PATTERNS AND PREVALENCE OF HYPERPARATHYROIDISM AND MINERAL BONE DISEASE IN PATIENTS WITH CHRONIC KIDNEY DISEASE AT THE KENYATTA NATIONAL HOSPITAL

THIS DISSERTATION HAS BEEN WRITTEN IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN INTERNAL MEDICINE, UNIVERSITY OF NAIROBI

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DECLARATION

I Dr Anne Mugera hereby certify that this is my original work and that it has not been submitted to any other university.

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Dr Anne N. N. Mugera

Dedication

I dedicate this thesis to my parents late Prof G. Mugera and Mrs Catherine Mugera for giving me the best inheritance in form of a good education.

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I give thanks to God the almighty for giving me life, good health peace of heart and sound mind.

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ABSTRACT

Background

Disorders of mineral metabolism, secondary hyperparathyroidism (SHPT), hyperphosphatemia, hypercalcemia, and deficiencies of vitamin D are common complications of chronic kidney disease (CKD). While their contributions to the development of renal osteodystrophy are well known, recent evidence has linked these factors to cardiovascular disease, including non-atherosclerotic vascular calcification, excessive activation of the renin-angiotensin system, hypertension, left ventricular hypertrophy, and death.

The obvious task ahead for health authorities in the developing world is to identify patients at risk and evaluate for SHPT because early intervention may slow or arrest the progression of both bone and cardiovascular disease.

Objective of the study

To determine and describe the patterns, prevalence of hyperparathyroidism and biochemical evidence of mineral bone disease in pre-dialysis patients with chronic kidney disease at the Kenyatta National Hospital.

Methodology

A cross-sectional survery was carried out in 214 patients with chronic kidney disease (CKD) consecutively recruited from the renal (nephrology) clinic, at the Kenyatta National Hospital, over a period of 3 months. Patients with CKD had their demographics, socio-economic and clinical history documented using an administered-interviewer questionnaire . Patients had their glomerular filtration rate (eGFR) estimated using Cockroft and Gault equation and staged as per the kidney disease outcome quality initiative (K/DOQI) criteria. CKD patients in stages 1 to 5, upon recruitment, had a study questionnaire administered to

determine the possible aetiology of kidney disease, presence or absence of diabetes mellitus (DM), method of management of chronic kidney disease and any clinical characteristics of bone disease. A structured physical examination was then carried out.

At enrollment 6ml of blood was drawn and the measurements of serum, blood nitrogen urea, creatinine, albumin, calcium, potassium, phosphorus, alkaline phosphatase, levels were determined using automated clinical chemistry analyzer. Serum intact parathyroid hormone (iPTH) assays were performed using electro-chemiluminescence immunoassay (ECLIA) on the fully automated immunoanalyzer Cobas Integra 400 Plus(Roche)Elecys.

Outcome Measures

Outcome measures were serum intact PTH levels, the KDOQI stages of CKD and biochemical features of bone turn-over.

Data management and Analysis.

All data was collected on a study proforma , and was entered into a computer data base using Microsoft Access computer software and statistical analysis was done using statistical package for social scientists (SPSS) version 15 after cleaning and verification.

Values were expressed as means, medians and standard deviations (SD).

Point prevalence of hyperparathyroidism was determined as a percentage of the number of patients with serum iPTH above the upper limit of normal, attending the renal clinic in CKD stages 1 and 5, to the total study population. Associations between the patients' socio-demographic data, presence of Diabetes Mellitus(DM), stage of chronic kidney disease and serum iPTH level were examined using chi-square test.

Differences in mean values in patients with or without DM were analyzed by Student's t-test, if normally distributed, or Mann -Whitney U test for skewed data, to determine statistical significance. Associations were considered significant only when p value was equal or less than 0.05.

Analysed data was presented in the form of tables, pie-charts and graphs

Results

A total of 214 patients with chronic kidney disease, who were not yet on dialysis, attending the renal clinic at the Kenyatta National Hospital over a period of 3 months were studied.

The study population was categorized into 5 groups as per K/DOQI staging of chronic kidney disease. CKD stage 1 had 7 participants, stages 2, 3,4 and 5 had 21, 70, 42 and 74 participants respectively.

The mean eGFR was 31.342 ±24.66 ml/min/1.73m^2. This prevalence, of hyperparathyroidism, was seen to increase as renal function, eGFR, declined.

The mean PTH level was 52.02 ±99.02 pg/ ml. There was significantly more low turn-over mineral bone disease observed in 78.4% (n= 109 out of 139) compared to high turn-over mineral bone disease observed in only 21.6%(n=30 out of 139) patients. Women were observed to have higher iPTH levels and more high turn-over bone disease was observed.

This study, did not observe a significant correlation between the presence of, diabetes mellitus, frequency of complaints of bone pain, or muscle weakness with hyperparathyroidism.

There was a significant positive association between phosphorus and higher levels of serum iPTH but no significant association was found between calcium and alkaline phosphotase.

Conclusion

This study demonstrated that hyperparathyroidism develops and progressively worsens as glomerular function declines.

However, the overall prevalence of hyperparathyroidism in CKD patients attending renal clinic at the Kenyatta National hospital was observed to be lower than it is worldwide.

This study showed a trend towards more women registering higher iPTH levels than the males. Biochemical high turn-over mineral bone disease was observed more in women, with CKD, than the men.

In comparison to statistics from western countries, there seems to be more biochemical low turn-over mineral bone disease in our patients as opposed to more high turn-over mineral bone disease in the western populations.

LIST OF ABBREVIATIONS

1.ABD	Adynamic Bone Disease
2.AED	Antiepileptic Drugs
3.ALP	Alkaline Phosphatase
4.ArMORR	Accelerated Mortality and Renal Replacement
5.bAP	bone specific alkaline phosphotase
6.BMD	Bone Mineral Density
7.CaR	Calcium-Sensing Receptor
8.CaxP	Calcium Phosphate product
9.CKD	Chronic kidney disease
10. CKD-MBD	Chronic Kidney Disease- Mineral Bone Disease
11. DEXA	Dual Energy X-ray Absorbptiometry
12. eGFR	Estimated Glomerular Filtration Rate
13. ESRD	End Stage Renal Disease
14. FGF-23	Fibroblast Growth Factor-23
15. GFR	Glomerular Filtration Rate
16. HD	Haemodialyis
17. HPT	Hyperparathyroidism
18. HTO	High turn-over bone disease
19. ICTP	serum carboxyterminal telopeptide of type I collagen
20. iPTH	intact Parathyroid Hormone
21. K/DIGO	Kidney Disease Improving Global Outcome
22. K/DOQI	Kidney Disease Quality Outcome Initiative
23. KNH	Kenyatta National Hospital
24. LTO	Low turn-over bone disease

25. MUO	Mixed uremic osteodystrophy
26. NKF	National Kidney Foundation
27. PICP	serum procollagen type I carboxyterminal propeptide
28. PTH	Parathyroid Hormone
29. RF	Renal Failure
30. ROC	Reciever Operating Curves
31. ROD	Renal Osteodystrohy
32. RRT	Renal Replacement Therapy
33. SEEK	Study to Evaluate Early Kidney Disease
34. SHPT	Secondary hyperparathyroidism
35. VALIANT	Valasartan in Acute Myocardial Infarcation Trial
36. VC	Vascular Calcification
37. Vit D	Vitamin D

1. LITERATURE REVIEW

1.1 Introduction

Chronic Kidney Disease (CKD) is a highly prevalent condition with increasing incidence in recent years. Currently ESRD is higher than 2000 per million population in Japan, about 1500 per million population in the US and about 800 per million population in the European Union [1-2].

