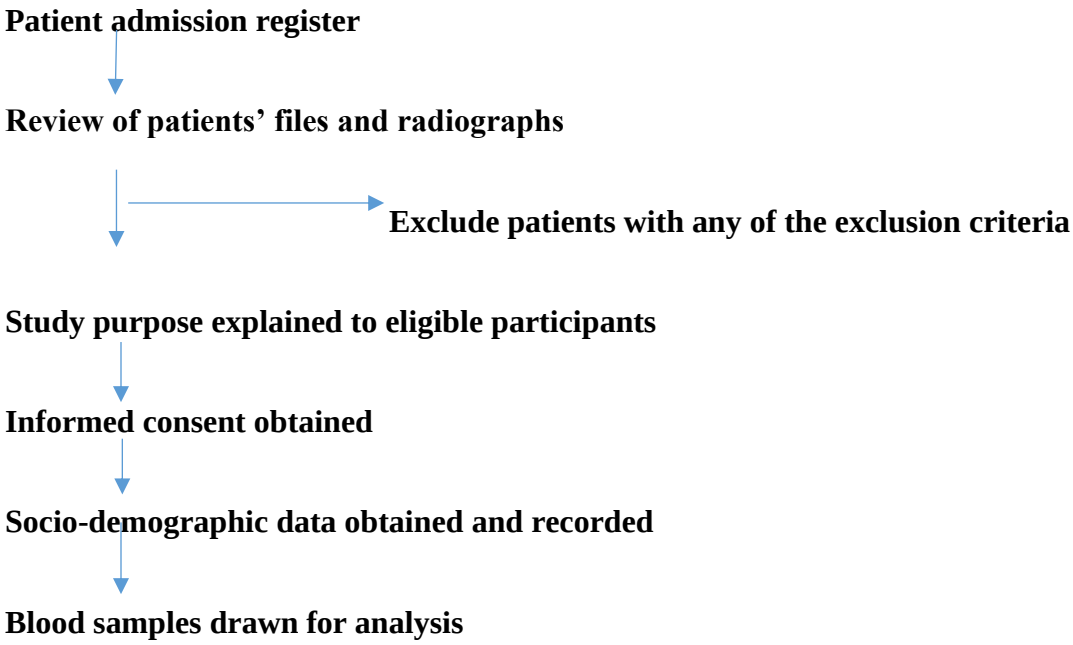

Figure 6: Study flow chart.

3.7.3 Definition of variables

- Serum Vitamin D levels
  - Vitamin D deficiency: ≤20 ng/ml (≤ 50 nmol/l)
  - Vitamin D insufficiency: 21- 29 ng/ml (52.5- 72.5 nmol/l)
  - Vitamin D sufficiency: ≥ 30 ng/ml (≥75 nmol/l)
- Albumin corrected serum calcium
  - Hypocalcemia: < 8.5 mg/dl (< 2.2 mmol/l)
  - Normocalcemia: 8.5- 10.2 mg/dl (2.2 – 2.7 mmol/l)
  - Hypercalcemia: > 10.2 mg/dl (>2.7 mmol/l)
- Age in years
- Gender – male or female

- Type of hip fractures: Hip fractures were subdivided into; Neck of femur fractures, intertrochanteric fractures and sub-trochanteric fractures.

3.7.4 Conceptual Framework

Reduced serum vitamin D and calcium levels are associated with increased risk to development of hip fragility fractures due to the associated decrease in bone strength and increased muscle weakness which leads to increased susceptibility to falls. Vitamin D deficiency is more common among the elderly due to various factors like decreased cutaneous synthesis, reduced exposure to sunlight, reduced intestinal absorption and impaired metabolism in the kidneys and liver. Other notable factors that contribute to hip fractures and supported by literature are the patients' characteristics such as age and gender.

