THE BONE MINERAL DENSITY AND VITAMIN D STATUS IN CHILDREN WITH MODERATE TO SEVERE CEREBRAL PALSY IN KENYATTA NATIONAL HOSPITAL AND ST THERESA MISSION HOSPITAL

By

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A thesis submitted in partial-fulfilment of the requirements of the University of Nairobi for award of the degree of Master of Medicine in Orthopaedic Surgery.

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DECLARATION

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

Where other people's work has been used, this has been properly acknowledged and referenced in accordance with the University of Nairobi's requirements.

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DEDICATION

I dedicate this Thesis to my family, the Thitais' for their continued love and support through the study and to the lecturers at the Department of Orthopaedic Surgery, University of Nairobi.

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ABBREVIATIONS

AED .....ANTIEPILEPTIC DRUG

BMD… .....BONE MINERAL DENSITY

BUA .....BROADBAND ULTRASOUND ATTENUATION

CP..... CEREBRAL PALSY

CYP..... CYTOCHROME P450

CPSK….....CEREBRAL PALSY SOCIETY OF KENYA

DBP..... VITAMIN D BINDING PROTEIN

DEXA .....DUAL ENERGY X-RAY ABSORPTIOMETRY

GMFCS.....GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM

GMFCS-ER….....GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM EXPANDED AND REVISED

KNH…..... KENYATTA NATIONAL HOSPITAL

QUS.....QUANTITATIVE ULTRASOUND

STMH… .....ST THERESA MISSION HOSPITAL KIIRUA

SOS… .....SPEED OF SOUND

UV..... ULTRAVIOLET

VDR.....VITAMIN D RECEPTOR

$25(OH)_2D3$……1A,25-DIHYDROXYVITAMIN D3

7-DHC..... ….7-DEHYDROCHOLESTEROL

25-OHD……..….. 25-HYDROXY-VITAMIN D

ABSTRACT

Background

Cerebral palsy is a common disorder among children with disabilities globally. The local burden is estimated to be 1 in every 300 children. Children with Gross Motor Classification System (GMFCS) III-V are usually immobile and are at high risk of developing low Bone Mineral Density (BMD) and low vitamin D levels. This leads to reduced bone strength and an increase in fracture risk. The life expectancy of children has improved due to advancements in medical care. It is therefore expected that there will be a rise in fracture incidence. There is scarce literature on bone quality in children with cerebral palsy in Kenya. Interventions such as timely supplementation of vitamin D has been found to reduce incidence of fractures. It is therefore important to have an updated baseline data on the level of Vitamin D and BMD in children with moderate to severe cerebral palsy in Kenya.

Study Objective:

To determine the bone mineral density and vitamin D status of children with moderate to severe cerebral palsy in Kenyatta National Hospital and St Theresa Mission Hospital.

study design: descriptive cross-sectional study

Study site: Kenyatta National Hospital and St Theresa Mission Hospital, Kiirua.

Methodology: 70 patients met the criteria using convenience sampling. A standard questionnaire was used to enter the demographical data, GMFCS level and drug use. A venous non- fasting sample was drawn for analysis of Vitamin D and a calcaneal quantitative ultrasound used to assess bone mineral density. The interpretation of the bone mineral density findings was done according to the International Society of Clinical Densitometry in 2013 and Vitamin D according to the American Academy of paediatricians.

Data processing: The collected data was analysed using the Statistical Package for the Social Sciences version 25.

RESULTS: Analysis of non- parametric data was done using spearman's rank. The significant demographic variables was analysed using multiple logistic regression models. Data variables were presented in frequencies and analysed using the chi- squared test and Fischer's exact test.

The prevalence of low BMD defined by a Z score less than -2 was 30%. Children with worse GMFCS had averagely lower BMD. An increase of a number of fractures by one is 2.11 times more likely in low BMD and 53% likely to occur in patients with less than normal vitamin D levels (P-Value 0.015). Of the total patients 55.7 % (n= 39) had less than sufficient levels of vitamin D. The use of Antiepileptic drugs was a significant determinant of vitamin D levels.

CONCLUSION

- The level of Bone Mineral density and Vitamin D in children with GMFCS III-V was low. This is in keeping with previous studies. Those from Institutionalized systems had lower levels than those from non-institutionalized systems.
- There was no statistical significance between GMFCS III-V and BMD. However, those with worse GMFCS had lower BMD.
- The use of AED was significant in influencing the level of Vitamin D but not BMD.
- There was a positive association between hypovitaminosis D and the total body surface area exposed to sunlight.
- Level of BMD and Vitamin D were highly predictive of fracture risk, with the right lower limb affected more than the other areas.
- There was no correlation between the age, sex, height and weight with the BMD and Vitamin D levels.
- There was no association between the calcaneal speed of sound with age, weight and height. However, there was a positive association between the speed of sound and BMD.

RECOMMENDATIONS

- Regular investigation of vitamin D status is necessary in children with cerebral palsy.
- Strongly recommend the need for supplementation of Vitamin D in children with cerebral palsy.
- There is a need for an increase in total body surface area exposed to sunlight in children with cerebral palsy.
- Public health sensitization on Vitamin D rich foods should be encouraged for this population.

- There should be regular screening of BMD using the calcaneal QUS in patients with neuromuscular disorders. It should be noted from this study that QUS is not as sensitive as DXA but has a role in screening due to its safety profile and lower cost.
- There is need for creation of a screening tool questionnaire using the identified predictive risk factors for deranged vitamin D and BMD in children with cerebral palsy.
- It should be the practice to follow up children who meet the criteria of osteoporosis with calcaneal QUS with DXA measurements for definitive diagnosis and management.

CHAPTER ONE:

INTRODUCTION

Cerebral palsy (CP) is among the commonest conditions associated with severe physical disabilities among children in the Kenyan society. Population studies done around the world have reported prevalence estimating from the range of 1.5-4 per 1000 live births of children (1, 2, 3, 4, 5). Low-income countries have slightly higher prevalence than developed countries
(22, 45). In South Africa, a study showed high prevalence of 10/1000 live births (3). ElTallawy et al in Egypt found a prevalence of 2/1000(4). This was almost similar in studies done in Uganda with a prevalence of 2·9/1000 live births (5). In Kenya, unpublished data by the Cerebral Palsy Society of Kenya estimates that 3 in 100 children in Kenya live with CP.

Vitamin D is essential in bone health. It plays an important role in maintaining peak bone mass and calcium haemostasis. Children with CP have high prevalence of low Bone Mineral Density (BMD) and low vitamin D (7). While clinical features of low vitamin D can be picked up in other children, children with CP present atypically. The disturbance in growth at the spongiosum layer doesn't give them the characteristic identifiable features such as widened epiphyseal growth plates (8). The factors associated with occurrence of low bone density in children with CP include low vitamin D, low calcium, immobility and use of antiepileptic drugs. Most of the risk factors are present from early childhood (6).

Children with CP are housebound and greatly depend on care givers for their nutritional status and exposure to sunlight. Poverty and urban living can limit these children's sunlight exposure and quality of nutritional intake. Jones et al, found iron sheet roofing material, lack of windows for informal dwellings and an overcrowded environment played a significant role (10).

The Gross Motor Function Classification System (GMFCS) is a system used for categorizing different levels of functioning within the disorder. The distinction between the various levels is based on child's functional abilities related to their gross motor movement (9). Those with GMFCS Level III-V have worse motor impairment and are a vulnerable group with multiple factors influencing their risk of impaired Vitamin D and BMD levels. This includes lack of physical activity, neuromuscular disorders, nutritional deficiency growth disturbance, use of antiepileptic drugs and sunlight exposure (8,9,10,11,12).

Low vitamin D and low BMD in these children puts them at a higher risk of getting fragility fractures following minor trauma with an estimated fracture incidence of fractures of 4% (13). Bones in children who are healthy are usually in a constant state of change i.e. remodelling with an accumulation of peak bone mass. The literature on children with neuromuscular disorders shows that they have lower peak bone mass and suboptimal accrual. This results in early occurrence of fractures (8). Moreover, the lack of verbal communication in those with severe cerebral palsy could lead to a delay in diagnosing fractures therefore increasing their morbidity.

Most studies on Cerebral palsy done have not focused on the levels of BMD and Vitamin D. While theoretical and clinical practice knowledge would point to impaired levels in nonambulatory patients there is conflicting data reported on this. Shin et al and Henderson et al reported that non ambulatory children compared to ambulatory children had a lower bone mineral density (13, 14). While Finbraten et al found no correlation between the BMD and vitamin D levels (12).

Studies have shown that early supplementation of Vitamin D can lower the risk of pathological fractures (17, 18). However, the international guidelines that have been made on Vitamin D supplementation do not address the requirements of these susceptible group (19, 20).

This study then demonstrates the levels of BMD and vitamin D in paediatric patients with advanced cerebral palsy in Kenya. It also provides information on patient demographic factors that influence these levels.

STUDY QUESTION

- **What is the bone mineral density and vitamin D status in children with moderate to severe cerebral palsy in Kenyatta National Hospital and St Theresa Mission Hospital?**

OBJECTIVES

Broad objective

To determine the bone mineral density and vitamin D status of children with moderate to severe cerebral palsy in Kenyatta National Hospital and St Theresa Mission Hospital.

Specific objectives

1. To determine the calcaneal bone mineral density in children with moderate to severe cerebral palsy with GMFCS III-V in urban and rural Kenya.
2. To assess the levels of vitamin D in children with moderate to severe cerebral palsy with GMFCS III-V in urban and rural Kenya.
3. To determine the association of bone mineral density and vitamin D level with the gross motor function classification system of children with moderate to severe cerebral palsy.
4. To determine the relationship between patients demographic characteristics and bone mineral density and vitamin D level.

CONCEPTUAL FRAMEWORK

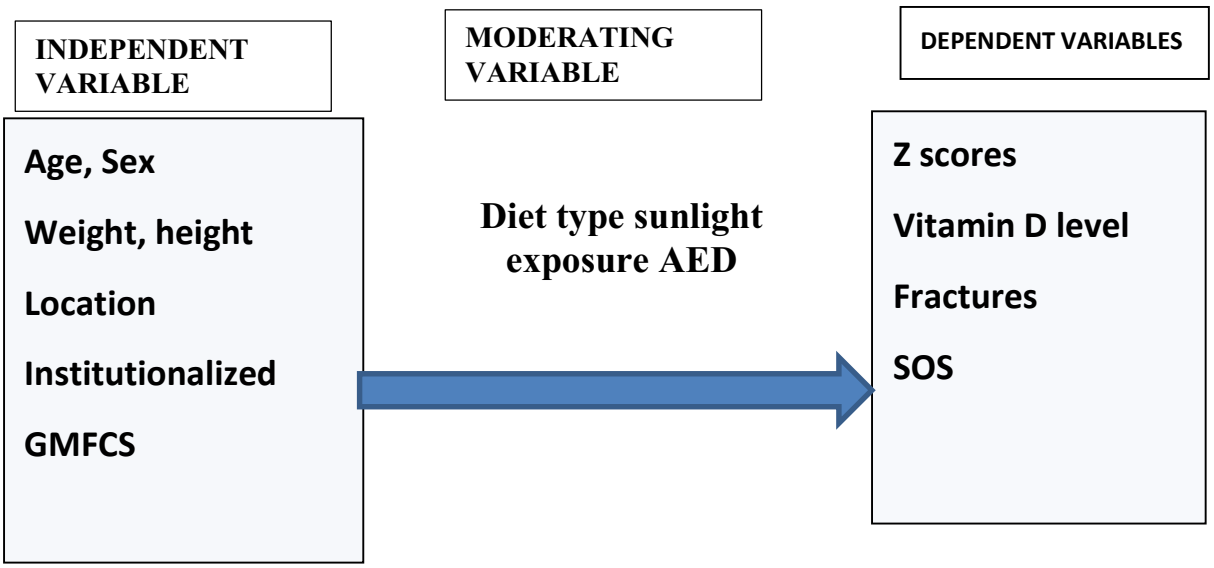

Figure 01: The conceptual framework model for factors that affect the BMD and Vitamin D levels

PURPOSE AND JUSTIFICATION

- This study will provide an updated baseline data on the level of Vitamin D and BMD in children seen in KNH and STMHK.
- The data will be useful in formulation of local Kenyan clinical guidelines on how often children with CP should be screened for vitamin D and BMD.
- The information from this study will influence the current practice of supplementation of Vitamin D in children with cerebral palsy.
- The patients' demographics characteristics identified in the study to be predictive of Low Vitamin D or BMD, may be used to formulate a focused screening tool for patients with cerebral palsy.
- The results will be useful to caregivers in understanding the importance of sunshine exposure and Vitamin D filled diet for children with CP.
- The study will highlight the role of the calcaneal quantitative ultrasound in assessing bone mineral density in children with cerebral palsy.

CHAPTER TWO:

LITERATURE REVIEW

Cerebral palsy was initially described by Little in 1862. He made a connection between bone, muscular deformities, joint and the neurological system. He associated them with difficulty in delivery, perinatal asphyxia and prematurity. He however did not use the terms cerebral palsy. This was later adopted by Osler in 1888 and later Freud. Freud then refined the concept of static encephalopathy and described brain changes linking them with different types of paresis (17).

There are various definitions that have been coined to describe cerebral palsy. However, consensus is that it is a group of disorders that permanently affects development of motor and posture of the immature brain (17). It is caused by non-progressive neuropathological lesions. The afflicted individuals manifest in an array of non- progressive disturbance of movement and posture that differ depending on part of the brain affected (2). The insult may occur either during the prenatal, perinatal period or during childhood up to the age of 24 months. It is not a purely motor disorder, these children also exhibit sensory, cognitive convulsive disorders and nutritional deficiencies (23, 24).

EPIDEMIOLOGY

Cerebral palsy (CP) is among the commonest conditions associated with severe physical disabilities among children in the Kenyan society. Population studies done around the world have reported prevalence estimating from the range of 1.5-4 per 1000 live births (1,2,3,4,19,40)

The estimated overall prevalence is 2 per 1000 live births (41,42,43). A population study done in the United States of America reported a stable rate of spastic CP as 1.86 in 1985 to 1.76 in 2002 (1). In Iceland the prevalence of CP between 1990 and 2003 did not change significantly ranging from 2.2-2.3(21). However, there were differences in the prevalence among Term and preterm births. There was a decrease from 1.5 to 0.9 live births for term babies and an increase from 33.7 to 114.6 for preterm births. This was explained by the increase in the number of caesarean sections done.

Low-income countries have been deemed to have slightly higher statistics than developed countries (22,45). In a rural setting in South Africa, a study showed high prevalence of 10/1000 live births (3). El-Tallawy et al in Egypt had rates that were similar to the international studies at a rate of 2/1000(4). In a study done in Uganda there was a prevalence of 2·9 per 1000 live births (5). In Kenya there are no available published statistics on the prevalence of CP.

ETIOLOGY

Cerebral palsy has been associated with insult occurring at different stages of the developing foetus up to the age of 2 years (17). During the prenatal period, it has been associated with maternal infections, exposure to toxins and kernicterus (22). The TORCHES group of infections (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, enterovirus and syphilis) has been known to cause damage to the brain as well as induce premature onset of labour. Toxins such as alcohol, heroin, marijuana and cocaine have been shown to cross the placental barrier resulting in significant foetal neurological damage (4).

In an African population cohort, the leading causes in various studies included birth asphyxia, kernicterus, and neonatal infections (25,26,27). This has largely been attributed to the challenges that affect the quality of antenatal and postnatal care in developing countries. However due to the early screening and availability of Rho(D) immune globulin, the incidence of kernicterus associated with incompatible rhesus has significantly reduced (23).