It is now accepted that the presence of chronic kidney disease (CKD) is associated with poor outcomes. In particular, cardiovascular events and mortality increases as the estimated glomerular filtration rate (eGFR) declines below 60 ml/min [3].

However, other investigations have also shown that most of the CKD patients will be affected by this morbidity and mortality excess before they reach end-stage renal failure and start on a chronic kidney replacement therapy programme [4-7].

Disordered mineral metabolism, secondary hyperparathyroidism (SHPT), and deficiencies of vitamin D are common complications of CKD. While their contributions to the development of renal osteodystrophy are well known, recent evidence has linked these factors to cardiovascular disease, including non-atherosclerotic vascular calcification, excessive activation of the renin-angiotensin system, hypertension, left ventricular hypertrophy, and death [8].

Patients with earlier stages of CKD by far outnumber those undergoing maintenance dialysis treatment, but the impact on mortality associated with SHPT in this group is unknown [9].

Large observational studies suggest that abnormalities of parathyroid hormone (PTH), calcium, phosphorus, 25-hydroxyvitamin D (25D), and 1, 25-dihydroxyvitamin D (1,25D) are associated with mortality on dialysis, and that management strategies to treat these disorders may improve survival. On the basis of these encouraging results, renewed emphasis has shifted to the screening and treatment of these abnormalities early in the course of CKD when they first develop and may be most amenable to therapy [3-9].

SHPT is an insidious disease that develops early in the course of CKD and increases in severity as the glomerular filtration rate deteriorates.

SHPT develops in the course of progressive renal insufficiency as an adaptive mechanism to maintain calcium and possibly phosphorus homeostasis. Biochemical evidence of abnormal parathyroid gland function is present in some patients with stage 2, in many patients with stage 3, and in most patients with stages 4 and 5 CKD, as judged by elevations in plasma PTH levels[10] . SHPT generally worsens as a function, over the number of years of treatment with dialysis. It may progress ultimately to an advanced stage that is refractory to medical treatment requiring surgical management by parathyroidectomy. [10–14].

Block et al in 1998 demonstrated that the severity of secondary HPT correlates directly with increased morbidity and mortality in the dialysis population [5, 14]. The most commonly cited morbidity associated with secondary HPT is renal osteodystrophy, which leads to characteristic skeletal complications. However, the alterations in mineral metabolism reach far beyond these commonly recognized complications and can cause significant effects including soft tissue calcification, alterations in lipid metabolism and glucose utilization, anemia, and an increased risk of cardiac-related death.

Due to the clinical significance of these complications, optimal control of the factors that contribute to secondary HPT should become a primary quality-of-care goal for nephrology clinicians.

The obvious task ahead for health authorities in the developing world is detect and treat kidney disease at the earliest possible stage

1.2 Epidemiology

Worldwide Statistics

Worldwide, it is estimated that over 1.1 million patients with end-stage renal disease (ESRD) currently require maintenance dialysis, and this number is increasing at a rate of 7% per year. If the trend continues, the number will exceed 2 million by 2010 [14].

This figure excludes developing countries, where there is less availability of and access to dialysis services, and is therefore an underestimate of the true demand.

North America - In the US, there is a rising incidence and prevalence of kidney failure. The number of patients enrolled in the end-stage renal disease (ESRD) Medicare-funded program has increased from approximately 10,000 beneficiaries in 1973 to 86,354 in 1983 and to 452,957 as of December 31, 2003. Several studies have demonstrated a high incidence of CKD among black Americans [16-18].

Hemodialysis (HD) patients are profoundly vitamin D deficient, yet ~60% of incident hemodialysis patients in the US are not treated with active vitamin D.

The SEEK (Study to Evaluate Early Kidney Disease) study, which involed One hundred fifty-three (153), US-based centers demonstrated SHPT was present in approximately 12% of those with eGFR values >80 ml/min/1.73 m^2, 17% of those with an eGFR of 70–79 ml/min/1.73 m^2, 21% of those with an eGFR

between 60 and 69 ml/min/1.73 m^2, and 56% of those with an eGFR <60 ml/min/1.73 m^2 [19].

Canadian Multicenter Cohort study demonstrated that PTH also rises relatively early at a GFR of 60, the PTH was actually already 2 times the upper limit of normal. Interestingly, when Valazquez and colleagues looked at over 14,000 people in the Valsartan in Acute Myocardial Infarction Trial (VALIANT), the deflection point was a GFR of 60; that is when the increase in cardiovascular risk really escalates, however, the VALIANT study did not study calcium(Ca), phosphorus(PO4), parathyroid hormone(PTH)[20].

From the ArMORR (Accelerated Mortality on Renal Replacement) study, approximately 40% of patients with stage 3 and 70% of patients with stage 4 CKD will have elevated PTH levels[21].

Europe-A multicentre study that evaluated the proportion of patients who met National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines for mineral status, and assessed the cost of therapy for mineral management of patients under haemodialysis treatment in Spain (1312 patients), found that the prevalence of patients outside K/DOQI targets was: calcium 50%, phosphorus 46%; calcium –phosphate product(CaxP) 33%; iPTH 77%. Poorly controlled serum phosphorus, CaxP and iPTH were associated with more expensive therapy for mineral management [22].

Africa- It is estimated that 2 to 3% of medical admissions in African countries are due to renal related complaints, the majority being glomerulonephritides, which in East and Central Africa are characterized by poor response to treatment and rapid progression to renal failure [23].

Incidence of CKD among indigenous Africans is unknown as there are no reliable statistics in all African countries. However, there is a general impression that CKD is at least three to four times more frequent, amongst

indigenous Africans, than in more developed countries, this is substantiated by analysis of the causes of death, reporting that uremia accounts for 1 to 1.5% of the total number of annual deaths among Egyptians both in predialysis era and for two decades thereafter [23].

In Egypt a cross-sectional study to determine prevalence of hyerpphosphotemia was conducted on 1005 chronic kidney disease stage 5 patients (CKD-stage 5) on HD for a period of more than 1 year in 38 dialysis centers. Hyperphosphatemia was found to be present in 69.1% of cases and a high calcium–phosphorus product was present in 30.2%. A higher calcium–phosphorus product was found among males [24].

Given the above data, disorders of mineral metabolism pose as a major problem in dialysis population in Egypt, (as an example of an African population). Data however in predialyis population is unkown. One may possibly extrapolate that that these disorders may be higher in the predialyis population.

Prevalence studies in adult black population of Natal showed that hypertension was present in 25% of urban Zulus, 17.2% of whites and 14% of Indians. In a ten-year study of 368 patients, chronic renal failure accounted for 10% of all medical admissions in one centre in Nigeria, the etiology was undetermined in 62%, of the remaining patients hypertension accounted for 61%, diabetes mellitus for 11% and chronic glomerulonephritis for 5.9%.

In Eastern Africa, chronic glomerulonephritis and hypertension are principal causes of chronic renal failure together with diabetes mellitus and obstructive uropathy [23,24].

Kenya

Swao made a contribution towards the magnitude of disorders of mineral metabolism in chronic kidney disease and renal osteodystrophy in 1980s and

found 67% clinical and 51.8 % biochemical evidence of renal osteodystrophy, based on elevated inorganic phosphate levels. Many of these patients did not live to show radiological signs of renal osteodystrophy [25].

Later Patel found 60% biochemical evidence of renal osteodystrophy using radioimmunoassay technique to determine hPTH, a 7.5% of renal osteodystrophy was obsereved by radiological evidence [26].

1.3 Pathophysiology of Secondary HPT

Normal bone and mineral metabolism:

In the absence of CKD, bone and mineral metabolism are influenced by the interaction of four primary factors: parathyroid hormone (PTH), calcium, vitamin D, phosphorus.