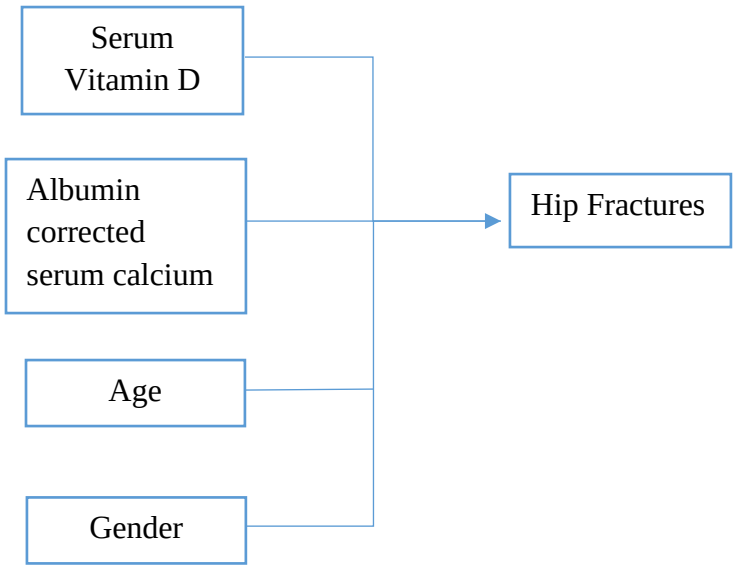

Figure 7: Conceptual Framework

3.7.5 Quality control

The Standard Operating Procedures for specimen collection, labeling, storage and transport were strictly adhered to minimize pre-analytical errors. The machine used for analysis were properly

calibrated using standard calibration methods and materials, and the tests assayed against controls. The Lancet laboratory carried out internal and external quality control.

3.8 Data management and analysis

Data was entered into Microsoft Excel 2013 in a password protected computer. Cleaning, coding and analysis was done using Statistical Package for Social Sciences version 23. Data cleaning was done to detect and correct discrepancies (missing data or extreme values) in the data. Univariate analysis was done to summarize the data/variables. The primary outcomes were the serum level of 25 hydroxycholecalciferol and calcium. Means with standard deviations as well as Median with IQR were reported to summarize the distribution of serum level of 25 hydroxycholecalciferol and calcium. Pearsons Chi Square test was done to look for association between serum calcium serum vitamin D with selected patient characteristics. A Fisher's exact test was used to test the association between Calcium level and gender. The study was conducted at 0.05-level of significance.

3.9 Ethical considerations

The study was undertaken after approval by the Department of Orthopedics, University of Nairobi and the KNH/UoN Scientific and Ethical Review Committee. The objectives and purposes of the study were clearly explained to eligible participants in a language they understood. Only patients who gave informed consent were recruited into the study after signing the consent form. The patients were assured that participation was voluntary and that medical attention would not be denied if they were to decline participation in the study. Patients were free to withdraw from the study at any point without discrimination. Confidentiality was maintained by storing the study proformas in a secure location and excluding the patients' names from the computerized data sheets. Only blood samples intended for the study was drawn and thereafter discarded after

analysis. A copy of the laboratory results was placed in the patients' file and disseminated to the health care providers to aid in patient care.

CHAPTER 4

RESULTS

Patient characteristics

A total of 65 patients were enrolled into the study after meeting the inclusion criteria.

The study participants were mostly female (58.5%). The mean age of the participants was 74.5 (SD=8.9) years, while the median age was 71.0 (IQR=15.0) years. A history of cigarette smoking and alcohol intake was present in 13.8% and 16.9 % of the study population respectively. The frequency of use of vitamin D and calcium supplements was 21.5%.

The patient socio-demographic and clinical characteristics are summarized in tables 1, 2 and 3 below.

Table 1: Patient characteristics.