In the perinatal period, the commonest condition associated with cerebral palsy is anoxia due to either placental abruption or tight nuchal cord (24). The frequency of cerebral palsy associated with just birth asphyxia is 1:3700 in full term live births (25). The other strongly associated factors include bronchopulmonary dysplasia, low birth weight and prolonged ventilation in the preterm (26). The incidence is higher in children born at < 28 weeks. They have almost 100-fold higher risk than infants born at term. Multiple gestations have also been associated with higher risk in developing cerebral palsy than singleton pregnancies. Some studies have shown a five-time higher prevalence (27). In the postnatal period associated factors include near drowning, suffocation, trauma associated with head injury and meningitis (26).

CLASSIFICATION

Cerebral palsy has been classified using various systems. It has been done so based on physiological, geographical (anatomical) and functional characteristics of the inflicted individual.

The ***physiological classification system*** describes the types of movement of the disorder that are present. This can either be:

- Spastic- this is the commonest movement disorder (80%). It is characterized by an increased tone and hyper-excitable tonic stretch reflexes that are dependent on velocity. This is due to a lesion affecting the pyramidal system.
- Dystonia – there is an increased tone in muscles that is not velocity dependent.
- Hypotonia- there is a reduced tone in the muscles. For a large number of the children with hypotonia, it's usually a transition phase and they later develop into spasticity. This is usually due to the masking done by lack of myelination in the early stages of development.
- Athetosis- characterised by abnormal writhing movements that are worse on intention. This usually occurs due to extrapyramidal lesions in the basal ganglia.
- Ataxia- this is associated with clumsy wide based gait.
- Mixed- it is usually rare for some of these movement disorders to occur alone, E.g. the ataxic type, and so majority of them have mixed movement disorders.

The ***geographic or anatomical classification*** describes the parts of the body that are affected. This can either be hemiplegia, diplegia, triplegia or quadriplegia. Other rare forms include monoplegia and double hemiplegia.

The ***Functional classification system*** commonly used is the Gross Motor Function Classification System (GMFCS). This describes self-initiated movements and mobility of the individual. This was described first by Palisano and his team in 1997(9). Later in 2007 together with Barlett and Livingstone they came up with the expanded and revised version referred to as the Gross Motor Function Classification System Expanded and revised (GMFCS E & R). The initial classification only included children to the age of 12 years but the expanded and revised version was to accommodate children between 12 to 18 years (28).

The motor function has been classified to five levels with each manifestation corrected to account for the different ages. For each of the levels there are different descriptions for the age bands. As the children grow and develop the descriptions tend to reflect the influence of the environment and personal factors.

The general theme of the levels is as follows:

- Level I: Walks without Limitations
- Level II: Walks with Limitations
- Level III: Walks Using a Hand-Held Mobility Device
- Level IV: Self-Mobility with Limitations; May Use Powered Mobility
- Level V: Transported in a Manual Wheelchair

The levels also coincide with the severity where:

- Level I- II Mild
- Level III- moderate
- level IV-V- Severe

This classification system is quick and easy to use and has been proven to be reliable in predictability of function of children with CP (30). This system has also been proven useful in predicting the motor development curve of these children. These curves have been useful in planning management and treatment programs and assessing the outcomes after treatment (32). Children at GMFCS I & II achieve peak performance in function at about age 5-7 years, 8 years for GMFCS III and 7 years for Level IV and V (33).

VITAMIN D

Vitamin D discovery has been dated all the way back to 1645. Deluca (34), Zhang et al (35) and Holick (36) have an interesting historical review of this vital amine bringing into view its role in metabolism of bone. . There has been an interest in Vitamin D with research growing looking into its role in bone health, neurological development, infections, cancer prevention and allergies (37).

Vitamin D is a fat-soluble secosteroids. The forms of Vitamin D include vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D2 has a double bond between the C22 and the C25 and a CH3 (methyl) group at its side chain C24. The difference in this side chain lowers the affinity of vitamin D2 for DBP therefore increasing its clearance from circulation as well as limiting its conversion and catabolism (38).

Vitamin D2 is naturally occurring through a photochemical reaction of a biological precursor, ergosterol. The yeast sterol ergosterol is converted into ergocalciferol by UV irradiation. It is predominantly considered as the first vitamin D analog (39).

Vitamin D3 is from 7-dehydrocholesterol (7-DHC) in the skin through two-steps. The B ring of the 7-DHC is broken down by UV radiation (spectrum 290–320 UVB) to form pre-D3 that is later isomerized to D3 (34).

Vitamin D metabolism is in three stages 25-hydroxylation, 1α-hydroxylation, and 24hydroxylation. These stages occur through cytochrome P450 (CYPs). Metabolites that are produced are transported bound to DBP and plasma proteins such as albumin with little in circulation. These transport proteins (DBP and albumin) are produced in the liver and patients with any form of liver disease, nephrotic syndrome and protein losing enteropathies will result in lower total vitamin D by-products and normal free concentrations (39).

Metabolism of vitamin

It is transformed to 25OHD by CYP enzyme that is likely CYP2R1s in the liver (41). The average lifetime for vitamin D3 it is approximately 2 months while 25OHD is approximately 15 days, and calcitriol hours (42). Vitamin D by-products are eliminated via bile into faeces and with very minimal excreted via the urinary system (39).

ROLE OF VITAMIN D

MUSCULOSKELETAL SYSTEM

Adequate vitamin D has been extensively studied in its role in preventing rickets and osteomalacia. There is controversy in its role in osteoporosis and fracture prevention (44). Randomized controlled trials meta-analysis illustrated a positive dose dependent response between fracture occurrence and supplementation of vitamin D (45). However the debate still sits on the fence on whether its solely the role of 1,25(OH)2D on calcium absorption or action on bone and cartilage resulting in normal bone turnover and development. With studies on mice demonstrating both a direct role and indirect role, the question still is: what is the optimum dose that is required for prevention of fractures (46).

VITAMIN D: MINERALIZATION

Bone is a living dynamic tissue that undergoes remodelling throughout life. The changes occur through an osteoblast osteoclast coupling interaction. New bone is formed when osteoblasts invade the pits created by osteoclasts and synthesize osteoid, the organic matrix. This matrix is then mineralized through a complex deposition of calcium phosphate crystals (hydroxyapatite). The process of mineralization is controlled tightly by various endocrine factors. 1α, 25-dihydroxyvitamin D3 acts either directly or indirectly in this control process.

The actions of 1α, 25-dihydroxyvitamin D3 has been tested both in vivo and in vitro (47). It works indirectly by increasing absorption of both phosphate and calcium from the intestines and kidney. The experiments done on Vitamin D Receptor knockout mice that were fed a rescue diet with augmented levels of phosphorus and calcium showed that the rescue diet was able to normalize the plasma Calcium and preventing osteomalacia (48).

The experiment on the indirect role was not able to eliminate all bone defects. This showed that there is influence through the direct action. This direct actions of 1α, 25(OH) 2D3 has been studied in vitro studies. The biological active form of 1α, 25(OH) 2D3) requires sequential hydroxylation in the hepatic and renal systems to be formed. At the kidney level the 1α hydroxylase enzyme is very paramount in this conversion. The enzymes expression and activity occurs primarily in the renal system but also has some extra renal sites. Some of these sites that have a direct role include the human osteoblast, megalin and cubilin receptors (49). The levels of active vitamin D the osteoblast can produce has been shown to be

sufficient enough in inducing alkaline phosphatase, osteocalcin, osteopontin and collagen type 1 (48). Enzymes such as alkaline phosphatase are integral in the early phase of bone mineralization.

The degradation products in this hydroxylation process have also been shown to influence preosteoblasts and mesenchymal stem cells into the osteogenic lineage as well as increase bone resorption of calcium and phosphate (50). 1α, 25(OH) 2D3 also activates nuclear vitamin D receptors and increases the expression of receptor activator of nuclear factor kappa-B ligand (RANKL).

VITAMIN D RECOMMENDED LEVELS

The Endocrine Society, National Osteoporosis Foundation and the Canadian Society of Endocrinology and Metabolism in 2011 published a clinical guideline on the "Evaluation, Treatment and Prevention of Vitamin D Deficiency (37). This was in order to give recommendations on screening of individuals who are at risk of insufficiency or deficiency. Their recommendations have been widely accepted for years in the developed countries.

There has been glaring lack of consensus on what is defined as deficiency, adequate or optimal levels of vitamin D for skeletal health as presented in table attached to the appendices (34,64). Institute of Medicine (IOM) and American Academy of paediatricians recommend levels above 20 ng/mL while the Endocrine Society recommends plasma levels above 30 ng/mL (75 nmol/L) as sufficient (57). Such debate has generated a sense of confusion among paediatricians and physicians on the appropriate levels of supplementation (58). These discussions have mainly been based on the adult population with very minimal data on the paediatric population. (67, 68, 69).

BONE MINERAL DENSITY

BONE MINERALIZATION PROCESS

Bone mineralization occurs through a biphasic stage. The first phase is within a Nano- sized matrix vesicles that is 100 nanometre in diameter. In this stage there is formation of hydroxyapatite crystals. The matrix vesicles bud from the outer surface membrane of osteoblasts, odontoblasts and hypertrophic chondrocytes. The concentration of phosphate in

the matrix is under the regulation of phosphohydrolases like alkaline phosphatase pyrophosphatase and adenosine triphosphatase and calcium binding proteins (45, 52) .

In the second phase there is crystal release from the vesicles with the preformed hydroxyapatite exposed into the extracellular matrix and deposited between collagen fibrils. The extracellular inorganic pyrophosphate is hydrolysed by Tissue nonspecific alkaline phosphatase to now promote mineralization (45,47).

CAUSES OF LOW BMD AND VITAMIN D IN PEDIATRICS WITH CEREBRAL PALSY

Bone mineralization process is genetically determined during development, however, postnatally there is influence from external factors. These include low vitamin D, immobility, nutrition status, use of anti-epileptic drugs and sunlight exposure.

VITAMIN D

Vitamin D has a crucial function in bone mineralization. Children with CP have derangements in the hormone levels. Langton et al in India reported 93% of children with CP had deranged Vitamin D levels. They found that despite the country being a tropical country 32% of the children had decreased Vitamin D and 61% had insufficiency. A control group of non- CP children had a prevalence of 13% with deficiency and 38% with insufficiency (60).

Akpinar et al found that the levels of 25-hydroxy vitamin D of paediatrics with CP when compared to non CP age and sex-matched children were lower (7). This was also seen by Mousomi et al when they compared the Vitamin D levels with normal healthy children (61).

In some studies the association between vitamin D and BMD showed no correlation but instead a correlation between the severity of CP had been established (6, 54, 55).

NUTRITION:

Nutrition status of these children is vital in determination of skeletal development. They are at risk of malnutrition than the average normal child. In a systematic review by Mergler et al the commonest cause was level of feeding difficulties extending from odynophagia, impaired control of tongue and lips, underdeveloped palate, swallowing difficulties, dentine issues and malabsorption syndromes(6,62). These were seen with an increase in the GMFCS. They also highlighted that there was a positive correlation between the triceps skin fold and BMD.

IMMOBILITY

Bone mineralization responds through osteogenic dynamic loads that are delivered through movement and exercises. Lack of adequate loading leads to a reduced periosteal bone expansion, increased porosity of bone resulting in slender weaker bones (7). Children with CP have neuromuscular conditions that predispose them to reduced daily activities. Authors have reported a correlation between higher GMFCS with a relative increased risk of lower BMD due to their immobilization (64).

Finbraten et al while comparing ambulation status children with CP found the main forecaster of low distal femur BMD Z-scores was immobility. The results also showed that the extents of the neuro-motor disability could be a predictor. He also concluded that the vitamin D status did not have an association with BMD z-scores (12)

Henderson et al reported an association between GMFCS, use of anticonvulsants BMD, triceps skinfold measured in children with CP. However, some parameter that did not show a relation to low BMD were temporary immobilization, calcium, phosphorus, age, sex, race, health status, 25-hydroxyvitamin D, osteocalcin, N-telopeptides and alkaline phosphatase levels(11).

ANTIEPILEPTIC DRUGS

Anti-epileptic drug use is common in paediatrics with CP due to their high risk. In a systematic review on children with CP in Africa, epilepsy was found to be among the highest comorbidities in children with CP. In Nigeria two studies reported a prevalence of 46.7% and 38% while in a cohort studied in Dar Es Salaam found 35% of the children had epilepsy (65). These drugs have been implicated in changes in the bone through decrease of 25(OH)D , hypocalcaemia, hypophosphatemia, increase in serum parathormone , high alkaline phosphatase and low BMD (66). The commonest drugs with these effects include phenobarbital, phenytoin, carbamazepine and primidone (67).

Valproic acid despite being a cytochrome P450 enzyme inhibitor, has also been shown to induce bone loss through two main mechanisms. A direct activation of osteoclasts through

rearrangement of the cytoskeleton. Indirect effect through endocrine complications resulting in hypothyroidism, hypogonadism, hyponatremia and mild hypocortisolaemia (68).

Studies have shown children taking AED have a prevalence of deficiency in Vitamin D varying from 47% to 75%. This was more pronounced in those taking a combination of the AED (7).

SUNLIGHT EXPOSURE

For centuries, exposure to Ultraviolet (UV) light has been understood as a strong determinant on vitamin D levels. About 90 % of this is through day to day casual sunlight exposure (69).

The intensity of UV and melanin content level contribute to the rate of D3 formation (40). Melanin blocks UVB from reaching 7-DHC, therefore impairing D3 synthesis. Holick's came up with a rule that says that sun exposure 1/4 of a minimal erythema dose (MED) over 1/4 of a body is equivalent to 1000 International Units (IU) oral vitamin D3. However, Webb and Engelsen thought there was no basis to this rule. They stated that the UVB intensity varies depending on the season and geographical latitude (70).

Sunlight/UVB radiation, exposure of arms and legs is equal to ingesting ~3,000 IU vitamin D3.this may be affected by melanin content, smog and cloth coverage (71).

Paediatrics with cerebral palsy with problems with immobility may have lower exposure rate increasing their risk of developing lower vitamin D levels. These patients rely on their care givers to take them out, they tend to find themselves housebound either due to their caregivers leaving to go to work or due to assumed social shame. (10).

CONSEQUENCES OF LOW BMD AND VITAMIN D

Low vitamin D levels in paediatric population with CP is associated with increased tendency of developing low bone mineral density. This predisposes them to sustaining painful fractures following minimal trauma (13). The conservative and surgical management of pathological fractures in these children is usually difficult.

They have associated hypovitaminosis D myopathy and muscle weakness. This results in reduced muscle strength, poor muscle coordination, muscular pain and paraesthesia. This then continues the vicious cycle of immobility, reduced weight bearing and osteopenia (72).

In the normal children who manifest with clinical symptoms due to widened growth plates in low vitamin D levels. These children do not have the normal expected features due to disturbance in growth (64).

FRACTURE

Low vitamin D and low BMD in these children puts them at a higher risk of getting fragility fractures following minor trauma (13).

In a systematic review the prevalence of fractures in paediatric population with CP is reported in two studies was 12% and 23%. The incidence of fractures was reported to be varied between 2.7% and 4.5%. The determinants found were immobilization, use of anticonvulsants, use of feeding tube and fracture in history (6).

Stevenson et al. in an evidence level of 2+, found the occurrence of bone fractures was estimated at 4% per year while in normal children was 2.5% . The presence of a gastrostomy catheter and a higher percentage body fat were associated with fractures. However, some factors showed no significant association were race, sex, GMFCS level, AED and Z-score (12).