The primary role of PTH is to maintain the extra cellular concentration of calcium within a narrow physiologic range. PTH acts directly on the bone to increase bone resorption, resulting in the release of calcium and phosphorus into the blood.

PTH also acts indirectly by stimulating an increase in active vitamin D, which in turn increases intestinal absorption of both calcium and phosphorus.

In addition, PTH acts directly on the kidney to increase both phosphorus excretion and calcium reabsorption (thereby helping to maintain normal serum calcium levels)

The second major factor that affects bone and mineral metabolism is the interrelationship between calcium and the calcium-sensing receptors (CaR). Secretion of PTH is controlled by the CaRs located on the surface of chief cells within the parathyroid glands.

These receptors are extremely sensitive to changes in extracellular calcium, resulting in the secretion of PTH secretion within seconds or minutes. As the

calcium concentrations increase, the CaRs are activated, thereby inhibiting the secretion of PTH from the parathyroid glands. Conversely, when serum calcium levels are low, the CaRs are inactivated, thereby increasing secretion of PTH from the parathyroid glands to maintain normal calcium homeostasis.

The third major factor, vitamin D, fulfills an essential role in maintaining skeletal integrity. Vitamin D helps maintain calcium and phosphorus homeostasis by modulating dietary absorption of calcium and phosphorus throughout the small intestine [27-30].

In the presence of low levels of calcium, vitamin D levels increase, thereby increasing calcium and phosphorus absorption in the small intestine. Vitamin D also induces bone resorbption and the release of calcium and phosphorus and decreases the excretion of these substances in the urine. In the parathyroid glands, vitamin D controls the synthesis of PTH.

Under normal physiologic conditions, 1, 25-dihydroxy vitamin D (calcitriol) is synthesized via a series of orchestrated steps. First, ultraviolet light converts 7-dehydrocholesterol to previtamin D2, which is then converted to vitamin D3 (cholecalciferol) [28-30].

Relatively minimal sun exposure is needed to synthesize cholecalciferol in the skin; 10-15 minutes of exposure provides more vitamin D3 than any known dietary source[31].However, in the absence of sun exposure, cholecalciferol can also be obtained naturally from the diet (though few foods other than fatty fish provide significant amounts of vitamin D), from foods that are fortified with vitamin D, or from vitamin D supplements [32-34].

Vitamin D2 (ergocalciferol) is an alternative vitamin D supplement derived from plants that is less biologically potent than vitamin D3 [32,35].

Vitamin D binding protein carries vitamin D2 and D3 to the liver, which converts them to 25-hydroxy vitamin D (calcidiol), the major circulating form of vitamin D that is measured by routine laboratory testing [36-38].

The enzyme 1-alpha hydroxylase, which is expressed primarily in the proximal tubule of the kidney, then converts 25-hydroxy vitamin D to 1,25-dihydroxy vitamin D, the biologically active form of the molecule [39-41].

This final 1-hydroxylation step is rate limiting, evidenced by circulating calcitriol levels that are 1000-fold lower than calcidiol levels, and is tightly regulated. Parathyroid hormone (PTH) stimulates 1-alpha hydroxylase activity, whereas phosphate and fibroblast growth factor 23 (FGF-23) inhibit activity [42-45].

Phosphorus, the central component of bone, is another factor that contributes to control of bone and mineral metabolism. Approximately 85% of phosphorus in a normal adult is located in the skeleton [46].

The interrelationship between phosphorus and vitamin D is well recognized. Studies have shown that vitamin D levels increase dramatically when serum phosphorus levels are low, thereby promoting increased intestinal absorption. Conversely, in the presence of hyperphosphatemia, the parathyroid glands may be resistant to the action of vitamin D. The normal route of excretion for phosphorus is primarily through the kidneys. When serum phosphorus levels are elevated, PTH acts directly on the kidneys to increase phosphorus excretion and normalize serum phosphorus levels [47-50].

Bone and mineral metabolism disruptions in Chronic Kidney Disease:

A loss of kidney function leads to a decline in circulating calcitriol concentrations [49, 50]. The reduction in calcitriol occurs despite a progressive rise in serum PTH concentrations, which stimulate 1-alpha hydroxylase activity. Reduced functional renal mass, phosphate retention, and other metabolites that accumulate in kidney failure contribute, in part, to 1-alpha hydroxylase inhibition and lower circulating calcitriol concentrations in CKD [51, 52].

Recently, a novel hormone, FGF-23, has been shown to be a central factor contributing to calcitriol deficiency in CKD. FGF-23 levels rise dramatically in moderate CKD and potently suppress 1-alpha hydroxylase gene expression.[53] Biologic motivation for minimizing vitamin D activity in CKD is not entirely clear but may serve to prevent further phosphate and calcium loading, which provoke vascular and soft tissue calcification in the setting of renal failure [54,55].

Insufficiently low concentrations of vitamin D substrate are also common in CKD patients. In a recent multisite study of 1814 CKD patients in the United States, the prevalence of overt vitamin D deficiency (25-hydroxy vitamin D levels < 15 ng/mL) exceeded 20% for patients with an estimated glomerular filtration rate < 30 mL/minute [49]. Lower 25-hydroxy vitamin D levels in CKD patients most likely reflect co-morbid illnesses and the associated lack of adequate sunlight exposure rather than a kidney-specific metabolic abnormality.

Bone resorption is a one-stage process, with osteoclasts resorbing mineral and osteoid together. In contrast, bone formation occurs in two stages: osteoblasts lay down osteoid, which subsequently becomes mineralized. The mineralization of bone matrix depends on the presence of adequate supplies of not only

vitamin D, in the form of its active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$ VitD], but also calcium, phosphorus, and alkaline phosphatase, and on a normal pH prevailing in the body environment. If there is a deficiency of the substances for any reason, or if there is severe systemic acidosis, then mineralization of bone will be defective [56, 57].

PTH, calcium, vitamin D, and phosphorus normally act in concert to maintain optimal levels of phosphorus and calcium and ensure bone integrity. In patients with CKD, the mechanisms that maintain homeostasis are disrupted. As the number of functioning nephrons decrease, the failing kidneys are unable to excrete phosphorus and a progressive increase in serum phosphorus levels and a consequential suppression of vitamin D activation ensues. In combination, these effects lead to a deficiency in biologically active vitamin D that, in turn, results in reduced absorption of calcium from the gastrointestinal tract, ultimately causing hypocalcaemia.

Because the CaRs are the major regulator of PTH, the series of events leading to hypocalcaemia is crucial to the development of secondary HPT. Hypocalcaemia causes inactivation of the CaRs on the parathyroid glands and results in an increase in PTH secretion. PTH, in turn, stimulates the release of calcium and phosphorus from the bone and increased activation of vitamin D, resulting in increased intestinal absorption of calcium as the body attempts to maintain normal calcium homeostasis. The ongoing inability to excrete phosphorus leads to continual over-stimulation of the parathyroid glands, tissue hyperplasia, and over secretion of PTH [58-60].This series of events leads to secondary HPT.

1.4 Clinical Consequences of Secondary HPT

The consequences of uncontrolled SHPT are manifest in multiple systems, with potentially devastating consequences on patient outcomes. Common clinical problems associated with secondary HPT include renal osteodystrophy, cardiovascular calcification, extraskeletal calcification, endocrine disturbances including, altered erythropoiesis and vitamin D synthesis as well as activation of the Renin-angiotensin system [26,31,61].

Skeletal complications of secondary HPT

Bone is a dynamic tissue that is constantly being remodeled. The action of osteoclasts to remove "old" bone is tightly balanced with the functions of osteoblasts that deposit "new bone" at sites where old bone was removed.