	Frequency n (%)
Age	
65-74	37 (56.9)
75-84	17 (26.2)
85 and above	11 (16.9)
Gender	
Male	27 (41.5)
Female	38 (58.5)

Table 2: Substance use

	Frequency n (%)
Smoking	
Yes	9 (13.8)
No	56 (86.2)
Alcohol	
Yes	11 (16.9)
No	54 (83.1)

Table 3: Vitamin D or Calcium Supplements

	Frequency n (%)
Yes	14 (21.5)
No	51 (78.5)

Serum Vitamin D and calcium levels

The prevalence of vitamin D deficiency was 48%, insufficiency 38% and normal Vitamin D was 14%. The mean serum Vitamin D was 21.5 ng/ml (SD =7.7) while the median value was 21.5 (IQR=11.9) ng/ml. This is shown in figure 8 below.

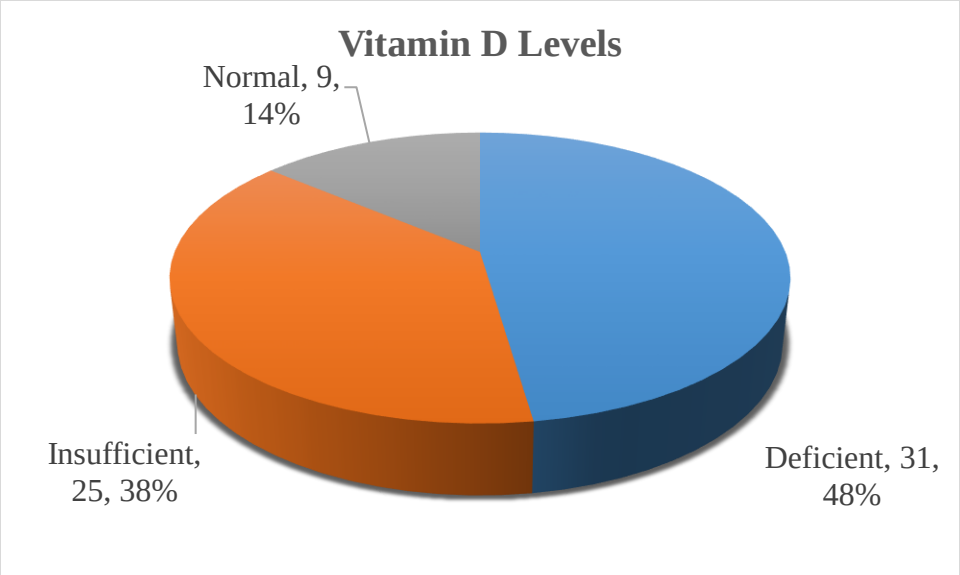

Figure 8: Vitamin D levels

The albumin adjusted calcium levels were normal in 89.2% of the study participants and low in only 10.8% of the participants as shown in table 4. The mean serum albumin adjusted calcium level was 2.3 (SD=0.1), while the median value was 2.4 (IQR=0.2).

Table 4: Calcium Levels

	Frequency n (%)
Low	7 (10.8)
Normal	58 (89.2)

Pattern of Hip Fractures

The most common fracture pattern was neck of femur (58.5%), followed by intertrochanteric (27.7%) then Sub-trochanteric (13.8%) as summarized in figure 9 below:

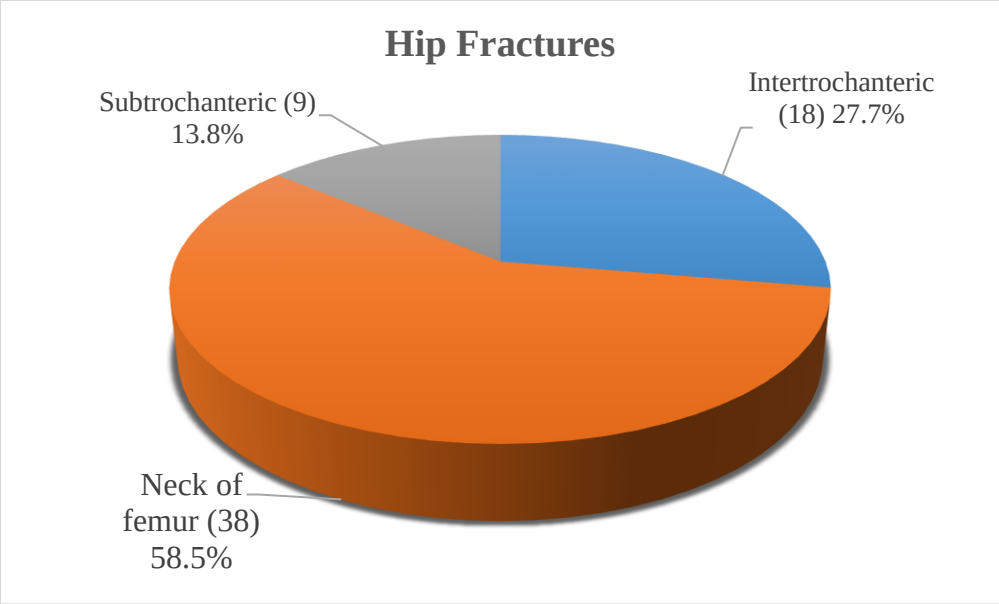

Figure 9: Hip fractures

Correlation of Serum Calcium and Vitamin D with Selected Patient Factors

A Pearson Chi Square test was done to check for association between vitamin D levels and gender, and there was no statistical significant association. A Fisher's Exact test was used to test the association between Calcium level and gender, and there was no statistical association between Calcium level and gender.

Table 5: Correlation of Vitamin D and, Calcium levels with Gender

	Male	Female	Total	p-value
Vitamin D				
Deficient	14 (56)	11 (44)	25 (100)	0.937
Insufficient	13 (52)	12 (48)	25 (100)	0.664
Normal	9 (60)	6 (40)	15 (100)	0.682
Calcium				
Low	1 (14.3)	6 (85.7)	7 (100)	0.224
Normal	26 (44.8)	32 (55.2)	58 (100)	

A Pearson correlation was done to ascertain the relationship between serum vitamin D level and calcium with age. There was a statistically significant, weak and negative correlation between age and the vitamin D level while there was no statistically significant relationship between Calcium level and age. This is as shown in table 6 below.

Table 6: Correlation of Vitamin D and Calcium level with Age

		Age
Vitamin D level	Pearson Correlation	-0.276
	p-value	0.026
	N	65
Calcium level	Pearson Correlation	-0.065
	p-value	0.607
	N	65

A Pearson Chi Square test was done to check for association between vitamin D levels and pattern of hip fractures. There were statistical differences in the Intertrochanteric fracture in respect to other fractures for the varying levels of vitamin D (p=0.018). There were differences in the proportions of the vitamin D levels (i.e. Deficient, Insufficient, and Normal) for the Intertrochanteric fracture when compared with the other fractures combined.

Table 7: Correlation of Vitamin D level and Hip fracture

	Deficient	Insufficient	Normal	Total	p-value
Intertrochanteric	6 (33.3)	6 (33.3)	6 (33.3)	18 (100)	**0.018**
Neck of femur	22 (57.9)	13 (34.2)	3 (7.9)	38 (100)	0.092
Sub-trochanteric	3 (33.3)	6 (66.7)	0 (0)	9 (100)	0.131

A Pearson Chi Square test was done to check for association between serum albumin adjusted calcium levels and type of hip fractures. There were no statistical differences between the hip fractures with the varying levels of calcium as shown in table 8.

Table 8: Correlation of Calcium level and Hip fracture

	Low	Normal	Total	p-value
Intertrochanteric	1 (5.6)	17 (94.4)	18 (100)	0.663
Neck of femur	4 (10.5)	34 (89.5)	38 (100)	1.000
Sub-trochanteric	2 (22.2)	7 (77.8)	9 (100)	0.298

A Pearson Chi Square test was done to check for association between use of supplements and type of hip fractures. There were no statistical association between the hip fractures and use of supplements as shown in table 9.