BMD has a strong association with pathological fractures in the elderly and it has been used to diagnose “osteoporosis”. There is very limited information on the relationship between fracture risk and low bone mass in paediatrics with chronic illness.

BONE MINERAL DENSITY

Bone mass increases with age in the healthy developing children in the presence of normal growth. During early stages of puberty, especially in girls, there is an acceleration of bone accrual. For those with CP, bone maturation can either be accelerated or delayed due to conditions that affect puberty. These factors include severity of impairment, nutrition and hormonal balance (6)

The BMD of children with marked CP after 10 years of age doesn’t keep pace with normal accrual rates (73). In published descriptive growth charts of children with CP seem to lack that growth seen in growing children (74).

In a Systematic review by Mergler et al that looked at the epidemiology of low BMD and risk factors associated with low BMD found that the prevalence of low BMD in the femur was 77%. The associated factors included immobility, feeding, fractures, AED and body fat (6).

Henderson et al on two studies looking at the distal femur found a relationship between triceps skinfold but showed no relationship with age, sex, race, immobilization calcium and serum 25-hydroxyvitamin D(11).

Alvarez et al found a correlation between higher GMFCS with a relative increased risk of lower BMD due to their immobilization. Finbraten et al while comparing ambulatory status of children with CP found that the predictor of low BMD was the inability to walk and degree of neuro motor impairment. They also found no correlation between Vitamin D and BMD.

ASSESSMENT OF BONE MINERAL DENSITY

The paediatric skeleton can be assessed by using various methods, these include; dual-energy radiograph absorptiometry (DXA), quantitative ultrasonography, quantitative computed tomography (QCT), high-resolution pQCT (HR-pQCT),peripheral QCT (pQCT), MRI, or plain films (radiogrammetry). DXA is the standard method for clinical measurements of bone density in children because of its reproducibility, low exposure to ionizing radiation and available paediatric reference data.

Three-dimensional densitometry methods (MRI, QCT, pQC and HR-pQCT) give information into volumetric bone mineral density (BMD) as well as the micro- and macro architecture This assesses bone in 3 dimensions as well as bone size and geometry. The two factors have been shown to influence bone strength. However, their use in clinical practice is limited in large part by the radiation doses , lack of paediatric normative data and the standardized scanning protocols. (76).

DXA corrects bone mineral for the area, but it does not offer measurement of the volume of bone. The British Paediatric and Adolescent Bone Group suggested that the children with propensity to low BMD and fracture should be considered for a DXA scan. This should be done if they also present with low trauma or recurrent fractures, back pain, change in mobility status, spinal deformity or loss of height (76).

Quantitative Ultrasound

The calcaneal QUS is the only recognized longitudinal transmission method to quantify bone health (77). The heel is the commonest site for measurement using quantitative ultrasound. The calcaneus is made up of mainly cancellous bone (90%) and a thin cortex. The posterior aspect of the calcaneus is measured from a medial to lateral position. These surfaces are parallel and flat.

The variables measured with QUS are speed of sound (SOS) and broadband ultrasound attenuation (BUA). The SOS relates to velocity of the signal and the broadband ultrasound attenuation reflects the signal through bone and weakening of the ultrasound signal. Bone density, bone composition and bone strength is shown through the change in velocity and amplitude. BUA is a predictor of fracture risk, independent of the levels of BMD (6). The frequency range that is used for bone characterization is of 0.1–1 MHz.

In vitro studies examining the relationship between calcaneal QUS and bone properties found that SOS was closely related to BMD. Significant correlations between SOS with microarchitecture indices of the bone, such as bone volume bone surface number of nodes, trabecular number and thickness were also discovered. Bone biomechanical studies revealed that Young's modulus, compressive modulus, ultimate strength and elasticity of bone were significantly associated with SOS (84).

Laugier et al showed that these indices could also discriminate subjects without and with fractures and predict the risk of future fractures (78). The indices that are measured by QUS also have an association with BMD, mechanical parameters of bone and bone microarchitecture.

The calcaneal Quantitative ultrasound is ideal for estimating BMD in this vulnerable population who have neuromuscular disorders who are less mobile and less cooperative. It is safe, non-invasive, no emission of ionization radiation, portable, lower cost and easily available. A relative disadvantage of QUS techniques is BMD differs between left and right foot. Calcaneal oedema has also been shown to reduce the BUA (79)

While feasibility is established, validity and sensitivity are yet to be established. There are studies that have shown QUS correlates with DXA, and thus has high diagnostic value for

osteoporosis (80). They also propose QUS to be used as a screening tool in the absence of DXA (81).

World Health Organization recommends the gold standard method of measuring BMD as DXA. In resource limited setting this method is not easily available and incurs a great cost to the patients. Therefore, the Quantitative ultrasound (QUS) is a favourable method in assessment of bone health. It has steadily gained popularity since its introduction in 1984 when Langton et al discovered that the transmission of Ultrasound through the calcaneus discriminated osteoporotic women from non-osteoporotic (82)

There is little scientific evidence on severity of vitamin D deficiency and Low BMD in paediatric population with neuromuscular disorders. While in theory it shows that paediatrics with moderate and severe cerebral palsy would have deranged levels. This has not been the case in some studies. There is no consensus on the international guidelines on how regular such a vulnerable population should have monitoring of Vitamin D levels and BMD .The remedy for this population with low bone mass who are susceptible to fractures are more limited than in adults. This therefore underscores the importance of accurate bone assessments and early detection of these deranged levels.

CHAPTER THREE:
PATIENTS AND METHODS

STUDY DESIGN

The study is a descriptive cross sectional study

STUDY SITES:

- Kenyatta National Hospital
- St Theresa Mission Hospital, (Kiirua)

KENYATTA NATIONAL HOSPITAL

Kenyatta National Hospital (KNH) is a public referral, teaching and research hospital that was established in 1901. The core business of KNH is to receive and treat patients who have been referred from lower-tier institutions for specialized management. The hospital is in upper hill area in Nairobi County, the capital and largest city in Kenya. The facility runs a paediatric neurology clinic weekly on Tuesday afternoon, with a review of patients with various neuromuscular disorders including Cerebral palsy. These children are subsequently sent to the occupational therapy department for further follow up. It is estimated that a total of about 70 children with moderate to severe cerebral palsy are seen in the hospital monthly with an approximate average of 3 new cases per month.

ST THERESA MISSION HOSPITAL, (KIIRUA)

This is a level 4 faith-based health organization founded in 1967 in the catholic diocese of Meru. The hospital is in Buuri Sub-County of Meru County. Meru County is the sixth largest County in Kenya and covers an area of 6,936 kilometres while Buuri has an area of 69.21 kilometers^2. The facility serves a population of approximately 29,685. It has a bed capacity of 235 and offers a variety of outpatient and inpatient health services. This facility is a representation of the up-country population. The facility runs a monthly cerebral palsy clinic run by an orthopaedic surgeon. The estimated number of children with moderate to severe cerebral palsy who attend this clinic is 60 patients.

STUDY POPULATION

Children with cerebral palsy who were being attended to at Kenyatta National Hospital and St Theresa Mission Hospital Kiirua.

INCLUSION CRITERIA

- Children with GMFCS III-V cerebral palsy between the age of 2 years and 12 years. These were children from whom consent from caregivers was given.

EXCLUSION CRITERIA

- Children with concomitant renal or hepatic failure based on clinical signs, symptoms and hospital records.

SAMPLE SIZE CALCULATION

According to a study done in 2017 by Tosun et al, the prevalence of low BMD in children with CP was 39.5% (62).

Using the Cochrane's formula

$$n = \frac{Z^2 pq}{e_2}$$

Where

n ..... Sample size

Z…… Standard deviation of 95th percentile (1.96) **p.....**estimated proportion of children with low BMD in children with cerebral palsy in Kenya (0.0395).

q .....(1-p)

e ..... confidence interval (0.05)

$$n = \frac{96^2 \times 0.395 \times (1 - 0.395)}{0.05^2} \quad 1.$$

$$n = 367.21$$

In this smaller population where prevalence of children in Kenya is 0.03.

$$Nn = \frac{n}{1 + \frac{n-1}{N}}$$

Nn……. Corrected sample size n…….

sample size recommendation

N…..... target population

$$\frac{367}{1 + \frac{367-1}{50}}$$

$$n = 44.1$$

Using convenience sampling **70 participants** were recruited into the study.

DATA COLLECTION AND ANALYSIS

Patient Recruitment

The approval was sought from the Orthopaedic department, University of Nairobi, KNH Ethics, Research and Standards Committee (KNH ERC) and STMHK ERC. Consent forms were given to the caregivers and institution managers. The consent form had a brief introduction, purpose of study, study procedure to be followed and the potential benefits of participating in the study. Any questions regarding the study was answered prior to signing theconsent form.

DATA COLLECTION

A questionnaire was administered by the interviewer. The identity of the participants was concealed, and a study number was assigned to each individual.

The questionnaire was used to gather the following:

- Socio- demographic information.
- Mobility using GMFCS level (III-V)
- Anticonvulsant therapy
- Dietary history
- Fracture history
- Vitamin D level
- Bone mineral Density level

PHYSICAL EXAMINATION

The children's functional status was categorized according to GMFCS. Other parameters assessed included age, weight and height.

VITAMIN D LEVEL ANALYSIS

A non- fasting venous sample of 1.5 millilitres was collected from the antebrachial vein. This was collected in a blood transfer device (BD) vacutainer Serum separator Tube (SST). It contained a spray coated silica and a polymer gel for serum separation. According to the manufacturers' specifications, after collection of the blood sample the SST were inverted 5 times. This ensured optimal performance through adequate contact and activation of the blood with the silica particles that act as the clot activators.

The specimen identification on the packaging material were labelled and written legibly using indelible ink markers. This included the patients' two names, a second unique study number and date of collection.

A 3-part packaging system was used to ensure safe handling and transportation of the samples. This involved a primary leak proof SST vacutainer, a secondary individual leak proof resealable plastic bag and a rigid outer specimen transport box. The samples from STMH were stored at 2-8ºC and delivered within 5 hours to the laboratory for processing. The ones from KNH were delivered within 30 minutes to the laboratory.

The machine used was the **the Roche Cobas e411 chemistry analyser**. This is a fully automated immune assay analyser. It uses a competitive protein binding assay electrochemiluminescence which is intended for the quantitative determination of total 25-OH vitamin D in human serum and plasma.

The machine samples a volume of 15 µL. It confers a functional sensitivity of 4.01 ng/mL (10.0 nmol/L) (coefficient of variation 18.5%). The Repeatability within-run precision at 15 ng/mL is ≤6.5% and reproducibility of intermediate precision at15 ng/mL ≤11.5%. The specification details of the machine are attached in the appendix.

The assay uses a vitamin D binding protein (VDBP) as a capture protein, which binds to both 25-OH D3 and 25-OH D2. The assay takes 27 minutes in a 3-step incubation process. In the first step, the sample is incubated with a pre-treatment reagent that releases bound 25-OH vitamin D from the VDBP. In the second step, the pre-treated sample is incubated with ruthenium labelled VDBP creating a complex between the 25-OH vitamin D and the ruthenylated VDBP. The third step involves the addition of streptavidin-coated micro particles and 25-OH vitamin D labelled with biotin. The free sites of ruthenium labelled VDBP become occupied, forming a complex of ruthenium labelled vitamin D binding protein and biotinylated 25-OH vitamin D. The entire complex then becomes bound to the solid phase through interaction of biotin and streptavidin.

The reaction mixture is aspirated into the measuring cells where the micro particles are magnetically captured onto the surface electrode. The unbound substances are then removed. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier and a value is generated.

Vitamin D interpretation was done according to the American Academy of paediatricians.

✞ **VITAMIN D INTERPRETATION:**

- **Severe deficiency <=5 ng/ml • Deficiency <=15 ng/ml • Insufficiency 15-20 ng/ml**
- **Sufficiency 20-100 ng/ml • Excess 100 ng/ml • Intoxication 150 ng/ml**

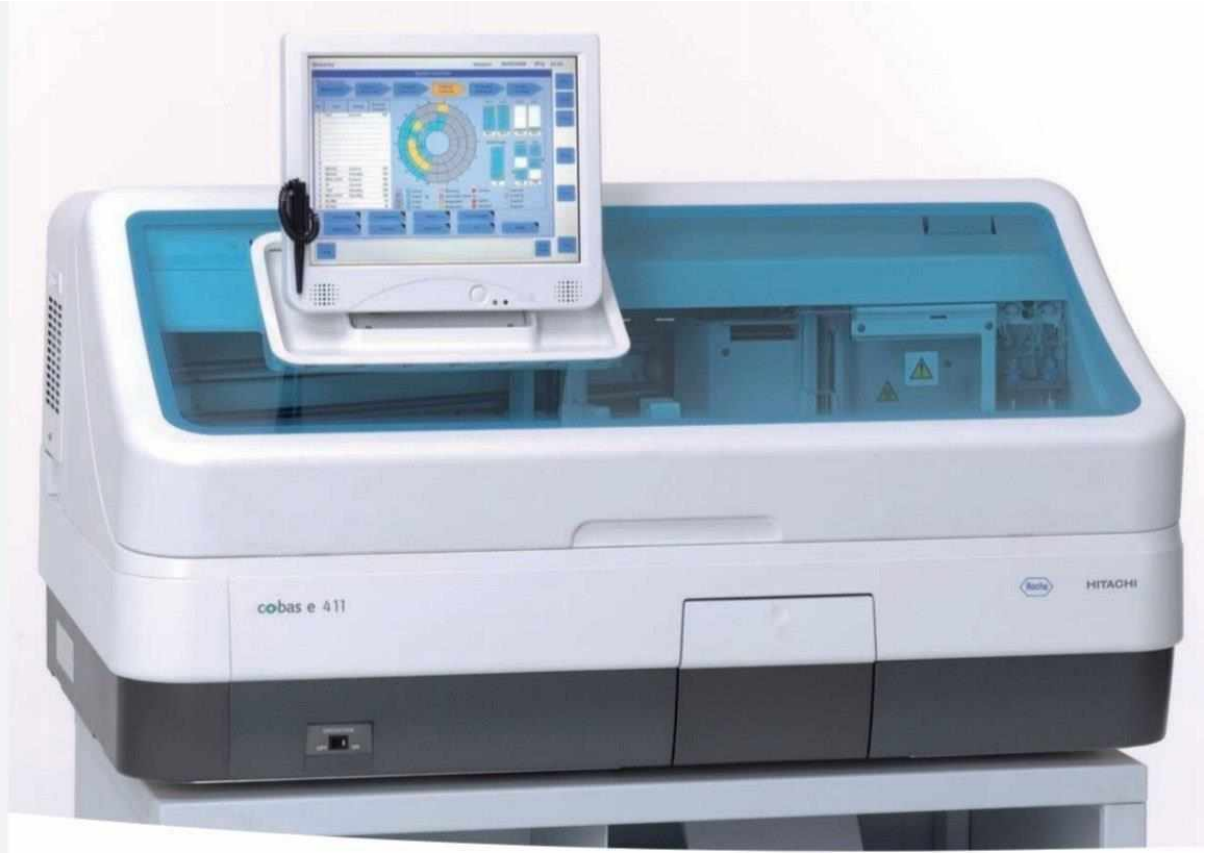

Figure 02 Roche cobase e 411 analyser

Figure 03 :Roche cobase e 411 analyser.

BONE MINERAL DENSITY ASSESSMENT

The bone mineral density parameters was measured using the **ultrasound bone densitometer Furuno CM-200 machine.** The machine uses ultrasound (QUS) to measure the speed of sound (SOS) in the heel.