PTH is the major stimulator of bone remodeling (both bone formation and bone resorbption). PTH interacts with receptor cells found on osteoblasts, leading to an increase in the number and activity of these bone-forming cells and the consequential formation of new bone tissue. One action of osteoblasts is the release of cytokines and growth factors that increase the number and activity of osteoclasts. Thus, PTH indirectly stimulates bone resorbption [31,61].

SHPT is characterized by osteitis fibrosa cystica with extensive bone marrow fibrosis and increased osteoclastic bone resorption [27,62].

Osteomalacia and rickets may develop reflecting aluminum intoxication, vitamin D deficiency, hypocalcaemia and acidosis.

As a result of increased plasma calcium-phosphate(CaxP) product due to phosphate retention deposition of different calcium-phosphate compounds within the soft tissues may develop (metastatic calcification).

Adynamic bone disease (ABD) is characterised by low bone formation rate without primary mineralization defect (in contrast to osteomalacia osteoid seam thickness is normal) and is related to iatrogenic over-suppression of parathyroid

hormone. High-turnover bone disease is the classic skeletal complication observed in patients with secondary HPT.[30]

As CKD progresses and PTH levels rise, the rates of bone resorption and formation increase, leading to the deposition of an immature, structurally inferior woven bone. As the severity of secondary HPT increases, fibrous tissue accumulates within the marrow space and adjacent bony trabeculae, leading to the characteristic pattern of bone marrow fibrosis that is often referred to as osteitis fibrosa cystica [63-65].

In recent years an increasing number of CKD patients are experiencing low-turnover bone disease, characterized by reductions in osteoclasts and osteoblasts and decreased bone remodeling. The most common type of low-turnover bone disease, adynamic bone disorder, is actually not a manifestation of secondary HPT, but is usually an unwanted side effect of the therapeutic interventions prescribed to treat it. Adynamic bone disorder is typically caused by the over suppression of PTH with vitamin D and/or the concurrent administration of calcium-based phosphate-binding agents that increases calcium levels and further inhibits PTH secretion. Since the bone is not actively being remodeled, patients with adynamic bone disorder often experience hypocalcaemia- the excess calcium is deposited in soft tissue and vasculature, thereby increasing the risk of calcification [31,63].

Regardless of the etiology of bone disease, skeletal changes that occur in patients with secondary HPT decrease the structural integrity of the bone, leading to a weakened bone matrix and increasing the risk of hypocalcaemia, vascular calcification, and calcific uremic arteriolopathy (characterized by calcification in medium-sized and small arteries) and of fracture.

The principal conclusion from the 2005 conference of KDIGO, was that the current descriptive nomenclature for this pathophysiologic process should be reconsidered. It is recommended that the term renal osteodystrophy be used exclusively to define the bone pathology associated with CKD. The many clinical, biochemical, and imaging abnormalities that have heretofore been identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome to be called chronic kidney disease-mineral and bone disorder (CKDMBD)[64].

CKD-MB is a systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following [64]:

- Abnormalities of calcium, phosphorus, PTH, or Vitamin D levels (Laboratory)
- Abnormalities of bone turnover, mineralization, volume, linear growth, or strength (Bone histology)
- Vascular or other soft tissue calcification(VC)

1.5 The radiological imaging techniques in the evaluation Renal Osteodystrophy

Hyperparathyroidism increases bone resorption, which may normalize serum calcium levels by releasing the osseous storage of calcium. The various sites of bone resorption include the subperiosteal region of the phalanges, the phalangeal tufts, proximal femur, proximal tibia, proximal humerus, distal clavicle, and calvarial trabeculae [64, 65].

Renal osteodystrophy may cause osteosclerosis, soft-tissue calcification, and bone resorption. The changes observed depend on the degree to which bone responds to parathyroid hormone. If the bone responds with an increased activity of osteoclasts and osteocytes, the result is bone resorption, which leads to release of calcium. Parathormone also inhibits net tubular phosphate reabsorption, leading to an increase in urinary phosphate that is limited by renal failure [66].

A rise in the calcium-phosphate ion product results in metastatic soft-tissue calcification. If parathyroid hormone levels are mildly elevated over a long period of time, its effect on bone tends to be anabolic. These effects include excessive maturation of osteoblasts leading to new bone formation and increased laying down of osteoid, which calcifies under the influence of secondarily elevated serum calcium levels [67].

Bone resorption typically is classified as subchondral, trabecular, endosteal, intracortical, subperiosteal, subligamentous, and subtendinous. Involvement of the hands and feet by subperiosteal resorption typically occurs along the radial aspect of the middle phalanges and the cortical bone of the tufts of the distal phalanges.

Subperiosteal resorption at the joint margins resembles marginal erosions of rheumatoid arthritis. Classically, the skull is affected by trabecular bone resorption, creating a salt-and-pepper appearance in the calvarium [65-67].

Sclerosis may appear patchy and nonspecific or it may show a characteristic pattern, such as predominant endplate involvement in the spine [65].

Soft-tissue calcifications may take the form of the large, cloudlike collections in a periarticular distribution known as tumoral calcinosis. These collections are composed mostly of calcium hydroxyapatite and may form a milky substance that may contain fluid levels. Tumoral calcinosis typically is periarticular and noted frequently around the hips and shoulders, although it also may be found around smaller joints [65-67].

The findings of renal osteodystrophy diagnosed with conventional radiography include osseous resorption, soft-tissue calcification, osteopenia, amyloid deposition, and fracture [68,69].

With introduction of more sophisticated diagnostic techniques and an earlier diagnosis as well as with improvement in management, radiological manifestations of chronic renal disease have changed. Typical radiological features of advanced(high turnover) bone disease {viz osteitis fibrosa/mixed uremic osteodystrophy}and of rickets/osteomalacia are now much less frequently revealed than previously [68].

Bone scans may reveal diffuse skeletal uptake of radiopharmaceutical with a "superscan" appearance that can be confused with metastatic disease. However, the extremities typically have a greater level of increased uptake with secondary hyperparathyroidism than is expected with metastatic disease. In addition, bone scans may reveal pseudofractures or sites of extraskeletal calcification, which also may be distinctive for secondary hyperparathyroidism. Bone scan findings

usually are supportive of, but are of limited primary diagnostic value to, renal osteodystrophy [65-69].

MRI scan helps evaluate the soft tissues for ligament rupture, and CTscan can help evaluate pathologic fracture. Amyloidosis may cause erosion in and around a joint, resulting in subtle radiographic signs, while amyloid deposits can be visualized directly on MRI.[66]

BMD measurement by quantitative computed tomography is valuable in differentiating cortical from trabecular bone, is particularly advantageous in CKD-MBD, where hyperparathyroidism can lead to sclerotic thickening of trabecular bone with increased BMD but stimulates resorption in cortical bone with significant reductions in BMD. In contrast, low-turnover bone disorders frequently result in reductions in trabecular BMD [69,70].

Plain X-ray films provide minimal information in the evaluation of CKD-MBD in the majority of CKD patients. Exceptions are advanced forms of bone disease such as severe osteitis fibrosa (subperiosteal resorption) or severe osteomalacia (Looser zones). However, radiographs remain an important part of the ongoing evaluation of CKD-MBD in children with CKD [68,69].

Symptoms due to these disorders, such as fractures and bone pain, generally do not occur until the patient is already on maintenance dialysis. However subclinical changes in bone remodeling begin when the GFR falls to half of its normal value, with approximately 50% of such patients already presenting histological bone lesions [64-68].