Table 9: Correlation of Use of Supplements and Hip Fracture

	Yes	No	Total	p-value
Intertrochanteric	4 (22.2)	14 (77.8)	18 (100)	0.934
Neck of femur	10 (26.3)	28 (73.7)	38 (100)	0.266
Sub-trochanteric	0 (0.0)	9 (100.0)	9 (100.0)	0.090

CHAPTER 5

DISCUSSION

Hip fragility fractures are common among elderly patients and occur as a result of minimal trauma such as falling from a standing height or less. Calcium and Vitamin D deficiencies represent some of the risk factors influencing the development of osteoporosis (75). Osteoporosis is associated with an increase in risk of fragility fractures occurring mainly in the spine, hip and wrist. The life time risk of fragility fracture has been reported to range from 33% - 44% in females and 20% - 27% in males (10,75,76).

Serum Vitamin D and calcium levels

The mean age of the study participants was 74.5 years with a predominance of females (58.5%). More women as compared to men had a deficient vitamin D levels, though this was not statistically different. This finding mirrors studies done in Western countries and Asia. A study done in China by Fu et al. reported a positive correlation between low serum 25 hydroxycholecalciferol and hip fractures among postmenopausal women (43).

This study showed that hypovitaminosis D is prevalent among elderly patients with hip fragility fractures. Among the study population, 48% had vitamin D deficiency 38% had vitamin D insufficiency while only 14% had normal serum vitamin D levels. These results are similar to those found by Ramason et al (41) in Singapore where vitamin D deficiency was 57.5%, insufficiency 34.5% and normal serum vitamin D at 8%. Such high prevalence has been found in other studies aamong patients with fragility fractures which documented vitamin D deficiency of between 55%-91.6%. However, this study reported lower frequencies of Vitamin D deficiency and insufficiency in comparison to Ramason et al and other studies in Western countries (41,45,77).

Previous similar studies have documented geographical and seasonal variations in the levels of vitamin D and calcium in the elderly with increased prevalence of Vitamin D deficiency during periods of spring due to decreased cutaneous synthesis in the winter months (77,78). It is possible that the slightly lower prevalence of hypovitaminosis in this study is because they were drawn from Nairobi and its environs where the climate is mostly sunny with little variations within the year. It can also be postulated that the small sample size, slightly lower mean population age and lower percentage of women could explain the differences observed. Besides 21% of the study participants had been on vitamin D and calcium supplementation prior to the study.

The albumin adjusted calcium levels were normal in 89.2% of the study participants and low in only 10.8% of them. In as much as it is expected that calcium absorption reduces with age, the findings are not surprising because calcium is highly regulated by parathyroid hormone and vitamin D. Besides, a considerable number of patients (21%) were on combined vitamin D and calcium supplements. Factors which could have contributed to calcium deficiency in 10.8% of the study population including kidney disease, liver disease, hypo-parathyroidism and diet were beyond the scope of this study and therefore not evaluated (62,67,69).

Hip fracture pattern

The most common type of hip fractures was neck of the femur at 58.5%, followed by intertrochanteric at 27.7% then sub-trochanteric at 13.8%. Studies have shown a high incidence intertrochanteric fractures increasing exponentially with age and commonly being associated with females (18,19,21). Studies in other regions have shown intertrochanteric fractures to be more common than other fracture patterns (22). This finding however contradicted what Tsabasvi et al. reported in their retrospective study in neighboring Tanzania where intertrochanteric fractures were the most common at 55.8% followed by neck of femur at 28.5% (24). This study found no

statistical differences, though the number of women in this category of fractures was more. Similar previous study by Fox et al also reported no difference in gender distribution (23).