The machine has a heel temperature sensor, foot plate, liquid crystal display (LCD), on board printer and an external connection portal to a PC. Its precise measurement has been optimized by a unique heel temperature sensor that does compensation of speed measurements. There is a height adjustable foot plate that can be adjusted to five levels by using the operating dial. This gives more accurate measurements by optimizing the position of the heel in an easy operation.

The measuring procedure involved using an ultrasonic applicator gel. The child was barefoot and in a stand-off the machine position, the gel was applied to the whole foot. The foot was then positioned and aligned in the cylinder and measurements taken. The machine takes about

10-20 seconds for LCD display of results. Two measurements were taken from each foot for analysis. The measurement of precision of the machine was Coefficient of variation of 0.5%.

Figure 04: Ultrasound bone densitometer Furuno CM-200 machine

The interpretation of the bone mineral density findings was done according to the International Society of Clinical Densitometry in 2013.

✞ **BONE MINERAL DENSITY INTERPRETATION : Z score**

- **Normal is.....>1.90**
- **LOW BONE MASS FOR CHRONOLOGICAL AGE is …… <-2.0**
- **OSTEROPOROSIS- z score equal to or less than -2.0 plus (A fracture of the lower limb or two long bone fractures in upper limb or two long bone fractures before age 10 or 3 long bone fractures before 19 years)**

DATA PRESENTATION AND ANALYSIS

The information from the questionnaire was scripted and results entered in the Statistical Package for the Social Sciences version 25.

The data collected was categorized, represented in tables and analysed using:

- Measures of central tendency: *means.*
- Measures of variability: *range, standard deviation and confidence of intervals*

The data on GMFCS in relation to the Z score and Vitamin D status was analysed using spearman's rank for the non-parametric data. This was also determined in multiple logistic regression models using the significant variables obtained at analysis.

The qualitative independent variables i.e., the GMFCS and the socio-demographics was presented in frequencies and analysed using the chi- squared test. However, for small numbers in the contingency table, less than 6 the Fischer's exact test was used.

The assessment of calcaneal BMD and the Vitamin D of children from both KNH and STMHK was analysed using Chi-square and ordinal logistic regression. All the statistical tests were at a 5% level of significance (alpha 0.05). The data findings were presented in tables, bar graphs and pie charts.

The table below gives a brief outline of the variables that were assessed during the study

DATA	**DATA TYPE**				**VARIABLE**
Sex, Weight, height *Location , Institutionalized, GMFCS, diet type, Sunlight exposure*	Nominal	Non-parametric	qualitative	Discrete	Independent
Age	Ratio	Parametric	quantitative	Continuous	Independent
GMFCS	Ordinal	Non-parametric	qualitative	Discrete	Independent
BMD status , Vitamin D3 status,	Ordinal	Non-parametric	qualitative	Discrete	Dependent
Z score, Vitamin D level, SOS, *AED dose, Number of fractures*	Interval	Parametric	quantitative	Continuous	Dependent

Table 01: Study Data variables

QUALITY CONTROL

The sample collection and measurement of the calcaneal bone mineral density were done by the primary researcher. This reduced the bias in the collection and measurement results. Two measurements were taken from each foot for analysis and an average was obtained for analysis.

ETHICAL CONSIDERATION

The recruitment of patients for this study was done under the World Health organization international ethical guidelines for biomedical research involving human subjects. COVID-19 WHO and Ministry of Health safety protocols were put in place to ensure safety of all the participants.

The Ethical approval to conduct this study was sort from the Department of Orthopaedic surgery University of Nairobi, Kenyatta National Hospital ethics and review Committee. All participants who were enrolled into the study were carefully explained to about the study. Their participation was voluntary and those who were not willing to participate, their management was not to be affected in any way. Confidentiality of the participants was strictly adhered to throughout the study.

A study number was used for identification of the participants and no personal identifiers were used. The results were communicated either during the visit or through a phone call. Following the results of the study any participants who required any intervention done immediate institution of treatment was done through a referral to the primary facility of research.

DISSEMINATION AND UTILITY OF RESULTS

The outcomes of the study are presented to the department of Orthopaedic surgery, University of Nairobi. A copy of the dissertation will be placed in the University of Nairobi library.

This data will be shared for publication in peer reviewed journal. These results may be a critical adjunct in decision making, management and follow up of children with cerebral palsy.

CHAPTER FOUR: RESULTS

A. Patient Demographic characteristics

A total of 70 patients were recruited into the study. Of these 50 were female and 20 were male. The female to male ratio was 2.5:1. The mean age for the patients was 9.71 (95% CI: 8.11 to 11.31) years, the youngest child was 5 years while the oldest was 12 years. Forty-one (58.6%) patients were recruited from Kenyatta National Hospital and 29 (41.4%) patients from St Theresa Mission Hospital Kiirua. Thirty of the patients were from an institutionalized system and 40 were from a family home setting.

The mean tibia length was 23.8 centimetres (95%CI: 22.5 to 25.1) and mean height of the patients was 108.47 (95% CI: 104.31 to 112.63) centimetres. The shortest patient was 70 centimetres while the tallest was 144 centimetres. The mean weight was 19.4 Kilograms (95% CI: 17.38 to 21.42). The lightest patient was 9 kilograms while the heaviest was 40 kilograms. The mean Basal Mass Index was 16 (95%CI: 15.1 to 16.9).

The mean age for the primary care giver was 36 years (95% CI: 33.7 to 38.55). The youngest primary care giver was 20 years while the oldest was 79 years.

Table 2 shows a summary of the demographic characteristics (i.e., biodata, demographic information, sunlight exposure) of the study participants.

Table 2: Demographic information of Study participants

Variable	N	Range	Minimum	Maximum	Mean	Std. Error	SD
Age (years)	70	7	5	12	**9.71**	0.819	6.853
Gestational age at birth (Weeks)	70	8	32	40	**37.56**	0.242	2.026
Birth Weight(kg)	69	2.6	1.4	4	**2.38**	0.061	0.507
Tibia Length (cm)	70	22.7	12.0	34.7	**23.8**	0.7	5.452
Height in (cm)	70	74	70	144	**108.47**	2.124	17.773
Weight (Kg)	70	31	9	40	**19.40**	1.026	8.585
Basal Mass Index	70	16.82	8.69	25.51	**16.00**	0.47	3.899
Age of Primary Care Giver (years)	70	59	20	79	**36.13**	1.237	10.352
% Body surface are exposed to sunlight	70	0.5	0.25	0.75	**0.41**	0.022	0.186
No of days exposed to sunlight per week:	70	3	4	7	**6**	0.138	1.155

Table 3: summarizes the demographic information of patients represented in frequencies and percentages.

Table 3: Demographic Information

Variable		*Frequency*	*Percent*
Gender	Male	20	28.6
	Female	50	71.4
	Total	70	100
Place of stay	Meru	29	41.4
	Nairobi	41	58.6
	Total	70	100
Location	K.N.H	41	58.6
	STMHK	29	41.4
	Total	70	100
Institutionalized	NO	40	57
	YES	30	43
	Total	70	100
GMFCS	III	20	28.6
	IV	24	34.3
	V	26	37.1
	Total	70	100

B. CALCANEAL BONE MINERAL DENSITY

I. BONE MINERAL DENSITY LEVEL

- **RIGHT BONE MINERAL DENSITY LEVEL**

Sixty-four (**64.3%** n=45) percent of the patients had normal right bone mineral density. The prevalence of low bone mass for chronological age on the right side was Twenty-four (24.3% n=17) percent. Eleven (11.4%, n=8) percent of the patients presented with osteoporosis. The diagram below represents the frequency and percentage levels.

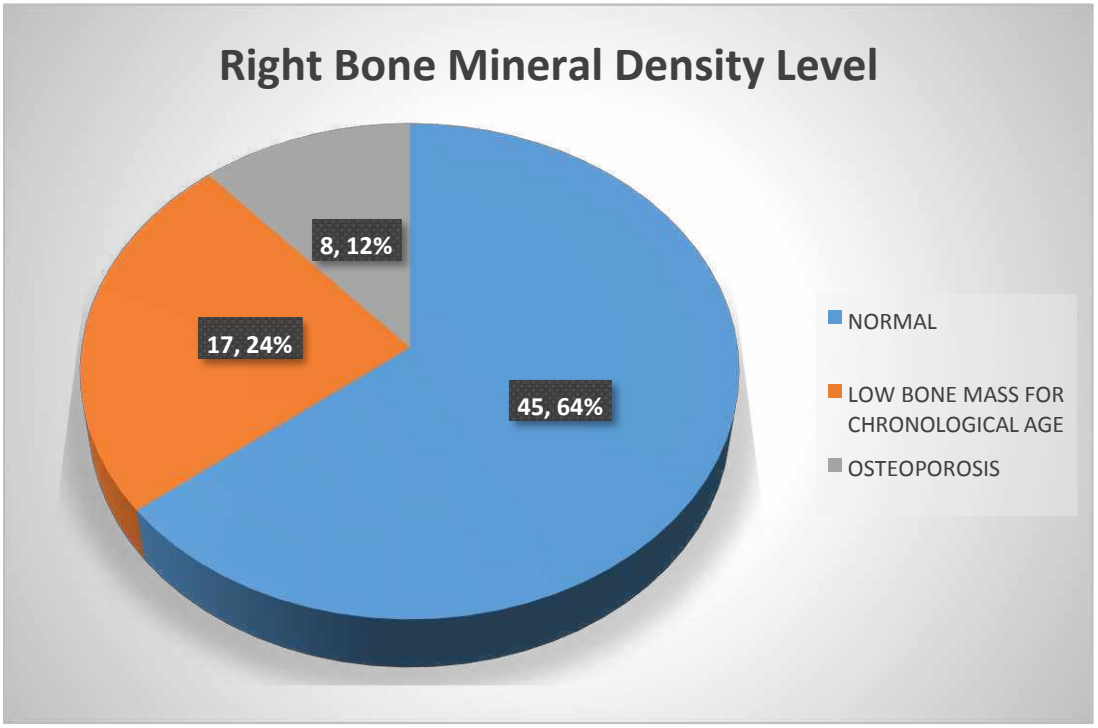

FIGURE 05: Right bone mineral density level

- **LEFT BONE MINERAL DENSITY LEVEL**

Seventy-three (**72.9**% n=51) percent of the patients had normal left bone mineral density. Approximately nineteen (18.6% n=13) percent presented with low bone mineral mass for chronological age and nine percent (8.6% n=6) were diagnosed with osteoporosis. The diagram below represents the frequency and percentage levels.

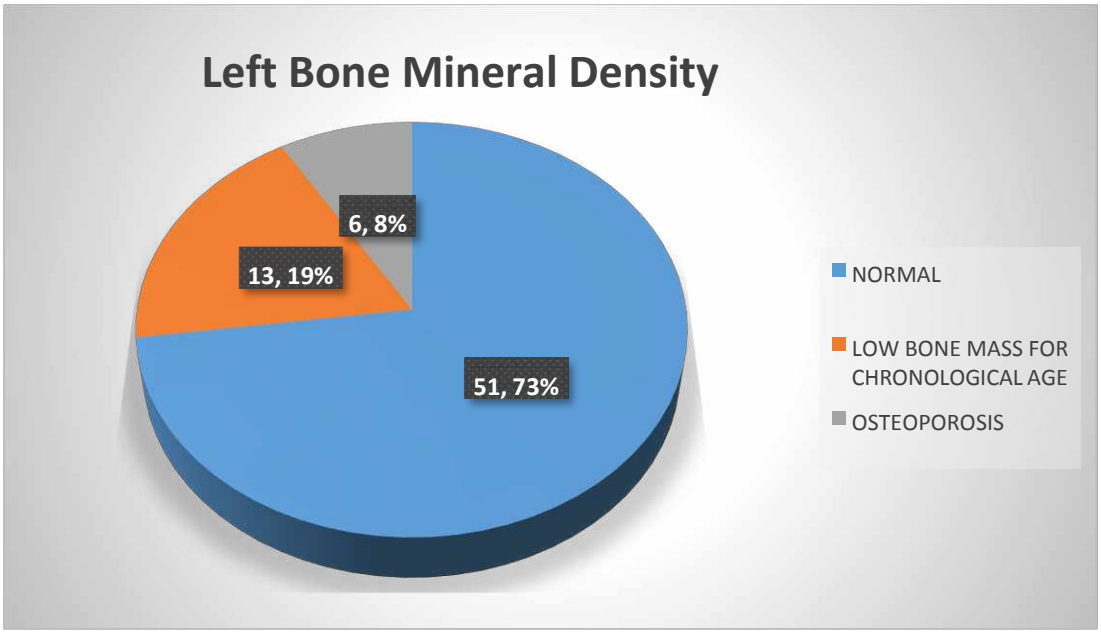

FIGURE 06: Left bone mineral density level

- **AVERAGE BONE MINERAL DENSITY LEVEL**

The average bone mineral density was calculated from the right and left foot measurements. Seventy (**70**% n= 49) percent of the patients had normal bone mineral density, twenty (**20**% n=14) had low bone mass for chronological age, while ten (**10%** n=7) presented with osteoporosis. The figure below illustrates the average bone mineral density.

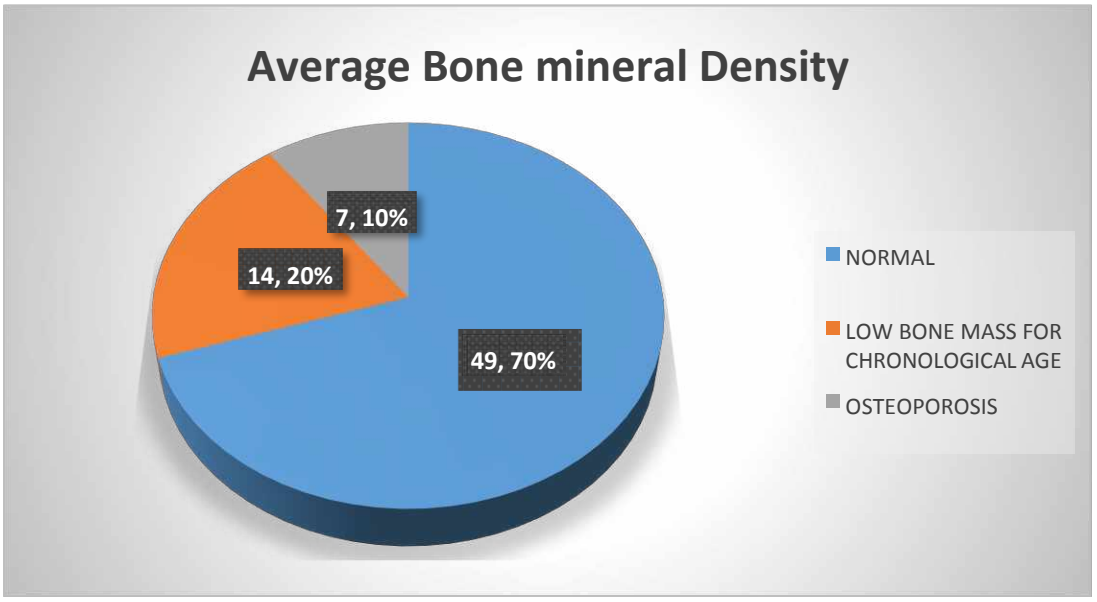

FIGURE 07: Average bone mineral density level

THE RELATIONSHIP BETWEEN THE PATIENTS' DEMOGRAPHIC CHARACTERISTICS AND BONE MINERAL DENSITY

LOCATION: KENYATTA NATIONAL HOSPITAL AND ST THERESSA MISSION HOSPITAL KIIRUA

There was no statistically significant difference on bone mineral density of right, left and average of both feet between patients seen at Kenyatta National hospital and those seen at STMHK. RIGHT (Chi-square value 2.81, DF=2. P-Value 0.245), Left (Chi-square 1.374, D.F= 2, P-Value 0.503) and Average (Chi-square 2.044, D.F 2, and P-Value 0.36).