1.6 Biochemical Markers In Evaluation Of Mineral Bone Disease

The most common forms of Chronic Kidney Disease-Mineral Bone Disease (CKD-MBD) are attributable largely to variations in the plasma levels of parathyroid hormone (PTH). As such, circulating PTH levels have been used as a surrogate indicator of bone turnover in place of the difficult and expensive methods of obtaining bone biopsies [67-69].

Intact PTH together with measurements of serum calcium, phosphorus, and alkaline phosphatase levels has been used to evaluate, diagnose, and guide the treatment of renal osteodystrophy [9, 70].

According to the K/IDGO guidelines of 2006, in dialysis patients, levels of intact-parathyroid hormone (iPTH) that are within or below the normal range of the assay are generally indicative of low bone turnover and levels of iPTH that are greater than 2–3 times the upper normal range of the assay are generally indicative of high bone turnover. (Level 1 evidence) [8].

The measurement of serum calcium and phosphorus alone is unhelpful in distinguishing between high and low bone turnover states.

Hypercalcaemia may be present in severe hyperparathyroidism, aluminium-related osteomalacia and ABD. Serum phosphate levels depend on numerous factors, including intake, use of phosphate binders and adequacy of dialysis, and are poor predictors of the type and severity of bone disease [71].

The measurement of total alkaline phosphatise lacks specificity for bone disease. Nevertheless, in the presence of a normal g-glutamyl transferase, elevated total alkaline phosphatase is suggestive of hyperparathyroid bone disease and low levels predict low turnover states [72].

Coen et al. found that a total alkaline phosphatase cutoff of 82.5 U/l (normal range 35-125 U/l) has a sensitivity of 75% and specificity of 100% in

discriminating ABD from hyperparathyroidism/mixed uraemic osteodystrophy [73].

Rix et al studied severity and frequency of skeletal demineralization by evaluation of biochemical markers of bone turnover ,(osteocalcin, PTH, bone-specific ALP, carboxyl terminal propeptide of type I collagen(PICP), carboxyl terminal telopeptide of type I collagen ICTP) as well as BMD(DEXA), showed that BMD Z scores of the femur and forearm significantly correlated to PTH and other biochemical bone markers.($p<0.05$ to $p<0.0001$). The biochemical bone turnover markers all showed strong correlation to PTH ($p<0.01$ to $p<0.0001$) [74].

Plasma bone specific alkaline phosphatase (bAP) values were compared with those of two other plasma markers of bone metabolism, namely ICTP(serum caboxyterminal telopetide of type 1 collagen) and intact parathyroid hormone (iPTH), for the correlations with bone histomorphometric parameters. Bone formation and resorption were highly correlated in these patients, and plasma bAP levels were positively correlated with bone resorption parameters, including osteoclast surface ($r = 0.39$, $P < 0.0001$) and osteoclast number/mm2 ($r = 0.36$, $P < 0.001$), and with bone formation parameters, osteoblast surface ($r = 0.50$, $P < 0.005$), and bone formation rate ($r = 0.91$, $P < 0.0001$). Plasma bAP level equal or higher than 20 ng/mL, either alone or combined with plasma iPTH of 200 pg/mL, had the highest sensitivity, specificity, and predictability values for the diagnosis of high-turnover bone disease [73,74].

Numerous other studies have shown that high-turnover bone (encompassing both osteitis fibrosa and mixed uremic osteodystrophy) is often associated with serum levels of intact PTH of over 400 pg/mL (44.0 pmol/L), though high-turnover lesions may be seen at lower intact PTH levels and low-turnover bone disease may occur at serum levels of intact PTH above 400 pg/mL (44.0 pmol/L [72-74].

The development of SHPT, which is characterized by parathyroid hyperplasia and enhanced synthesis and secretion of PTH.

Without active suppression of PTH, the parathyroid glands can develop areas of micronodular change that can progress to macronodoular adenomas. Parathyroid nodularity is irreversible and is associated with decreased levels of vitamin D receptors. Thus, an important reason to recognize and treat SHPT early is to prevent hyperplasia of the parathyroid gland [67,75].

A receiver operating characteristics (ROC) analysis (in essence, a diagnostic meta-analysis) of using PTH to diagnose high-turnover disorders revealed an estimate of the sensitivity 93% (95% CI, 87% to 97%) and a specificity of 77% (95% CI, 62% to 87%), using threshold PTH levels between 150 and 200 pg/mL.. Studies performed using PTH to diagnose low-turnover bone disorders use levels of 60 pg/mL as the threshold. In this case, the estimated sensitivity and specificity from the ROC analysis were 70% and 87%, respectively. Thus, PTH is also useful in detecting high-turnover bone disorders as well as low-turnover bone diseases [70-73].

Correlations, of intact PTH, with bone histology, have shown iPTH to be better predictive of pathological findings, and to be the best "noninvasive" marker of bone turnover [73-75].

1.7 Parathyroid Hormone and Bone Response of the Diabetic Patient

Over the past decade diabetic patients with nephropathy have now emerged as the single largest group on renal replacement therapy. The incidence of diabetic patients entering a renal replacement program has increased by about 125% in Canada and 450% in the USA [76].

Diabetes is the most common cause of end-stage kidney disease, and renal osteodystrophy is more pronounced in diabetic than in non-diabetic haemodialysed patients [77].

Adynamic bone disease is common, and appears to be unique to the diabetic patient with chronic kidney disease suggesting that, the development of diabetic nephropathy and renal failure may add another dimension to the bone pathology. Earlier bone loss in the course of diabetic nephropathy is suggested by the finding of low bone mineral density (BMD) in Type 1 diabetic men with microalbuminuria [77] .

A Frecnh study done on 40, mainly type 2, non-dialysed diabetic patient with CKD (GFR<60ml/min/1.73m2), using total body dual energy X-ray absorbptiometry (DEXA) scans measurements, demonstrated T-scores for total body (initial − 0.61±1.11, final−1.11±1.40;P< 0.001) and femoral neck (initial −1.88±0.15, final−2.07±0.15;P < 0.05) progressively declined over a 2year period[78].

The main feature of the histology of bone in the diabetic patients with chronic kidney disease is the reduced or low normal volume of bone associated with reduced indices of both bone formation and resorption [79,80].

Earlier observations confirmed lower circulating iPTH in diabetic patients with end-stage kidney disease than non-diabetic patients with comparable diseases and duration of dialysis [79-80].

A study done to examine the effects of high glucose concentration on PTH secretion, demonstrated a direct suppressive effect of high concentration of glucose on PTH secretion from cultured bovine parathyroid cells. Although the mechanism of such a suppressive effect remains to be elucidated, the results of this study may provide clues to understanding of the secretory activity of parathyroid glands in diabetic patients with or without renal failure [81].

Justification of the study

CKD is a worldwide public health problem associated with an increasing incidence and prevalence of patients with kidney failure requiring RRT, most of who will die before renal replacement therapy (RRT) is initiated, and high cost of care.

Studies have demonstrated that severity of secondary HPT correlates directly with increased morbidity and mortality in the dialysis population, this morbidity mortality excess is attributed to cardiovascular disease [5, 14].

SHPT and other disorders of mineral metabolism are potentially modifiable risk factors. SHPT begins during earlier stages of CKD, and little is known about the severity of SHPT in a pre-dialysis population.

Studies have shown black (African) Americans manifest more severe SHPT and 1,25VitD deficiency than Caucasians. However, no studies have examined the prevalence and severity of mineral metabolism disorders, in CKD, within East and Central African pre-dialysis population.

Data on American/European population, as often is the case, may not necessarily apply to the African population due to social-economic factors, ethnic and nutritional habits and genetic factors.