Correlation between Vitamin D and calcium levels and selected patient characteristics

There was a statistically significant, though weak, association between age and the serum level of vitamin D. Notably, there was a statistical significant differences observed for the Intertrochanteric fracture in respect to other fractures for the varying levels of vitamin D. The overall fracture risk in various levels of vitamin D has been explored before in osteoporosis. However, many authors have disagreed on the optimum serum 25 (OH) D levels associated with increased fracture risk. In 2010, Melhus et al found that a serum 25(OH) D below 40nmol/l suggested an increased fracture risk (47). Cauley et al in 2008 had reported that 25(OH) D ranges between 60-70 nmol/l were associated with the lowest risk of fracture (4). Van Schoolar in 2008 found that serum 25 (OH) D less than or equal to 30 nmol/l were associated with the greatest fracture risk(46).There was no statistically significant association between the serum calcium levels or vitamin D with patient age and gender.

Conclusion

In conclusion, the prevalence of vitamin D deficiency and insuffiency was high in this study. However, majority of the participants had normal serum calcium levels. There was a statistically significant, though weak, association between serum vitamin D levels and age.

Strengths and limitations

This is the first study of this nature to be done in Kenya. The small sample size could not allow generalization of the results to the general population. There was a recall bias on the use of Vitamin D and calcium supplements. Inability to assess bone mineral density by DEXA scan due to cost

and availability limited the ability to objectively diagnose osteoporosis. X-ray standardization of exposure was not possible because radiographs were taken from different places and using different machines.

Recommendations

Screening for vitamin D deficiency and supplementation where necessary in elderly patients with fragility hip fractures should be recommended due to the high incidence of vitamin D insufficiency and deficiency reported in this study.

A larger prospective case control study to compare vitamin D and calcium levels in elderly patients with and without hip fragility fractures is recommended.

A similar study using DEXA scan to objectively diagnose osteoporosis in fragility fractures.

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APPENDIX I: DATA COLLECTION SHEET

Case Number_____ Age____ Gender____ Level of education_____

Mechanism of injury:

History of smoking: Yes No

History of Alcohol use: Yes No

Medications in use:

Use of vitamin D and calcium supplements:

If yes above, which drug and dose: ……..

For women only:

Do you experience Menses Yes No?

If No, age at menopause ___ Years

Timelines

a. Date of Injury Time of Injury Am/Pm
b. Date of admission
c. Date of sample collection Time of sample collection Am

Radiographic (X- ray) Observations

Neck of femur fracture

Intertrochanteric fracture

Sub-trochanteric fracture

Serum level of:

a) 25 hydroxycholecalciferol

b) Albumin corrected serum calcium

APPENDIX II: CHOMBO CHA UTAFITI

Nambari ya usajili_____ Umri____ Jinsia____ Kiwango cha elimu_____

Unatumia Sigara Ndio La

Unatumia Pombe Ndio La

Unatotumia dawa zozote Ndio La

Iwapo jibu lako ni ndio hapo juu, dawa gani na kiwango gani……....

Unatumia dawa za kuongeza kiwango cha Vitamini D na Kalisi Ndio La

Iwapo jibu lako ni ndio hapo juu, dawa gani na kiwango gani……..

Wanawake pekee:

Unapata damu ya mwezi Ndio La .

Kama La, iliacha ukiwa umri upi___

Muda

a. Tarehe uliyoumia Saa uliyoumia Asubuhi/Jioni
b. Tarehe uliyolazwa hospitalini
c. Tarehe ambayo sampuli ya damu ilitolewa
d. Saa ambayo sampuli ya damu ilitolewa Asubuhi

Picha ya x-ray

Neck of femur fracture

Intertrochanteric fracture

Sub-trochanteric fracture

Kiwango cha

a) Vitamini D
b) Kalisi ukizingatia albumini

APPENDIX III: PARTICIPANT INFORMATION

Introduction

My name is Dr George W. Musila. I'm a post graduate student of orthopedics surgery at the University of Nairobi. The purpose of this statement is to inform you about a research study that I'm carrying out. I'm doing a study on Calcium and vitamin D serum levels in patients with hip fractures at KNH. The purpose of this study is to determine the patterns of serum vitamin D and calcium and document the types of hip fractures.