THE GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM: **III-V**

There was no statistically significant association between the gross motor function classification system of children with moderate to severe cerebral palsy and the right bone mineral density (Chi-square value 2.834, DF= 4 and P-Value 0.586).

The table below illustrates the association between GMFCS level and the Right foot BMD measurements.

Table 7: Association between Gross Motor Function Classification System and the right bone mineral density

		GMFCS			Total	Chisquare	DF	Pvalue
RIGHT BONE MINERAL DENSITY LEVEL		**III**	**IV**	**V**		2.834	4	0.586
	NORMAL	14	17	14	45			
	LOW BONE MASS FOR CHRONOLOGICAL AGE	5	4	8	17			
	OSTEOPOROSIS	1	3	4	8			
Total		**20**	**24**	**26**	**70**			

There was no statistically significant association between the gross motor function classification system of children with moderate to severe cerebral palsy and the Left bone mineral density (Chi-square 6.039; DF 4 and P-Value 0.196). The table below illustrates the association between GMFCS level and the Left foot BMD measurements.

Table 8: Association between Gross Motor Function Classification System and the left bone mineral density

		GMFCS			Total	Chi-Square	DF	P-Value
LEFT BONE MINERAL DENSITY		**III**	**IV**	**V**				
	NORMAL	15	20	16	51	6.039	4	0.196
	LOW BONE MASS FOR CHRONOLOGICAL AGE	5	2	6	13			
	OSTEOPOROSIS	0	2	4	6			
Total		**20**	**24**	**26**	**70**			

There is no statistically significant association between the average right and left foot calcaneal bone mineral density and the level of gross motor function classification system (chi-square 2.923; DF 4 and P-value 0.571). The Table below shows the associations.

Table 09: Association between Gross Motor Function Classification System and the Average feet bone mineral density

		GMFCS			Total	Chi-square	DF	P-Value
AVERAGE BMD		**III**	**IV**	**V**				
	NORMAL	14	19	16	49	2.923	4	0.571
	LOW BONE MASS FOR CHRONOLOGICAL AGE	5	3	6	14			
	OSTEOPOROSIS	1	2	4	7			
Total		**20**	**24**	**26**	**70**			

AGE, GENDER, HEIGHT

There was no statistically significant relationship between age and average Bone mineral density (OR 1.02; P-Value 0.526).

There was no statistically significant association between Patients' gender and average bone mineral density (Chi-square value 1.05; DF 2; P-Value 0.592).

There was no statistically significant relationship between patients' height and the average bone mineral density (OR=0.99; P-Value 0.609).

There was no statistically significant relationship between patient's weight and average bone mineral density (OR=1.01; P-Value 0.712).

NUTRITION: COMMON MEAL AND FOOD PREPARATION

There was no statistically significant relationship between the common meal and Average bone mineral density (vegetarian OR= 1.8; P-Value 0.348; Animal products OR= 1.07; PValue 0.952 reference both). There was no statistically significant relationship between mode of food preparation and average bone mineral density (OR= 0.63; P-Value 0.406).

TABLE 10: Association between BMD and type of meal

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**1.269**	**3.56**	**0.551**	**5.294**	**1**	**0.021**	**0.188**	**2.349**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**2.631**	**13.9**	**0.639**	**16.966**	**1**	**<0.001**	**1.379**	**3.883**
COMMON MEAL	**Vegetarian**	**0.592**	**1.8**	**0.63**	**0.882**	**1**	**0.348**	**-0.643**	**1.828**
	Animal products	**0.072**	**1.07**	**1.187**	**0.004**	**1**	**0.952**	**-2.255**	**2.398**
	BOTH	**0a**		**.**	**.**	**0**	**.**	**.**	**.**

SUNLIGHT EXPOSURE

There was no statistically significant relationship between the average number of days a patient is exposed to sunlight and the bone mineral density (OR=0.82; P-Value 0.365).

There was no statistically significant relationship between hours of exposure to sunlight and average bone mineral density (OR=1.31; P-Value 0.421). The table below demonstrates this association.

Table 11: Relationship between total hours of exposure to sunlight and average bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**-0.346**	**0.71**	**1.324**	**0.068**	**1**	**0.794**	**-2.942**	**2.249**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**1.015**	**2.76**	**1.343**	**0.572**	**1**	**0.45**	**-1.617**	**3.648**
	EXPOSURE TO SUNLIGHT (HOURS)	**-0.199**	**0.82**	**0.22**	**0.819**	**1**	**0.365**	**-0.631**	**0.232**

ANTI-EPILEPTIC DRUGS

There was no statistically significant difference between those who were on anti-epileptics and those without in relation to average bone mineral density. The table below illustrates this association.

Table 12: Relationship between anti-epileptic drugs and average bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**1.037**	**2.82**	**0.42**	**6.102**	**1**	**0.014**	**0.214**	**1.859**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**2.392**	**10.94**	**0.522**	**20.995**	**1**	**0**	**1.369**	**3.415**
AED USE	**YES**	**0.327**	**1.39**	**0.531**	**0.379**	**1**	**0.538**	**-0.713**	**1.367**
	NO	**0a**		**.**	**.**	**0**	**.**	**.**	**.**

FRACTURE NUMBER

An increase of number of fractures by one was 2.54 times more likely to be due to low bone mineral density for chronological age on the right limb (OR=2.54; P-Value 0.006). On the Left limb an increase in the number of fractures by one on the left limb was 2.12 more likely to be due to low bone mineral density for chronological age (OR 2.12; 95% CI: 1.12 to 4.02; P-Value 0.021).With the average of left and right calcaneal bone mineral density ,every

increase of a number of fractures by one was 2.11 times more likely due to reduced bone mineral density (OR=2.11; 95% CI: 1.12 to 3.96; P-Value 0.021).

The table below demonstrates the association between fracture number and right foot BMD.

Table 13: Relationship between fracture number and right bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**0.866**	**2.38**	**0.335**	**6.687**	**1**	**0.01**	**0.21**	**1.523**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**2.459**	**16.7**	**0.48**	**26.236**	**1**	**0**	**1.518**	**3.4**
FRACTURE NUMBER		**0.932**	**2.54**	**0.338**	**7.624**	**1**	**0.006**	**0.27**	**1.593**

The table below demonstrates the association between fracture number and left foot BMD.

Table 14: Relationship between fracture number and Left bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**1.286**	**3.62**	**0.365**	**12.413**	**1**	**0**	**0.571**	**2.001**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**2.679**	**14.6**	**0.521**	**26.462**	**1**	**0**	**1.658**	**3.699**

FRACTURE NUMBER	**0.752**	**2.12**	**0.326**	**5.328**	**1**	**0.021**	**0.114**	**1.391**

The table below demonstrates the association between fracture number and the average left and right foot BMD.

Table 15: Relationship between fracture number and Average bone mineral density

		Estimate	***OR***	***Std. Error***	***Wald***	***df***	***Sig.***	***95% Confidence Interval***	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**1.106**	**3.02**	**0.35**	**9.997**	**1**	**0.002**	**0.421**	**1.792**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**2.48**	**11.9**	**0.488**	**25.852**	**1**	**0**	**1.524**	**3.436**
FRACTURE NUMBER		**0.745**	**2.11**	**0.323**	**5.32**	**1**	**0.021**	**0.112**	**1.377**

SPEED OF SOUND AND BONE MINERAL DENSITY

Relationship between Right speed of sound and Right bone mineral density

A patient with osteoporosis was 2% less likely to have an increased speed of sound (SOS) on the right limb (OR: 0.98; 95%; P-Value 0.007). There was statistical significance between the SOS and BMD (P value 0.007)

Table 16: Relationship between Right speed of sound and Right bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**-21.818**	**0**	**8.299**	**6.911**	**1**	**0.009**	**-38.084**	**-5.551**
	LOW BONE MASS FOR CHRONOLOGICAL AGE	**-20.204**	**0**	**8.242**	**6.009**	**1**	**0.014**	**-36.359**	**-4.049**
Location	**RIGHT SOS (m/s)**	**-0.015**	**0.98**	**0.006**	**7.24**	**1**	**0.007**	**-0.026**	**-0.004**

Relationship between Left speed of sound and Left bone mineral density

Patients with osteoporosis (low bone density) on the left side were 3% less likely to have a unit increase in the speed of sound on the left limb (OR=0.97; P-Value <0.001).

Table 17: Relationship between Left speed of sound and Left bone mineral density

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**NORMAL**	**-44.83**	**0**	**12.616**	**12.627**	**1**	**<0.001**	**-69.556**	**-20.104**

	LOW BONE MASS FOR CHRONOLOGICAL AGE	**-43.148**	**0**	**12.515**	**11.886**	**1**	**0.001**	**-67.678**	**-18.618**
Location	**LEFT SOS (m/s)**	**-0.031**	**0.97**	**0.008**	**13.016**	**1**	**<0.001**	**-0.047**	**-0.014**

VITAMIN D

LEVEL OF VITAMIN D

55.7 % (n= 39) of the total patients had less than sufficient levels of vitamin D with 44.3% (n=31) of the patients with sufficient vitamin D levels. Approximately thirty nine percent (38.6% n=27) presented with insufficient levels of vitamin D. Fourteen percent (14.3% n=10) were diagnosed to have vitamin D deficiency and only three percent (2.9% n=2) had severe vitamin D deficiency.

This is summarized in the pie chart and bar graph below.

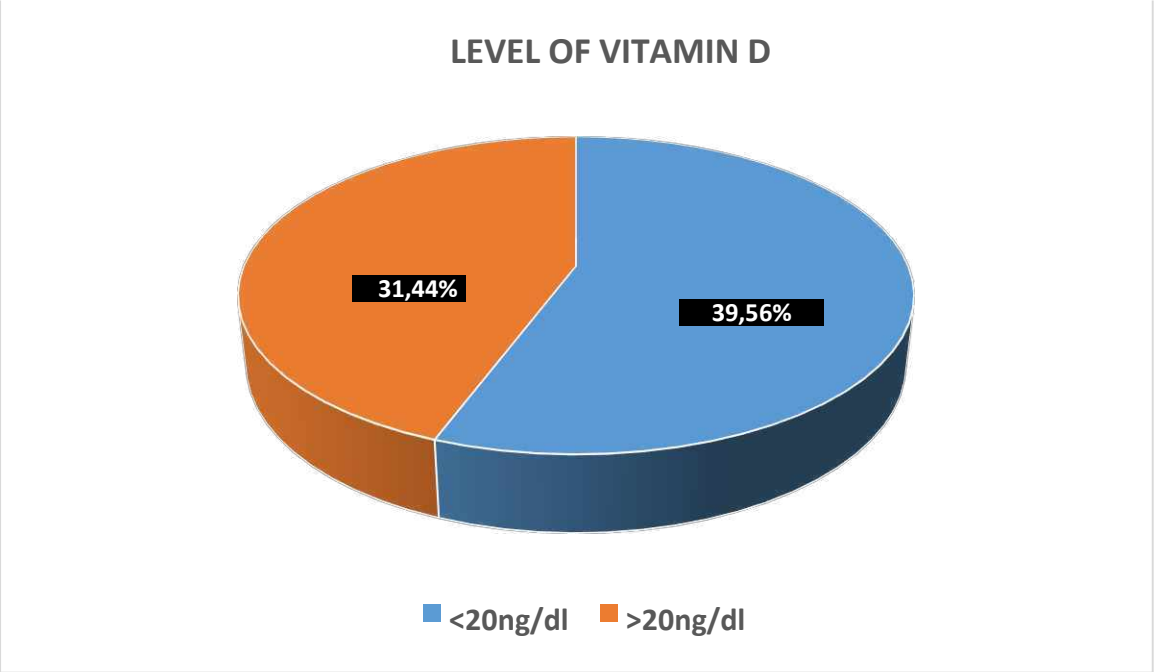

FIGURE 08: VITAMIN D LEVELS

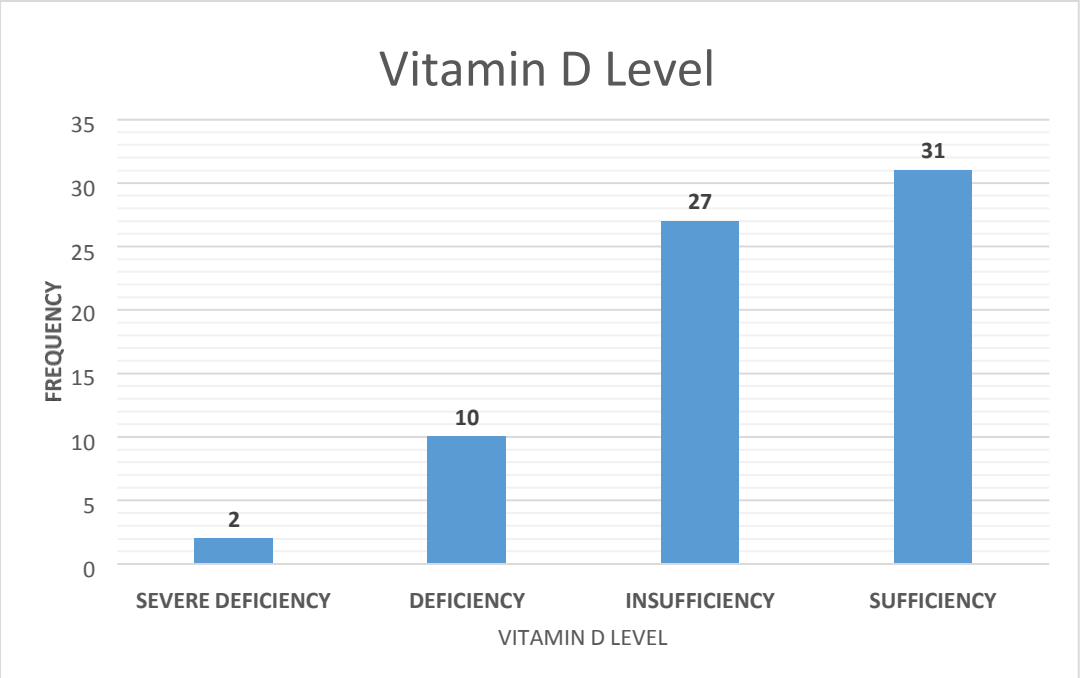

Figure 09: Vitamin D levels

THE RELATIONSHIP BETWEEN THE PATIENT'S DEMOGRAPHICS AND VITAMIN D LEVEL

LOCATION: KENYATTA NATIONAL HOSPITAL (URBAN) AND ST THERESSA MISSION HOSPITAL KIIRUA (RURAL)

There was a statistically significant association between the patients' location and the level of Vitamin D (Chi-square 13.067, DF 3 and P-value 0.004).

Table 18: Association between the Patients' Location and the levels of Vitamin D (ng/ml)

		Location		Total	Chi-square	DF	P-value
		URBAN	**RURAL**				
		Absolute number					
VITAMIN D LEVEL OF SUFFICIENCY	SEVERE DEFICIENCY	0	2	2	13.067	3	0.004
	DEFICIENCY	2	8	10			
	INSUFFICIENCY	21	6	27			
	SUFFICIENCY	18	13	31			
Total		41	29	70			

THE GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM: **III-V**

Relationship between GMFCS and Vitamin D levels

Patient classified as GMFCS III were 6.62 times more likely to have sufficient levels of Vitamin D as compared to those in class V (OR 6.62; P-Value 0.004). There was no statistically significant difference in vitamin D levels between GMFCS IV and V, despite IV being 1.77 times more likely to have sufficient levels (OR 1.77 P- Value 0.285).