No studies have examined racial difference in the prevalence and severity of disorders of mineral metabolism in pre-dialysis patients. Therefore, the knowledge of the magnitude of disorders of mineral metabolism in chronic kidney disease and their prompt recognition as a non-traditional risk factor of morbidity and mortality in CKD may generate data for early intervention.

Swao set out to determine the early biochemical and radiological changes in patients with Chronic Renal Failure pre and during dialysis, the study population was only 31 patients, biochemical makers used to determine renal osteodystrophy were inorganic phosphate and alkaline phosphatase [24]. Many cross-sectional and population-based studies indicate that serum phosphorous levels remain within normal range in most patients until GFR has reached 10-15% of normal, demonstrating that serum phosphorus is a late rather than an early consequence of CKD [27, 28,29].

Patel sought to describe clinical, radiological and biochemical evidence of renal osteodystrophy (ROD) by use of iPTH, the study population was 41 patients, serum iPTH was determined using radioimmunoassay, these assays theoretically detected only the intact molecule PTH-(1-84), which is biologically active [26]. The midregion and C-terminal-circulating fragments, which are greatly increased in renal insufficiency, are usually not detected by these assays [74]. Several investigators have shown the presence of high-circulating fragment levels, mostly PTH-(7-84) detected by the currently available chemiluminite assays, iPTH assays, in patients with end stage renal disease ESRD [75].

The minimum sample size in this study is 188 subjects, thereby increasing the power of the study compared to studies done by Swao[24] and Patel[26] .

The severity of hyperparathyroidism is an important factor of treatment response to Vitamin D therapy [84].

This study proposes to determine the prevalence and patterns of hyperparathyroidism and mineral bone disease in CKD patients at the Kenyattta National Hospital. The Data generated from this study will sensitize clinicians on the magnitude of hyperparathyroidism as a non-traditional risk factor for cardiovascular disease.

The secondary prevention interventions, recommended from this study may assist to slow or arrest the progression of both bone and cardiovascular disease; these will benefit all patients with hyperparathyroidism.

Research Questions:

What is the magnitude and severity of hyperparathyroidism amongst patients with CKD patients in this region?

What is the pattern of mineral bone disease, high turn-over and low turn-over, in pre-dialysis patients with CKD?

3. OBJECTIVES

3.1 Broad objective:

To evaluate the patterns and prevalence of hyperparathyroidism in chronic kidney disease patients attending renal clinic at KNH.

3.2 Specific objectives

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1. To determine the levels and evaluate the severity of iPTH elevation at the various KDOQI stages of chronic kidney disease.
2. To determine the point prevalence of hyperparathyroidism of the patients attending the renal clinic at the KNH.
3. To determine and document biochemical evidence of bone turnover by evaluation of serum intact parathyroidhormone iPTH and alkaline phosphotase (ALP) levels.
4. To correlate the characteristics of age, gender and presence of diabetes mellitus with the patterns of iPTH.

5. To compare the patterns/levels of iPTH at each CKD stage to the K/DOQI recommendations and possibly identify quality of control of HPT.

4. MATERIALS AND METHODS

4.1 Study Design

This study was a descriptive cross-sectional study.

4.1.1 Study Area

The designated area for the study was Renal Clinic of the Kenyatta National Hospital, Nairobi.

4.1.2 Study population

The study population consisted of accenting adolescents of ages 13 years and consenting adult individuals diagnosed with Chronic Renal Failure.

4.1.3 Study Duration

Enrolment was done from December 2008 to March, 2009.

4.2 SAMPLE SIZE

A total number of 214 CKD patients were studied, calculated using the formula

$$n = \frac{Z^2 \times p(1-p)}{d^2}$$

Description:

n = required sample size
z = confidence level at 95% (standard value of 1.96)
p = estimated prevalence of SHPT (60%)
d = margin of error at 7% (standard value of 0.07)

4.3 PATIENT SELECTION

4.3.1 Inclusion Criteria

1. Chronic Kidney Disease with GFR $\leq$90ml/min/1.73m^2.
2. Ascenting persons over the 13 years of age and consenting adults (above 18yrs)
3. Patients not on dialysis
4. Signed written informed consent and ascent for patients below 18years of age.

4.3.2 Exclusion criteria

1. GFR $\geq$ 90ml/min/1.73m^2
2. Use of glucocorticoids/ biphosphonates/other drugs that affect bone metabolism eg. Antiepileptic drugs
3. Patients on dialysis
4. Patients who decline to participate in the study

4.3.3 Case definition

Chronic Kidney Disease : A Chronic Kidney disease patient will be considered one who has an estimated GFR $\leq$90ml/min/1.73m2 at time of recruitment with evidence of a previous estimated GFR of less than 90 ml/min/1.73m2 at least 3 months prior to recruitment into the study.

Stages of CKD according to the US National Kidney Foundation and the Kidney Disease Outcomes Quality Initiative (K/DOQI) [12,64].

Stage 1: Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies) with normal or raised glomerular filtration rate (≥90 mL per min per 1·73 m^2)

Stage 2: Glomerular filtration rate 60–89 mL per min per 1·73 m^2 with evidence of kidney damage

Stage 3: Glomerular filtration rate 30–59 mL per min per 1·73 m^2

Stage 4: Glomerular filtration rate 15–29 mL per min per 1·73 m^2

Stage 5: End-stage renal disease; glomerular filtration rate <15 mL per min per 1·73 m^2

Parathyroid Hormone

Normal intactPTH [Intact PTH 15-65pg/ml] {chemiluminescence assay (ECLIA Roche)}

Hyperparathyroidism (HPT) - [Intact PTH X 1+1 upper limit of normal iPTH][64]

Patterns of Hyperparathyroidism

The following criteria, to describe patterns of hyperparathyroidism, were applied [8]:

- Mildly elevated PTH [Intact PTH {> 65pg/ml to1.5 X 65pg/ml(upper limit of normal iPTH)}

- Moderately elevated PTH [{1.5-2 X65pg/ml(upper limit of normal iPTH)]
- Severe PTH [Intact PTH >2 X65pg/ml(upper limit of normal iPTH]

Chronic kidney disease-mineral bone disease (CKD-MBD): was defined as an abnormality of intact PTH and alkaline phosphotase.

Alkaline phosphotase levels and intact PTH were evaluated to distinguish between high and low turnover bone disease [8,73].

The following criteria will be applied:

- High-turnover bone disease [Intact PTH >1.5xnormal and ALP >200U/L]
- Low-turnover bone disease [Intact PTH <10pg/ml/btw10-65pg/ml and ALP <82.5 u/L]

3.4 Parameters Evaluated

- Blood samples were collected at study visit 1 (baseline). Blood was collected for serum creatinine, serum iPTH, Calcium, phosphorus, albumin, and alkaline phosphatase.
- Total serum Calcium was corrected for serum albumin using the equation: *Corrected Calcium= Ca* [40- measured serum albumin]x 0.02 + measured serum Calcium. (A typical correction is that for every 1 g/l that the albumin concentration is below 40g/l, the calcium concentration is 0.02 mmol/l below what it would be if the albumin concentration was normal)
- Samples for serum creatinine, calcium, phosphorus, albumin, and alkaline phosphatase were run at a central laboratory in the department of

biochemistry, University of Nairobi. These samples were analyzed with a routine automated analyzer .

- Serum intactPTH was run at clinical biochemistry department of the Nairobi Hospital, using chemiluminescence assay (ECLIA Roche)

- Laboratory reference ranges were as follows:
    a. Serum intact PTH 15-65pg/ml
    b. Serum creatinine 60-130µmol/l
    c. Serum calcium 2.02-2.65µmol
    d. Serum phosphorous 0.81-1.62 µmol
    e. Serum alkaline phosphotase 42-141IU/L
    f. Serum albumin 35 -54 g/l

- For the purposes of this study, the key variables of interest were the distribution of intact PTH values and alkaline phosphotase.