Procedures to be followed in the study

Participation in this study is voluntary. Should you accept to participate, the following is a summary of what the study involves:

1. Obtaining information such as age, gender and level of education

   NOTE: your name and hospital identification number will not be included in this information for your privacy
2. Obtaining information on your date and time of injury.
3. Obtaining information regarding your hip fracture diagnosis. The information you give will be verified from your medical records.
4. Thereafter, approximately 5mls of blood will be withdrawn for purposes of laboratory analysis of your levels of vitamin D, calcium and albumin level. This will take about 10 to 15 minutes of your time.

Risks and costs incurred

You may feel slight pain/ discomfort when the blood sample is drawn. There may be slight swelling at the site of the needle prick, but this will disappear by itself after a few days. The amount of blood that will be drawn will not affect your health.

Your rights as a participant

Your participation in this research is voluntary and in the event that you refuse to participate in this study, your treatment will not be affected. If you choose to participate and not answer certain questions, you are free to do so. You are free to terminate the interview and withdraw from the study at any time. You are free to ask questions before signing the consent form.

Assurance of confidentiality

All your responses as well as your results will remain confidential. Your individual responses will be stored in a locked place under my control and will only be seen by my statistician and I.

Benefits to you as a participant

Your participation in the study and the laboratory tests done are free of charge but the findings will be used for your individual benefit. Information obtained will improve knowledge amongst health care providers at the Kenyatta National hospital.

Compensation: Participants will not receive any monetary compensation for participating in this study.

Contacts: If you have any questions, please do not hesitate to ask. Clarifications may also be sought from:

DR GEORGE MUSILA

P.O BOX 2681- 90100, Machakos

TEL: 0721-819600

The Secretary

KNH/UoN Ethics and Review Committee

Tel 2726300 Ext: 44102

I Request you to sign the attached consent form.

APPENDIX IV: CONSENT FORM

I hereby give my written and informed consent to allow myself or to allow my…… participate in this study on Vitamin D and Calcium Levels in elderly patients presenting with hip fragility fractures at Kenyatta national hospital.

I have been adequately explained to about the study by Dr. George Musila. I do this with the full understanding of the purpose of the study and procedures which include a physical examination being carried out on me, blood sample being drawn from my vein and answering questions in the questionnaire which have been explained to me. I understand that my rights will be respected, and confidentiality maintained at all times. I also understand that the consent is voluntary, and I am at liberty to withdraw from the study without my care being affected.

Print Name of Participant/ Next of kin ……...

Signature / Left thumbprint of subject ……

Date ……

Investigator's statement:

I, the Principal Investigator, have fully informed the research participant on the purpose and implication of this study.

Signed ..... Date …….....

APPENDIX V: UJUMBE KWA MSHIRIKI KWENYE UTAFITI

Kitambulisho.

Mimi ni Daktari GEORGE W MUSILA, mwanafunzi wa shahada ya juu katika Upasuaji wa Mifupa katika chuo kikuu cha Nairobi. Sababu kuu ya ujumbe huu ni kukujuliza kuhusu utafiti ambao natekeleza.

Nafanya utafiti kuhusu kiwango cha vitamini D na kalisi katika damu kwa wagonjwa wakongwe walio vunjika kwenye kiuno.