Table 19: Relationship between GMFCS and Vitamin D levels

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**SEVERE DEFICIENCY**	-3.038	**0.05**	0.757	16.099	1	**<0.001**	-4.522	-1.554
	DEFICIENCY	-1.038	**0.35**	0.405	6.562	1	**0.01**	-1.833	-0.244
	INSUFFICIENCY	0.953	**2.59**	0.401	5.648	1	**0.017**	0.167	1.739
GMFCS	**III**	1.809	**6.62**	0.623	8.446	1	**0.004**	0.589	3.03
	IV	0.57	**1.77**	0.533	1.144	1	**0.285**	-0.474	1.614
	V	0a		.	.	0	.	.	.

AGE, GENDER and BMI

There was no statistically significant relationship between the patient's age (P-value 0.064), gender (P-Value 0.271) and BMI (P-Value 0.709) and the Vitamin D level.

NUTRITION: COMMON MEAL AND FOOD PREPARATION

There was no statistically significant relationship between the common meal (P-Value 0.700) and mode of meal preparation (P-Value-0.267) and the level Vitamin D.

SUNLIGHT EXPOSURE

Relationship between the time of exposure to sunlight and Vitamin D levels

There was no statistically significant relationship between the total number hours in a day a patient was exposed to sunlight (P-value 0.924) and numbers of days per week a patient was exposed to sunlight and vitamin D levels (P-Value 0.396). However, there was statistical significance in those with deficiency (P-Value 0.006) and severe deficiency with number of hours per day and number of days per week (P-Value 0.001).

There was a statistically significant relationship between the percentage of total body surface area (TBSA) exposed to sunlight and vitamin D level ; 25 % TBSA (P-value 0.017) and 50% TBSA (P-value 0.048). The table below illustrates this relationship.

Table 20: Relationship between Total body surface area exposed to sunlight and Vitamin D

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**25 %**	**0.557**	**1.746**	**0.234**	**5.672**	**1**	**0.017**	**1.104**	**-2.761**
	50%	**-0.183**	**0.833**	**0.093**	**3.910**	**1**	**0.048**	**0.694**	**0.998**
	75%	**-0.006**	**0.994**	**0.106**	**0.004**	**1**	**0.951**	**0.808**	**1.222**
TBSA	**100%**	**0a**		**.**	**.**	**0**	**.**	**.**	**.**

VITAMIN D SUPPLEMENTATION AND ANTIEPILEPTIC DRUGS

There was no statistically significant relationship between Vitamin D supplementation and vitamin D levels (P-value 0.323).

Patients on anti-epileptic drugs were 83% less likely to have sufficient vitamin D levels as compared to patients who were not on anti- epileptic drugs (OR=0.17; P-Value 0.001). This is demonstrated in the table below. However, there was no statistically significant relationship between specific anti-epileptic and the vitamin D levels. See tables below demonstrating this relationship.

Table 21: Relationship between Antiepileptic drugs use and Vitamin D levels

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**SEVERE DEFICIENCY**	**-4.859**	**0.008**	**0.832**	**34.124**	**1**	**<0.001**	**-6.49**	**-3.229**
	DEFICIENCY	**-2.809**	**0.06**	**0.512**	**30.131**	**1**	**<0.001**	**-3.812**	**-1.806**
	INSUFFICIENCY	**-0.73**	**0.48**	**0.393**	**3.45**	**1**	**0.063**	**-1.5**	**0.04**
AED USE	**YES**	**-1.77**	**0.17**	**0.512**	**11.962**	**1**	**0.001**	**-2.772**	**-0.767**
	NO	**0a**		**.**	**.**	**0**	**.**	**.**	**.**

Table 22: Relationship between specific anti-epileptic drugs and Vitamin D levels

		Estimate	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
							Lower Bound	**Upper Bound**
Threshold	**SEVERE DEFFICIENCY**	**-3.948**	**1.108**	**12.688**	**1**	**0**	**-6.121**	**-1.776**
	DEFFICIENCY	**-1.669**	**0.825**	**4.098**	**1**	**0.043**	**-3.285**	**-0.053**
	INSUFFICIENCY	**0.669**	**0.787**	**0.723**	**1**	**0.395**	**-0.873**	**2.211**
AED	**Phenobarbital**	**-0.065**	**0.927**	**0.005**	**1**	**0.944**	**-1.882**	**1.752**
	Phenobarbital + Diazepam	**19.642**	**0**	**.**	**1**	**.**	**19.642**	**19.642**
	None	**1.381**	**0.875**	**2.489**	**1**	**0.115**	**-0.334**	**3.096**
	Valproic	**-1.253**	**1.345**	**0.868**	**1**	**0.352**	**-3.889**	**1.383**
	Phenytoin	**-2.809**	**2.092**	**1.803**	**1**	**0.179**	**-6.909**	**1.292**
	Diazepam + Valproic	**-2.809**	**2.092**	**1.803**	**1**	**0.179**	**-6.909**	**1.292**
	Valproic + phenytoin	**0.093**	**1.226**	**0.006**	**1**	**0.94**	**-2.311**	**2.497**
	Phenobarbital + Valproic	**-1.069**	**0.975**	**1.203**	**1**	**0.273**	**-2.979**	**0.841**
	Phenotoin + Phenobarbitone	**0a**	**.**	**.**	**0**	**.**	**.**	**.**

FRACTURE NUMBER

An increase in the number of fractures by one unit was 53% less likely to happen to patients with sufficient Vitamin D levels (OR= 0.47; P-Value 0.015)

Table 23: Relationship between Number of fractures and Vitamin D levels

		Estimate	*OR*	*Std. Error*	*Wald*	*df*	*Sig.*	*95% Confidence Interval*	
								Lower Bound	**Upper Bound**
Threshold	**SEVERE DEFFICIENCY**	**-4.031**	**0.02**	**0.816**	**24.387**	**1**	**<0.001**	**-5.631**	**-2.431**
	DEFFICIENCY	**-2.106**	**0.12**	**0.432**	**23.803**	**1**	**<0.001**	**-2.952**	**-1.26**
	INSUFFICIENCY	**-0.343**	**0.71**	**0.309**	**1.227**	**1**	**0.268**	**-0.949**	**0.264**
FRACTURE NUMBER		**-0.746**	**0.47**	**0.306**	**5.93**	**1**	**0.015**	**-1.346**	**-0.145**

DISCUSSION

The aim of the study was to establish the bone mineral density status and vitamin D levels in children with cerebral palsy (GMFCS III, IV and V). This was conducted in two facilities Kenyatta National Hospital (urban) and St Theressa Mission Hospital Kiirua (rural). A total of 70 children were recruited in the study. The Bone mineral density was measured using the ultrasound bone densitometer Furuno CM-200 machine. Measurements were taken from both Left and Right feet and average of both feet analysed. The interpretation of the bone mineral density findings was done according to the International Society of Clinical Densitometry in 2013 and Vitamin D according to the American Academy of paediatricians. 100% of the children from STMHK were from an Institutionalized system while 96% from KNH were from a family home setting.

The results demonstrated the prevalence of low BMD defined by a Z score less than -2 was 30%. From the 30%, 20% had low bone mass for chronological age, while 10% presented with osteoporosis. The right foot normal Z score measurements were lower compared to the left (9%). This was similar to results demonstrated in a Systematic review by Mergler et al, where the prevalence of low BMD ranged from 27%-77% (6). The mean BMD in this study was -1.06 while in the systematic review the ranges varied from -2.4 to -3.4 (6). The difference in the findings could be explained by the use of superior methods of measuring BMD such as DXA. Most of the studies used DXA either at the distal femur or the lumbar spine.

The studied demographic characteristics that could be determinants of low BMD included Age, sex, weight, height, GMFCS, use of AED, diet, sunlight exposure and previous history of fractures. There was no statistically significant relationship between Age (P-Value 0.526) and sex (P-Value 0.592). This was also seen by Henderson et al (11) and Finbraten et al (12). All the children in this study had a BMI less than 18.5 with no statistical significance.

There was no statistically significant relationship between the common meal and Average bone mineral density (vegetarian OR= 1.8; P-Value 0.348; Animal products OR= 1.07; PValue 0.952 reference both). Eighty percent (80%) of the patients reported that the

constituents of their diet was predominantly vegetarian, this was an indirect indicator of the socio-economic status of the participants interviewed. In this study the data that was collected in relation to the common meal was assessed in only two categories. This could have been sensitive to informational bias. A proper dietary assessment using food diaries would have been a better assessment tool. This might also explain why the results did not correlate with other studies (6, 62). However, this was not a primary goal in this study. The children from the rural setting (institutionalized) were able to provide a weekly menu while those who were from the urban setting (non-institutionalized) the information was reported from the care givers. This may have had a slight bias in analysis from the urban setting. It is also important to note that the patients taken care of in a home setting, only one participant had another sibling requiring special needs. The institutionalized systems were primarily based on taking care of many children with neuromuscular disorders, especially cerebral palsy. The extent of care could also explain these findings. These same differences in institutionalized and noninstitutionalized care of children with cerebral palsy was highlighted by Tosun et al and Mergler et al (6,62).

There was no statistically significant relationship between mode of food preparation and average bone mineral density (OR= 0.63; P-Value 0.406). This is because 71% of the children had their food blended due to different feeding problems associated with cerebral palsy.

Children with worse GMFCS had averagely lower BMD. Similar results were seen by Shin et al, Henderson et al and Frinbaten et al (12,13,14). However, there was no statistically significant association between the average calcaneal bone mineral density and the level of gross motor function classification system (P-value 0.571). This was different compared to other studies (6) that predominantly used DXA as a measure of BMD. This highlights the lower sensitivity of the calcaneal QUS in identifying those with low BMD compared to DXA as well as difficulty is assessing children with contractures.

There was no statistical significance between the bone mineral density and the use of antiepileptic drugs. This was reported by Chen et al (83) in their study on ‘The effect of anticonvulsant use on bone mineral density in non-ambulatory children with cerebral palsy’.

Children with cerebral palsy have numerous risks factors in developing fragility fractures. In this study, 17 (24%) children had history of fractures with 6 (35%) children with more than one fracture reported. This prevalence was slightly higher than a systematic review that

showed a prevalence of fractures to be between 12%-23% (6,12). The commonest site was the lower limb, specifically the right lower limb. This was similar to a study done by Mughal et al (13).

This study demonstrated that on the right any increase in number of fractures on the affected limb by one was 2.54 times due to low BMD and 2.12 times on the left. This was reflected in the lower values of bone mineral density on the right limb compared to the left limb. (Right: P-Value 0.006; left P-Value 0.021). With the average values of both right and left feet, every increase of a number of fractures by one was 2.11 times more likely due to low BMD (PValue 0.021). BMD therefore seems to have a strong association with pathological fractures seen in children with moderate to severe cerebral palsy (6, 12, 13).

This study showed a positive association between the SOS and BMD. There was no association with age, weight and height. The patients with osteoporosis were 2% less likely to have an increased speed of sound (SOS) on the right limb (OR: 0.98; 95%; P-Value 0.007). On the left those with osteoporosis (were 3% less likely to have a unit increase in the speed of sound (OR=0.97; P-Value <0.001). The published papers on speed of sound assessed healthy children or children with other haematological disorders with none with cerebral palsy (85,86). The information from this study will provide a baseline for children with cerebral palsy.

VITAMIN D

Vitamin D is essential for normal skeletal development and mineralization. The aim of this study was to demonstrate the prevalence and severity of the vitamin D deficiency in children with CP and its relation to patient demographic characteristics.

This study found 55.7 % (n= 39) of the total patients had less than sufficient levels of vitamin D with 44.3% (n=31) of the patients had sufficient vitamin D levels. This was also mirrored in many studies with Langton et al reporting levels as high as 93% (6, 54, 55, 60). In this study, approximately 38.6% (n=27) presented with insufficient levels of vitamin D, 14.3% n=10) vitamin D deficiency and only three percent (2.9% n=2) had severe vitamin D deficiency. Despite the lack of significant difference between the two groups of children, those from institutionalized systems were 77.6% more likely to develop less than normal Vitamin D levels compared to 22.4 % from non- institutions.

Only 6 participants from the study were on Vitamin D supplementation and one third of them had less than 20ng/ml with the average duration on medication being 6 months. Approximately less than 10 % were aware of any Vitamin D levels done within the last one year. The commonest tests assessed for skeletal health was calcium and phosphate. This also reflected why most of the children were predominantly on calcium only based supplements. The cost of testing Vitamin D is almost 10 times the cost of other tests. This is also not covered by the national hospital insurance Fund. While some patients had Vitamin D levels requested for, financial constraints limited their capability in having the tests done.

Studies have shown that there is a correlation between the GMFCS and the level of Vitamin D (6). This is demonstrated in this study where patients classified as GMFCS III were 6.62 times more likely to have sufficient levels of Vitamin D as compared to those in class V (PValue 0.004). There was no statistically significant difference in vitamin D levels between patients in GMFCS IV and V despite those in IV being 1.77 times more likely to have sufficient levels (P- Value 0.285). Toopchizadeh et al found no correlation between GMFCS and vitamin D levels. However, their study used >30ng/ml as sufficient while our study used levels > 20ng/ml according to American Academy of Paediatricians.

Epilepsy has been shown to frequently coexist with cerebral palsy. Among the 70 children 59% were taking anti-epileptic drugs. The commonly used drug was phenobarbital and phenytoin, this was also reported by Sato et al (6,67). Other drugs used included sodium valproate and diazepam. Patients on anti-epileptic drugs were 83% likely to have less than normal vitamin D levels compared to patients who were not on anti- epileptic drugs (P-Value 0.001). Other studies concurred with the findings with low Vitamin D levels varying from 47%-75% in those taking AED. The findings were more pronounced in those taking drug combinations (7). This could explain the higher percentage seen in this study as 90% of the children were on combination drugs. In view of the use of combinations of anticonvulsants among the patients in this study the impact of individual anticonvulsants was not analysed.

Sun exposure was limited for those who were from the institutionalized setting with average exposure time of 2-3 hours and amount of body exposure approximately 25%. Those from non- institutions had approximately 4-5 hours a day and 50 % total body surface area exposed. This could be attributed to the high number of children with Cerebral Palsy who are taken care of in the institutions and limited number of caregivers.

There was no statistically significant relationship between the number of hours in a day a patient was exposed to sunlight (P-value 0.924) and numbers of days per week a patient was exposed to sunlight and vitamin D levels (P-Value 0.396). However, there was statistical significance in those with severe deficiency with total number of hours per week (P-Value 0.001). There was a statistically significant relationship between the percentage of total body surface area (TBSA) exposed to sunlight and vitamin D level; 25 % TBSA (P-value 0.017) and 50% TBSA (P-value 0.048). This was in keeping with previous studies (40,69,70). However, levels in children from different setups would provide better conclusion. This is because the children from the institutionalized systems all had similar total body surface area exposure and duration of exposure. Therefore, the efficacy of sunlight exposure on vitamin D levels could not be determined.

This study found that an increase in the number of fractures by one unit was 53% likely to occur in patients with less than normal vitamin D levels (P-Value 0.015). These findings mirrored similar findings by Mughal et al (13).