4.3.5 Sampling method

Consecutive sampling was used to recruit patients at visit to the KNH Renal Clinic over a period of 3 consecutive months, till the sample size of 214 was attained. This clinic runs once a week, every Friday morning except on public holidays

4.4 METHODS

4.4.1 Screening and Recruitment

All patients' files which had a documented result of creatinine from the KNH Renal laboratory at least three months prior to the study visit were screened.

The patients whose estimated GFR, was less than 90ml/min/1.73/m2 for a period of 3 months or more were enrolled into this study. The GFR was estimated using the Cockroft Gault formula with the aid of an internet based medical equations calculator [83].

All patients with eGFR of less than 90ml/1.73/m2 were screened using a screening questionnaire (appendix 3). Patients who meet the inclusion criteria were informed of the study and requested to fill the consent/ascent form (appendix 2). Those who gave consent/ascent were subsequently recruited into the study.

Participants were staged according to the NKF-K/DOQI staging system.[12,64]

4.4.2 Clinical methods.

An investigator administered study proforma [appendix 4] and questionnaire was used to collect data from the recruited patients. Data which consisted of socio demographic data to include age, gender; marital status and place of residence was filled in by the participant.

Data on clinical status at the time of presentation was obtained through interview.

Information on possible etiology of kidney disease, medical history of fractures, bone pain/tenderness, presence of diabetes, current medications were recorded.

Detailed physical examination was conducted.

4.4.2 LABORTORY METHODS

About 6 ml of blood was drawn from the cubital vein in sterile plain vacutainer for urea, creatinine, sodium, potassium, calcium, phosphate, albumin, alkaline phosphotase and intact PTH.

The blood samples were immediately transferred to the laboratory and serum samples, for determination of biochemical markers, were then frozen at -20 degree Celsius until time of analysis.

The measurements of serum, blood nitrogen urea, creatinine, albumin, calcium, potassium, phosphorus, alkaline phosphatase, levels were determined using automated clinical chemistry analyzer Cobas Integra 400 Plus (Roche); serum iPTH assays were performed in Nairobi Hospital special chemistry unit, using electro-chemiluminescence immunoassay (ECLIA) on the immunoanalyzer (Elecys).

To ensure quality was maintained, the lab tests were carried out in biochemistry laboratory of the University of Nairobi and the KNH renal laboratory, with exception of the intact PTH, according to the AVL 9181electrolyte analyzer operations manual.

The results were analyzed after daily calibration using standard calibration methods and materials and tests assayed against controls.

To calculate creatinine clearance, a single measured serum creatinine level was used. The glomerular filtration rate (GFR) was estimated using the corrected Cockroft and Gault formula [82] thus:

$$\text{GFR (ml/min)} = \frac{[140\text{-age (yrs)}] \times \text{weight (kg)} \times \text{constant}}{\text{Plasma creatinine (micromoles/L)}}$$

Constant=1.23 in males and 1.04 in females.

The calculated clearance was reduced by 15% for women, 20% for paraplegic, and 40% for quadriplegic patients.

The formula was calculated using a free Internet-based clinical equations calculator (MDCalc) [83].

All patients recruited in this study underwent the standard care as offered at the KNH renal clinic.

4.5 DATA MANAGEMENT AND ANALYSIS

A questionnaire was used to collect information about participants' demographics and information, medical, medication history, and clinical status at the time of presentation (appendix 4).

All data collected on the study proforma was entered into a computer data base using Microsoft Excel computer software and statistical analysis was done using statistical package for social scientists (SPSS) version 15 after cleaning and verification.

Values were expressed as means, medians and standard deviations (SD) unless otherwise indicated.

Point prevalence of hyperparathyroidism was determined as a percentage of the number of patients attending the clinic in CKD stages 1to 5 of the total study population.

Associations between the patients' socio-demographic data, presence of Diabetes Mellitus, staging of chronic kidney disease and serum iPTH levels were examined using chi-square test.

Differences in mean values in patients with or without diabetes mellitus, male and female were analyzed by Student's t-test, if normally distributed, or Mann-Whitney U test for skewed data, to determine statistical significance.

Associations were considered significant only when p value was equal to or less than 0.05.

The data was presented using descriptive statistics then presented using tables, pie charts and graphs.

5. ETHICAL CONSIDERATIONS

The study was undertaken after approval by the Department of Internal Medicine, University of Nairobi and the Kenyatta National Hospital Scientific and Ethical Review Committee.

Cases eligible to participate in the study were included only after providing consent following the process as outlined below:

1. The cases were informed that the project involves local research.
2. They were told the purpose of the research.
3. The procedures of the study were explained clearly with full details of all the tests to be done.
4. They were assured that participation is voluntary and that no medical attention would be denied should they decline to participate.
5. The subjects were informed of the medical benefits and also physical and any psychological harms to their satisfaction prior to being included in this study.
6. The subjects were assured of full and free access to their results and that therapeutic interventions would be recommended where the need arises, according to accepted standards of practice.
7. It was asserted that confidentiality would be strictly maintained and all data would be securely stored and only revealed upon a need-to-know basis and that all costs regarding investigations in this study would be borne by the principal investigator.

Following the full explanation and acceptance by the patient of the above, the subject was requested to sign the consent form (appendix 2).

Results

A total of 713 individuals with CKD attending the KNH-renal clinic between December 2008 and March 2009 were screened for eligibility into the study. 495 of these patients were excluded, 492 on the basis of either, having an eGFR above 90ml/min /1.73m2 or eGFR less than 90ml/ml/min/1.73m2 but for a duration less than 3 months, while 3 declined to give consent.