Utaratibu utakao fautiliwa katika huu utafiti

Kuhusika katika utafiti huu ni kwa kujitolea. Iwapo utakubali kuhusika katika huu utafiti, ufuatao ndio muhtasari yatakayotendeka kataka huu utafiti:

1. Ujumbe kuhusu umri, jinsia, kiwango cha elimu. Fahamu kuwa jina lako na nambari yako ya hospitali hazitahusishwa ili kulinda faragha yako.
2. Kunakili ujumbe kuhusu siku na saa uliyoumia.
3. Kunakili ujumbe kuhusu ulivyovunjika katika mfupa wako wa kiuno. Ujumbe huu utachunguzwa katika nakala zako za hospitali.
4. Baada ya hayo, takriban mililita 5 za damu zitachukuliwa kwa minajili ya kupima kiwango cha vitamini D, kalisi na albumini. Hii itachukua muda wa takribani dakika 10 au 15.

Madhara au gharama kwako

Utahisi kiwango kidogo cha uchungu wakati damu itakapokua inatolewa. Sehemu ambapo damu itatolewa pia inaweza kufura kiasi kidogo lakini uvimbe huu utapona baada ya masaa au siku chache bila kuhitaji matibabu ya ziada. Kiwango cha damu kitakachotolewa hakitadhuru afya yako kwa namna yoyote.

Haki zako kama mshirika

Kujihusisha kwako katika utafiti huu ni kwa hiari yako na iwapo hautashiriki katika utafiti huu matibabu yako hayatadhurika kwa namna yoyote. Utakua huru kuhusika hata iwapo hutajibu maswali mengine. Zaidi ya hayo, utakua huru kusitisha majadiliano au kujitoa katika utafiti huu wakati wowote. Pia unao uhuru wa kuuliza maswali yoyote kabla kutia sahihi yako kwenye fomu ya ridhaa.

Faida kwako kwa kushiriki katika utafiti huu

Hakutakua na malipo ya ziada utakayolipa ili kufanyiwa vipimo hivi lakini majibu haya yatakua ya muhimu katika matibabu yako. Ujumbe utakaopatikana kutoka utafiti huu utasaidia wahudumu wa afya katika kutibu wagonjwa wengine wenye ugonjwa kama wako.

Fidia

Watakaoshiriki kwenye utafiti huu hawatapata fidia yoyote ya kifedha.

Jinsi ya mawasiliano

Iwapo utakua na swali yoyote, wasiliana nasi kwa anwani zifuatazo:

Dkt. GEORGE MUSILA

SADUKU LA POSTA, 2681-90100

MACHAKOS

TEL: 0721-819600

Katibu,

Kamati kuu ya utafiti ya KNH/UON

TEL: 2726300 Ext. 44102.

Nakuomba utie sahihi yako kwenye fomu ya ridhaa ambayo imeunganishwa.

APPENDIX VI: FOMU YA RIDHAA

Natoa idhini andishi na ninayoilewa ili kuniruhusu kushiriki au inayoruhusu …..……..wangu kushiriki katika utafiti huu kuhusu Vitamini D na kiwango cha kalsiamu kwa wagonjwa wakongwe walio vunjika kwenye kiuno.

Nimepewa maelezo kuhusu utafiti huu na dakitari George Musila. Ninafanya hivi kwa vile naelewa lengo kuu la utafiti huu na taratibu zitakazohusishwa kama vile kujibu maswali katika fomu ambayo nimepewa maelezo yake, na kutolewa damu mkononi. Ninaelewa kuwa haki zangu zitaheshimiwa, na suala la kuhifadhi utambuzi wangu utadumishwa wakati wote. Pia nime elewa kuwa idhini ya kushiriki ni ya kujitolea, na nina uhuru wa kujiondoa katika utafiti huu bila matibabu yangu kuathiriwa.

Jina la mshiriki au pili ya jamaa …….

Sahihi au alama ya kidole gumba ……..

Tarehe …….

Kauli ya mchunguzi

Mimi Dkt. G Musila, mchunguzi mkuu katika utafiti huu nimemweleza mshiriki huyu kuhusu madhumuni ya utafiti huu kwa kina.

Sahihi ……... Tarahe …….