CONCLUSION

- The level of Bone Mineral density and Vitamin D in children with GMFCS III-V was low. This is in keeping with previous studies. Those from Institutionalized systems had lower levels than those from non-institutionalized systems.
- There was no statistical significance between GMFCS III-V and BMD. However, those with worse GMFCS had lower BMD.
- The use of AED was significant in influencing the level of Vitamin D but not BMD.
- There was a positive association between hypovitaminosis D and the total body surface area exposed to sunlight.
- Level of BMD and Vitamin D were highly predictive of fracture risk, with the right lower limb affected more than the other areas.
- There was no correlation between the age, sex, height and weight with the BMD and Vitamin D levels.
- There was no association between the calcaneal speed of sound with age, weight and height. However, there was a positive association between the speed of sound and BMD.

RECOMMENDATIONS

- Regular investigation of vitamin D status is necessary in children with cerebral palsy.
- Strongly recommend the need for supplementation of Vitamin D in children with cerebral palsy.
- There is a need for an increase in total body surface area exposed to sunlight in children with cerebral palsy.
- Public health sensitization on Vitamin D rich foods should be encouraged for this population.
- There should be regular screening of BMD using the calcaneal QUS in patients with neuromuscular disorders. It should be noted from this study that QUS is not as sensitive as DXA but has a role in screening due to its safety profile and lower cost.
- There is need for creation of a screening tool questionnaire using the identified predictive risk factors for deranged vitamin D and BMD in children with cerebral palsy.
- It should be the practice to follow up children who meet the criteria of osteoporosis with calcaneal QUS with DXA measurements for definitive diagnosis and management.

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APPENDICES

Appendix I: STUDY TIMELINES

	JULY-DEC 2020	DEC-JAN 2020	FEB-APRIL 2021	MAY 2021	MAY 2021
PROPOSAL DEVELOPMENT					
ETHICAL CLEARANCE					
DATA COLLECTION					
DATA ANALYSIS					
RESULTS PRESENTATION, AND DISSEMINATION					

Appendix II: BUDGET

ITEM	**COST(KSH)**
Research fees(KNH/ERC)	2500
Statistician	30000
Laboratory charges	180,000
Transport	10000
Stationery	3000
Ultrasound bone densitometer	45000
Contigencies	25000
Total	**295,500/=**

Appendix III: **CONSENT FORMS/ fomu ya idhini**

Title of Study: **BONE MINERAL DENSITY AND VITAMIN D STATUS IN CHILDREN WITH MODERATE TO SEVERE CEREBRAL PALSY IN KENYATTA NATIONAL HOSPITAL AND ST THERESA MISSION HOSPITAL**

Principal Investigator: **DR THITAI JULIET**

Institutional Affiliation : **UNIVERSITY OF NAIROBI**

Co-Investigators and institutional affiliation: Kenyatta National Hospital and St Theresa Mission Hospital Kiirua

INTRODUCTION:

My name is Dr Thitai Juliet, I would like to tell you about a study that I am conducting. The purpose of this consent form is to give you the information you need to help you decide whether or not your child should participate in the study. Feel free to ask any questions about the purpose of the research, what happens if your child participates in the study, the possible risks and benefits, the rights of your child as a volunteer, and anything else about the research or this form that is not clear.

You should understand that:

i) Your decision to participate is entirely voluntary ii) Your may withdraw from the study at any time without necessarily giving a reason for your withdrawal

iii) Refusal to participate in the research will not affect the services your child is entitled to in this facility. We will give you a copy of this form for your records.

PURPOSE OF THE STUDY

This study aims to understand the bone mineral density status and vitamin D levels of children with cerebral palsy. There will be approximately 50 children who will be enrolled in

the study. This will involve taking a blood sample for analyzation of Vitamin D level and a calcaneal Ultrasound to determine the Bone mineral density.

ARE THERE ANY RISKS FOR PARTICIPATING IN THE STUDY?

All medical research has the potential to inflict some psychological, social, emotional and physical risks. One such risk is loss of privacy. We will keep everything you tell us as confidential as possible. We will use a code number that will be used to identify your child.

Your child may also feel some discomfort when withdrawing the blood sample and may have a small bruise or swelling. In case of any injury, illness or complication related to this study, contact us right away at the number provided at the end of this document.

ARE THERE ANY BENEFITS BEING IN THIS STUDY?

Your child may benefit by receiving free testing. The results will be communicated to you during your visit or through a phone call. Your child will be referred to a hospital for care and support if necessary.

The information gathered in this study is a major contribution to science and management of children with cerebral palsy.

If you have further questions or concerns about your child participating in this study, please call or send a text message to the number below.

For more information about your child's rights as a research participant you may contact

- The Secretary/Chairperson, Kenyatta National Hospital-University of Nairobi Ethics and Research Committee Telephone No. 2726300 Ext. 44102 email uonknh_erc@uonbi.ac.ke. The study staff will pay you back for your charges to these numbers if the call is for study-related communication.

  For more information contact Dr Thitai Juliet 0710425735

CONSENT FORM

The person being considered for this study is unable to consent for him/herself because he or she is a minor (a person less than 18 years of age). You are being asked to give your permission to include your child in this study.

Parent/guardian statement

I have read this consent form or had the information read to me. I have had the opportunity to discuss this study and all my questions have been answered and explained in a language that I understand. I have had my questions answered by him or her in a language that I understand. I have been explained to the risks and benefits of the study. I also understand that a copy of this form will be given to me after signing.

I understand that my child's participation is voluntary and that I may choose to withdraw from the study at any time. Signing this form doesn't mean that I have given up my child's legal rights.

I agree voluntarily for my child to participate in this study:

Yes …… No……

I agree to have my child undergo Calcaneal Ultrasound testing:

Yes…….. No……

I agree to have my child's blood withdrawn for Vitamin Ds level testing:

Yes…….. No……

Parent/Guardian signature /Thumb stamp: _____

Date _____

Parent/Guardian printed name: _____

Researcher's statement

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given his/her consent.

Printed Name: _____

Date: _____

Signature: _____

Role in the study: _____

FOMU YA IDHINI

SOMO: WIANI WA MADINI YA MFUPA NA VITAMINI D KATIKA WATOTO KENYA WALIIONA NA KUPOOZA KWA UBONGO (CEREBRAL PALSY) KATIKA HOSPITALI YA RUFAA YA JUU NCHINI KENYA NA ST THERESA MISSION

MSHIRIKI MKUU: DR THITAI JULIET

SHULE : Idara ya Upasuaji, Kitivo Cha Tiba, Shule Ya Sayansi Ya Afya, Chuo Kikuu Cha Nairobi.

HOSPITALI: HOSPITALI YA RUFAA YA JUU NCHINI KENYA NA ST THERESA MISSION KIIRUA

UTANGULIZI:

Majina yangu ni Dr Thitai Juliet , niruhusu nikueleze kuhusu utafuti kabla ya mtoto wako kuwa mshariki au la. Unaweza uliza swali lolote kuhusu utafiti huu. Haki zako kama mshiriki ni kama zifuatavyo

I) Uko na haki ya kuelewa uhuru wako kukubali ama kukataa kushiriki katika utafiti huu

II) Uko na haki ya kutoka katika utafiti huu hata baada ya kukubali unapogeuza nia

III) Uko na haki ya kupewa matibabu yote bila chuki wala fitina baada ya kukataa kushiriki tena katika utafiti huu

MALENGO

Nafanya utafiti wa wiani wa madini ya mfupa na vitamini D katika watoto kenya waliiona na kupooza kwa ubongo (cerebral palsy). Katikau huu utafiti tunasaka washiriki 50. Tutaoa damu kidogo kuangalia kiasi ya Vitamini D. Maambukizi ya mfupa madini wiani (BMD) tutatumia mzunguko ultrasound.

Je kuna adhari gani kushiriki katika utafiti huu?

Utafiti wowote wa kiafya unaweza kuwa na adhari kama vile kuzambaa kimakosa kwa ujumbe wa kibinafsi na pia uchunguzi waweza kuwa na maswali ya kufedhehesha. Mikakati tuliyoiweka ni ya kuzuia upeperushaji usio wa hiari wa ule ujumbe tutakaokusanya kama vile kutotumia majina ya washiriki. Badala yake tutatumia nambali maalum ya kuwatambulisha itakayojulikana tu ma mtafiti. Iwapo maswali uoyote ya kuaibisha itakuwepo, mshiriki akona hiari ya kukataa kujibu na pia hiari ya kukataa kuendelea kushiriki hata baada ya kupeana saini.

Je, kuna faida gani kushiriki

Ukishiriki katika huu utafiti, utampa mtoto wako nafasi ya kufanyiwa utafiti bila malipo. Utafiti huu utawapa wafanyakazi wa huduma za afya na watunga sera na maarifa kuhusu somo hili.
vitamini D ngazi na mfupa madini wiani. Wale wagonjwa na kuhusishwa na mfupa wa chini wiani madini itakuwa ilipendekeza kuwa na vitamini D virutubisho.

Ijapo una maswali, usisite kuwasiliana nasi wakati wowote kwa namna zilizotadhrishwa. Iwapo ungetaka kujua Zaidi haki zako kama mshiriki, tafadhali wasiliana na mwenyekiti au katibu wa Kamitii ya utafiti ya Hospitali ya Kitaifa ya Kenyatta na Chuo Kikuu cha Nairobi kwa simu 2726300 Ext. 44102 au barua pepe uonknh_erc@uonbi.ac.ke.

Dr Thitai Juliet -0710425735

IDHINI KUTOKA KWA MZAZI/MLEZI WA MTOTO ANAYESHIRIKI KWA UTAFITI

Kwa sababu anayeshiriki katika utafiti huu ni mtu ambaye hajafikisha miaka 18 nimekubali kepeana ruhusa kwake. Sitarajii manufaa yeyote ya kifedha kutokana na utafiti huu.

Nimeelezwa kwa kina yakwamba utafiti unaofanywa hautatumika kukandamizaandamiza au kuhujumu matibabu Ya mtoto wangu.

nimekubali kupeana ruhusa ili mtoto aendelee na utafiti huu
SAHIHI…….. TAREHE……..

Minekubali mtoto afanyiwe uchunguzi wa wiani wa madini ya mfupa

SAHIHI…….. TAREHE……..

Nimekubali mtoto atolowe damu kuangalia kiwango cha Vitamini D

SAHIHI…….. TAREHE…….

JINA LA MZAZI/MLEZI

…….

Hati ya Ruhusa

Ninathibitsha yakwamba nimetoa maelezo sahihi kwa mhusika kuhusu huu utafiti na yale yote yaliyomo kwa ustadi, naye mhusika ametoa uamuzi wa kushiriki bila ya kushurutishwa.

Jina ya mchinguzi…….

Sahihi ya mchunguzi……

Tarehe……

Appendix IV: **MINOR**

ASSENT DOCUMENT

/HATI NDOGO YA IDHINI

TITLE: **BONE MINERAL DENSITY AND VITAMIN D STATUS IN CHILDREN WITH MODERATE TO SEVERE CEREBRAL PALSY IN KENYATTA NATIONAL HOSPITAL AND ST THERESA MISSION HOSPITAL**

Investigator: **DR THITAI JULIET**

I am conducting a research study about the bone mineral density and vitamin D status in children with cerebral palsy in Kenya.

This research study is a way to understand more about our children. There will be about 50 children who will also participate in this research. If you decide to participate, you will be asked a few questions. You should know that this research will involve taking a blood sample and doing an Ultrasound on you. This will benefit you in getting free testing on the status of your bone health. Due to withdrawal of blood sample you will feel some mild discomfort and a small swelling might form after. Once the study is completed, a report will be written on what was learned. If any results are abnormal, treatment will be started.

The study will not include your name or details. You do not have to be in this study if you do not want. If you choose not to participate, it will not affect your treatment or access to care.

Your parents have also been informed on what the study is about.

If you decide to participate, kindly sign your name here

I,_____, want to participate in this research study.

Signature ……

Date……

HATI NDOGO YA IDHINI

SOMO: WIANI WA MADINI YA MFUPA NA VITAMINI D KATIKA WATOTO KENYA WALIIONA KUPOOZA KWA UBONGO (CEREBRAL PALSY) KATIKA HOSPITALI YA RUFAA YA JUU NCHINI KENYA NA ST THERESA MISSION HOSPITAL

MSHIRIKI MKUU: DR THITAI JULIET

Nina fanya utafiti kuhusu wiani wa madini ya mfupa na vitamin D katika watoto Kenya waliona kupooza kwa ubongo katika hospitali ya rufaa ya juu nchini kenya na st theresa mission kiirua. Unaweza uliza swali lolote kuhusu utafiti huu. Katikau huu utafiti tunasaka washiriki 50. Tutaoa damu kidogo kuangalia kiasi ya Vitamini D . Maambukizi ya mfupa madini wiani (BMD) tutatumia mzunguko ultrasound. Majina ako hyatawekwa kwa utafiti huu.

Iwapo hutaruhusu kuendelea na utafiti huu, utapewa matibabu zako zote bila kuonewa.

Wazazi wako wameshaelezwa kuhusu utafiti huu.

Ikiwa umekubali kuendele

SAHIHI…….. TAREHE……..

Appendix V: DATA COLLECTION SHEET

DEMOGRAPHIC DATA

DATE: _____ **STUDY ID:** _____

AGE: _____ **DOB:** _____

GENDER: **PLACE OF STAY** _____

WEIGHT: **HEIGHT**_____

GESTATIONAL AGE AT BIRTH _____

BIRTH WEIGHT _____

LOCATION **K.N.H** ☐ **STMHK** ☐

INSTITITIONALIZED ☐ **YES** ☐ **NO**

GMFCS LEVEL ☐ **III** ☐ **IV** ☐ **V**

PRIMARY CAREGIVER

- **Who is the primary caregiver of the child?**

☐ **FATHER** ☐ **MOTHER**

☐ **GRANADFATHER** ☐ **GRANDMOTHER**

☐ **EMPLOYEE**

OTHERS……..

- **What is the age of the primary caregiver? ……**

- **What is the main source of income of the primary caregiver?**

……

- **How many other children are in the household? .....**

- **Do any of the other children require special care and need? .....**

if yes :please specify……..

……

……

- **Which of the following was more commonly prepared for the child's meals in the last one month**

☐ **Animal products**

☐ **Vegetarian**

☐ **Both**

- **How is the food commonly prepared?**

Whole food **Y/N ……..**

Blended /pureed **Y/N ……**

- **How many times in a week is the child exposed to sunlight …….**

- **What hours of the day is the child exposed to sunlight?**

  …….

- **On an average how many hours per day is the child exposed to sunlight**

  …….

- **On average how much of the Childs body is exposed during sunbathing**

25% …….. 50%.....75%

…….. 100%.....

- **Is the child taking any vitamin D supplements?**

YES ☐ **NO** ☐

IF YES:

DRUG …….

DOSE: ……

DURATION ON MEDICATION……..

LAST INTAKE……

- **Has the child been tested for vitamin D levels…….**

If YES when was the last test……

- **Is the child on any antiepileptic medication?**

  …….

DRUG	CLASS	Y/N	DOSE	DURATION ON MEDICATION	LAST INTAKE
PHENOBARBITAL	Barbiturate				
CARBAMAZEPINE	Iminostillbene				
VALPROIC ACID	Aliphatic carboxylic acid				
PHENYTOIN	Hydantoin				
DIAZEPAM	Benzodiazepine				
PRIMIDONE	Deoxybarbiturate				

OTHERS:

…….

…….

……

AVERAGE NUMBER OF CONVULSIONS SEEN IN A MONTH? .....

- **HAS YOUR CHILD EVER HAD ANY LOW ENERGY FRACTURE……**

IF YES:

NUMBER ……

LOCATION(S)…….

VITAMIN D LEVEL …….

BMD LEVEL……
SOS…….

Appendix VI: GROSS MOTOR FUNCTION CLASSIFICATION SYSTEM – EXPANDED AND REVISED (GMFCS – E & R)

LEVEL I: Infants move in and out of sitting and floor sit with both hands free to manipulate objects. Infants crawl on hands and knees, pull to stand and take steps holding on to furniture. Infants walk between 18 months and 2 years of age without the need for any assistive mobility device.

LEVEL II: Infants maintain floor sitting but may need to use their hands for support to maintain balance. Infants creep on their stomach or crawl on hands and knees. Infants may pull to stand and take steps holding on to furniture.

LEVEL III: Infants maintain floor sitting when the low back is supported. Infants roll and creep forward on their stomachs.

LEVEL IV: Infants have head control but trunk support is required for floor sitting. Infants can roll to supine and may roll to prone.

LEVEL V: Physical impairments limit voluntary control of movement. Infants are unable to maintain antigravity head and trunk postures in prone and sitting. Infants require adult assistance to roll.

CHILDREN

LEVEL I: Children floor sit with both hands free to manipulate objects. Movements in and out of floor sitting and standing are performed without adult assistance. Children walk as the preferred method of mobility without the need for any assistive mobility device.

LEVEL II: Children floor sit but may have difficulty with balance when both hands are free to manipulate objects. Movements in and out of sitting are performed without adult assistance. Children pull to stand on a stable surface. Children crawl on hands and knees with a reciprocal pattern, cruise holding onto furniture and walk using an assistive mobility device as preferred methods of mobility.

LEVEL III: Children maintain floor sitting often by "W-sitting" (sitting between flexed and internally rotated hips and knees) and may require adult assistance to assume sitting. Children creep on their stomach or crawl on hands and knees (often without reciprocal leg movements) as their primary methods of self-mobility. Children may pull to stand on a stable surface and cruise short distances. Children may walk short distances indoors using a hand-held mobility device (walker) and adult assistance for steering and turning.

LEVEL IV: Children floor sit when placed, but are unable to maintain alignment and balance without use of their hands for support. Children frequently require adaptive equipment for sitting and standing. Self-mobility for short distances (within a room) is achieved through rolling, creeping on stomach, or crawling on hands and knees without reciprocal leg movement.

LEVEL V: Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent movement and are transported.

Some children achieve self-mobility using a powered wheelchair with extensive adaptations. **LEVEL I:** Children get into and out of, and sit in, a chair without the need for hand support. Children move from the floor and from chair sitting to standing without the need for objects for support. Children walk indoors and outdoors, and climb stairs. Emerging ability to run and jump.

LEVEL II: Children sit in a chair with both hands free to manipulate objects. Children move from the floor to standing and from chair sitting to standing but often require a stable surface to push or pull up on with their arms. Children walk without the need for a handheld mobility device indoors and for short distances on level surfaces outdoors. Children climb stairs holding onto a railing but are unable to run or jump.

LEVEL III: Children sit on a regular chair but may require pelvic or trunk support to maximize hand function. Children move in and out of chair sitting using a stable surface to push on or pull up with their arms. Children walk with a hand-held mobility device on level surfaces and climb stairs with assistance from an adult. Children frequently are transported when traveling for long distances or outdoors on uneven terrain.

LEVEL IV: Children sit on a chair but need adaptive seating for trunk control and to maximize hand function. Children move in and out of chair sitting with assistance from an adult or a stable surface to push or pull up on with their arms. Children may at best walk short distances with a walker and adult supervision but have difficulty turning and maintaining balance on uneven surfaces. Children are transported in the community. Children may achieve self-mobility using a powered wheelchair.

LEVEL V: Physical impairments restrict voluntary control of movement and the ability to maintain antigravity head and trunk postures. All areas of motor function are limited. Functional limitations in sitting and standing are not fully compensated for through the use of adaptive equipment and assistive technology. At Level V, children have no means of independent movement and are transported. Some children achieve self-mobility using a powered wheelchair with extensive adaptations.

BETWEEN 2ND AND 4TH BIRTHDAY BETWEEN 4TH AND 6TH BIRTHDAY BEFORE 2ND BIRTHDAY

Level I: Children walk at home, school, outdoors, and in the community. Children are able to walk up and down curbs without physical assistance and stairs without the use of a railing. Children perform gross motor skills such as running and jumping but speed, balance, and coordination are limited. Children may participate in physical activities and sports depending on personal choices and environmental factors.

Level II: Children walk in most settings. Children may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas, confined spaces or when carrying objects. Children walk up and down stairs holding onto a railing or with physical assistance if there is no railing. Outdoors and in the community, children may walk with physical assistance, a hand-held mobility device, or use wheeled mobility when traveling long distances. Children have at best only minimal ability to perform gross motor skills such as running and jumping. Limitations in performance of gross motor skills may necessitate adaptations to enable participation in physical activities and sports.

Level III: Children walk using a hand-held mobility device in most indoor settings. When seated, children may require a seat belt for pelvic alignment and balance. Sit-to-stand and floor-to-stand transfers require physical assistance of a person or support surface. When traveling long distances, children use some form of wheeled mobility. Children may walk up

and down stairs holding onto a railing with supervision or physical assistance. Limitations in walking may necessitate adaptations to enable participation in physical activities and sports including self-propelling a manual wheelchair or powered mobility.

Level IV: Children use methods of mobility that require physical assistance or powered mobility in most settings. Children require adaptive seating for trunk and pelvic control and physical assistance for most transfers. At home, children use floor mobility (roll, creep, or crawl), walk short distances with physical assistance, or use powered mobility. When positioned, children may use a body support walker at home or school. At school, outdoors, and in the community, children are transported in a manual wheelchair or use powered mobility. Limitations in mobility necessitate adaptations to enable participation in physical activities and sports, including physical assistance and/or powered mobility.

Level V: Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control arm and leg movements. Assistive technology is used to improve head alignment, seating, standing, and and/or mobility but limitations are not fully compensated by equipment. Transfers require complete physical assistance of an adult. At home, children may move short distances on the floor or may be carried by an adult.

YOUTH

Level I: Youth walk at home, school, outdoors, and in the community. Youth are able to walk up and down curbs without physical assistance and stairs without the use of a railing. Youth perform gross motor skills such as running and jumping but speed, balance, and coordination are limited. Youth may participate in physical activities and sports depending on personal choices and environmental factors.

Level II: Youth walk in most settings. Environmental factors (such as uneven terrain, inclines, long distances, time demands, weather, and peer acceptability) and personal preference influence mobility choices. At school or work, youth may walk using a handheld mobility device for safety. Outdoors and in the community, youth may use wheeled mobility when traveling long distances. Youth walk up and down stairs holding a railing or with physical assistance if there is no railing. Limitations in performance of gross motor skills may necessitate adaptations to enable participation in physical activities and sports.

Level III: Youth are capable of walking using a hand-held mobility device. Compared to individuals in other levels, youth in Level III demonstrate more variability in methods of mobility depending on physical ability and environmental and personal factors. When seated, youth may require a seat belt for pelvic alignment and balance. Sit-to-stand and floor-to-stand transfers require physical assistance from a person or support surface. At school, youth may self-propel a manual wheelchair or use powered mobility. Outdoors and in the community, youth are transported in a wheelchair or use powered mobility. Youth may walk up and down stairs holding onto a railing with supervision or physical assistance. Limitations in walking may necessitate adaptations to enable participation in physical activities and sports including self-propelling a manual wheelchair or powered mobility.

Level IV: Youth use wheeled mobility in most settings. Youth require adaptive seating for pelvic and trunk control. Physical assistance from 1 or 2 persons is required for transfers. Youth may support weight with their legs to assist with standing transfers. Indoors, youth may walk short distances with physical assistance, use wheeled mobility, or, when positioned, use a body support walker. Youth are physically capable of operating a powered wheelchair. When a powered wheelchair is not feasible or available, youth are transported in a manual wheelchair. Limitations in mobility necessitate adaptations to enable participation in physical activities and sports, including physical assistance and/or powered mobility.

Level V: Youth are transported in a manual wheelchair in all settings. Youth are limited in their ability to maintain antigravity head and trunk postures and control arm and leg movements. Assistive technology is used to improve head alignment, seating, standing, and mobility but limitations are not fully compensated by equipment. Physical assistance from 1 or 2 persons or a mechanical lift is required for transfers. Youth may achieve self-mobility using powered mobility with extensive adaptations for seating and control access. Limitations in mobility necessitate adaptations to enable participation in physical activities and sports including physical assistance and using powered mobility

Appendix VII

Roche e411 Chemistry Analyzer Highlights

Feature	cobas e 411 analyzer
System	Fully automated, immunoassay analyzer for random access processing of ECL-based immunoassays (**cobas e** system format)
Types of modules	1. **cobas e** 411 disk analyzer 2. **cobas e** 411 rack analyzer 3. Optional System Table (cabinet); Optional System Table Extension (for printer)
System components	Self contained bench top analyzer comprising an analytical unit and a customized user interface
System interfaces	RS232 serial interface, bidirectional
Through put	Up to 86 tests/hour
Number of reagent	18 channels (reagent slots) for maximum of 18 tests channels
Programmable test parameters	N/A, programming-by-loading (PBT) concept, application data are transferred without operator intervention from the 2D barcode of the reagent pack (RP) into the instrument database
Sample material	Serum/plasma, urine, others
Sample input/output	1. Disk Model: 30 positions for samples, calibrators and controls 2. Rack Model: 15 racks with 5 samples each (= 75 samples in/out) 3. STAT port: STAT samples are processed with priority
Sample volume	10 – 50 µl
Sample clot detection	Standard (pressure sensor)

Sample barcode types	Code 128; Codabar (NW 7); Interleaved 2 of 5; Code 39
Control unit	Microsoft® Windows® XP-based panel PC
Calibrator/QC input	**cobas e** system-specific barcoded CalSet vials on disk or racks
Calibration methods	Lot calibration (L-cal); Reagent Pack (RP) calibration (R-Cal)
QC methods	1. Individual QC and cumulative QC 2. Up to 100 controls pre-programmable 3. Preventive QC after calibration of the stand-by **cobas e** packs
Data storage capacity	1. The memory contains data files necessary for the analyzer and software to work together: • - Reagent Data File: Up to 300 reagent packs • - Sample Data File: Up to 2000 test records (for samples and controls) • - Calibration Data File: Up to 160 calibrators • - QC Data File: Capacity up to 100 controls • - Operating Parameter Data File: Up to 305 reagent applications • - Up to 20 operator IDs
Electrical requirements	1. 230/110 Volts AC; 1,000 kVA (disk), 1,250 kVA (rack) 2. Frequency: 50 Hz or 60 Hz +/- 0.5%
Water/Waste requirements	1. Water: Bacteria free, de-ionized water supply, resistance of < 10 µS/cm 2. Liquid waste: Onboard waste container (4 liter), direct drain optional
Operating conditions	1. Ambient temperature: 18 to 32°C 2. Ambient humidity: 20 to 80% RH (without condensation) 3. Heat Output: 2,879 kJ/hr (analyzer unit) 4. Noise Output: 60 dBA (stand-by), 63 dBA (operation avg.)
Physical dimensions	1. Width (disk/rack): 120 cm / 170 cm 47.2 in / 67 in 2. Depth (disk/rack): 73 cm / 95 cm 28.7 in / 37.4 in

	3. Height: 80 cm / 31.4 in (closed top cover) 109 cm / 43 in (opened top cover)
Weight	1. Disk: 180 kg / 397 lbs 2. Rack: 250 kg / 551 lbs

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19th March 2021

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KENYATTA NATIONAL HOSPITAL
APPROVED
19 MAR 2021
KNH/UoN-ERC
P. O. BOX 20723 - 00202 NAIROBI

Dear Dr. Thitai

RESEARCH PROPOSAL – THE BONE MINERAL DENSITY AND VITAMIN D STATUS IN CHILDREN WITH MODERATE TO SEVERE CEREBRAL PALSY IN KENYATTA NATIONAL HOSPITAL AND ST. THERESA MISSION HOSPITAL (P689/12/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 19th March 2021 – 18th March 2022.

This approval is subject to compliance with the following requirements:

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

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

Yours sincerely,

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

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Orthopaedic Surgery, UoN
Supervisors: Dr. George Museve, Dept.of Orthopaedic Surgery, UoN
Dr.Edward Gakuya, Dept.of Orthopaedic Surgery, UoN

11% Confirmed

The Bone Mineral Density And Vitamin D Status In Children With Moderate To Severe Cerebral Palsy In Kenya

ORIGINALITY REPORT

11%	8%	9%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	1%
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3	"Cerebral Palsy", Springer Science and Business Media LLC, 2020 Publication	1%
4	L. K. Bachrach, C. M. Gordon. "Bone Densitometry in Children and Adolescents", PEDIATRICS, 2016 Publication	1%
5	Submitted to Mississippi State Board for Community & Junior Colleges Student Paper	<1%
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7	A. Tatay Díaz, D.M. Farrington, F.J. Downey Carmona, M.E. Macías Moreno, J.J. Quintana	<1%

10/09/2021 Dr V.M. MUSTICO

NIDA Clinical Trials Network

Certificate of Completion

is hereby granted to

JULIET THITAI

to certify your completion of the six-hour required course on:

GOOD CLINICAL PRACTICE

MODULE:	STATUS:
Introduction	N/A
Institutional Review Boards	Passed
Informed Consent	Passed
Confidentiality & Privacy	Passed
Participant Safety & Adverse Events	Passed
Quality Assurance	Passed
The Research Protocol	Passed
Documentation & Record-Keeping	Passed
Research Misconduct	Passed
Roles & Responsibilities	Passed
Recruitment & Retention	Passed
Investigational New Drugs	Passed

Course Completion Date: 7 December 2020

CTN Expiration Date: 7 December 2023

Tracee Williams, Training Coordinator
NIDA Clinical Coordinating Center

Good Clinical Practice, Version 5, effective 03-Mar-2017

This training has been funded in whole or in part with Federal funds from the National Institute on Drug Abuse, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272012010000024C.

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Study Registration Certificate

1. **Name of the Principal Investigator/Researcher**
   DR THITAI JULIET WANJIKU
2. **Email address:** drthitaijuliet@gmail.com **Tel No.** 0710425735
3. **Contact person (if different from PI)** N/A
4. **Email address:** N/A **Tel No.** N/A
5. **Study Title**
   THE BONE MINERAL DENSITY AND VITAMIN D STATUS IN CHILDREN WITH MODERATE TO SEVERE CEREBRAL PALSY IN KENYATTA NATIONAL HOSPITAL AND ST THERESA MISSION HOSPITAL
6. **Department where the study will be conducted** OCCUPATIONAL THERAPY
   (Please attach copy of Abstract)
7. **Endorsed by KNH Head of Department where study will be conducted.**
   Name: WAKVILWA SILAS **Signature** ..... **Date** 29/3/2021
8. **KNH UoN Ethics Research Committee approved study number** P 68/9/121/2020
   (Please attach copy of ERC approval)
9. I DR THITAI JULIET commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.
   Signature ..... **Date** 29/03/2021
10. **Study Registration number (Dept/Number/Year)** 01 e Physiotherapy /12/2021
    (To be completed by Medical Research Department)
    29 MAR 2021
11. **Research and Program Stamp**

All studies conducted at Kenyatta National Hospital must be registered with the Department of Medical Research and investigators must commit to share results with the hospital.