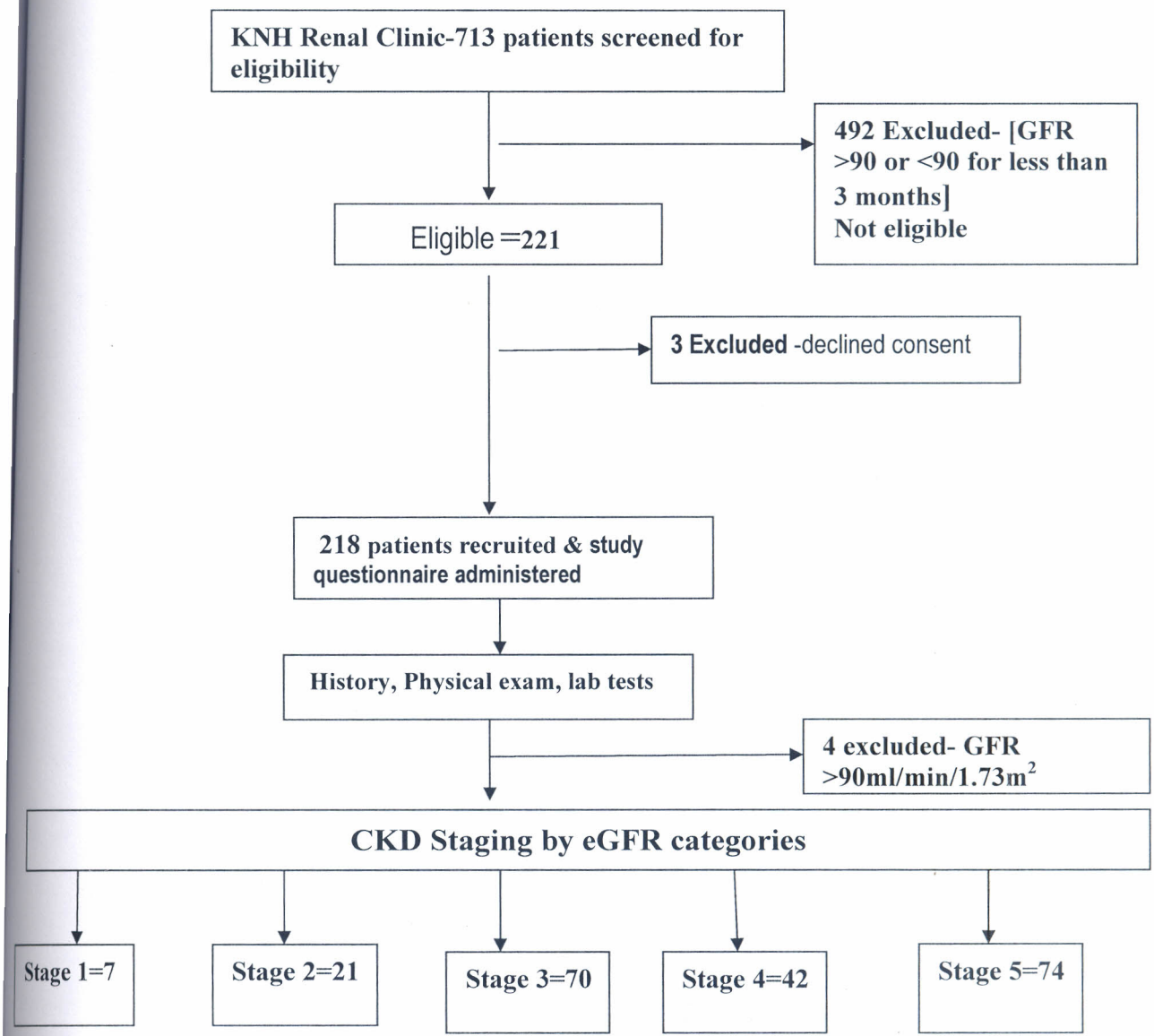
The 218 patients, who gave consent or ascent, were interviewed and had a physical examination and blood drawn for laboratory investigations. 4 of the recruited participants were found to have a eGFR above 90ml/ml/min/1.73m2 and therefore excluded.

The final study population comprised of 214 participants, all pre-dialysis patients with CKD.

The study population was categorized into 5 groups as per K/DOQI staging of chronic kidney disease. CKD stage 1 had 7 participants, stage 2 21, stage 3 70, stage 4 42 and stage 5 74 participants respectively. Fig 1 below illustrates the patient recruitment flow chart.

Fig 1: PATIENT RECRUITMENT FLOW CHART

214 patients were recruited between December 2008 and March 2009.



A study population of 214 patients aged between 15 and 95 years with a peak age of 60-69 years was recruited into the study. The mean age was 50.83 (±17.00) years with median and modal age at 52.0 and 65 years, respectively.
The mean age in males was 53.87 ±16.81and females 47.75±16.70. This was significantly different $p<0.01$, with males being older than females.
There were 100 males (46.7%) and 114 females (53.3%) with a male to female ratio of 1.0:1.1.

There were more males compared to females in the married category 59.6% and 40.4% respectively, fewer males were single compared to females 22.6% versus 77.4%. There were also more females in the widowed and separated categories 88% and 70% , respectively, compared to 12% and 30%, respectively, in males.
There were more females (81.8%) without formal education group than males (18.2%). The number of females declined gradually through primary and secondary education levels, the females being more compared to males in these two categories.
However, at tertiary education level, the males dominated with 73.5% compared to 26.5% of females.
Table 1 shows the socio-demographic characteristics of the study population.

Table 1: Socio-demographic characteristics of the CKD patients

Parameter	No	Male Total Number	Male percentage %	Female Total number	Female percentage	Total % within gender
Age in years						
10 - 19yrs	8	3	**3.0**	5	**4.4**	**3.7**
20 - 29yrs	20	7	**7.0**	13	**11.4**	**9.3**
30 - 39yrs	34	13	**13.0**	21	**18.4**	**15.9**
40 - 49yrs	33	12	**12.0**	21	**18.4**	**15.4**
50 - 59yrs	38	17	**17.0**	21	**18.4**	**17.8**
60 - 69yrs	47	27	**27.0**	20	**17.5**	**22.0**
70 - 79yrs	28	17	**17.0**	11	**9.6**	**13.1**
>= 80yrs	6	4	**4.0**	2	**1.8**	**2.8**
Total	214	100	**100**	114	**100**	**100.0**
Marital Status						
Married	146	87	**59.6**	59	**40.4**	**68.9**
Single	31	7	**22.6**	24	**77.4**	**14.6**
Widowed	25	3	**12.0**	22	**88.0**	**11.8**
Separated	11	3	**30**	7	**70**	**4.7**
Total	**212**	**100**	**47.2**	**112**	**52.8**	**100**
Education Level						
No formal education	11	2	**18.2**	9	**81.8**	**5.2**
Primary	58	19	**32.8**	39	**67.2**	**27.5**
Secondary	93	43	**46.2**	50	**53.8**	**44.1**
Tertiary	49	36	**73.5**	13	**26.5**	**23.2**
Total	**211**	**100**	**47.4**	**111**	**52.6**	**100**

The study population comprised 63.6% (n=136) non-diabetic and 36.4% (n=78) diabetic subjects.

As per K/DOQI staging of chronic kidney disease, majority of the study patients were in CKD stage 3, 4 and 5 comprising n=70(32.7%), n=42 (19.6%) and 34.6%(n=74) respectively with the highest numbers being observed in stage 5. Stage 2 had 9.8%(n=21) while stage 1 had only 3.3%(n=7). Table 2 shows the distribution of the study poulation for each CKD stage.

Table 2: K/DOQI Staging of chronic kidney disease in study population

CKD stage	Frequency	Percentage %
Stage 1(GFR≥ 90ml/min/1.73m2)	7	3.3
Stage 2 (GFR 60 - 89ml/min/1.73m2)	21	9.8
Stage 3 (GFR 30 - 59ml/min/1.73m2)	70	32.7
Stage4 (GFR 15 - 29ml/min/1.73m2)	42	19.6
Stage 5 (GFR < 15ml/min/1.73m2)	74	34.6
Total	214	100.0

The possible etiologies of CKD, as recorded on patients clinical notes, were observed as follows: 78.5% of the patient population had history of hypertension, 36.4% diabetes mellitus, while 33.2% had both hypertension and diabetes. Other etiologies included nephrotic syndrome 8.9%, Human Immunodeficiency Virus(HIV) 7.0% Obstructive nephropathy 3.7%, Systemic Lupus Erythematosus (SLE) 2.3%, Hepatitis B 1.4%, Polycytic Kidney disease 1.4%, Tuberculosis of the kidney 1.4%, Rheumatoid arthritis 0.9% and glomerulonephritis 0.5%.

Of note is that the data represented may not be a true representation of the actual etiologies of CKD. Firstly, because patients with CKD invariably will have hypertension whatever the aetiology, hence the proportion of patients with hypertension, as a probable aetiology, in this study is over represented.

Secondly, patients with nephrotic syndrome, HIV, SLE, rheumatoid arthritis would be included in the entity glomerulonephritis, therefore the proportion of glomerunephritis is under represtended.

Table 3 illustrates the distribution of etiological factors associated with CKD in the study population.

Table 3: Possible etiologies for Chronic Kidney Disease in the study population

Possible Risk Factor for CKD	No. of Pts	Percent %
Hypertension	168	78.5
Diabetes Mellitus	78	36.4
Nephrotic syndrome	19	8.9
HIV	15	7.0
Obstructive nephropathy	8	3.7
SLE	5	2.3
Hepatitis B	3	1.4
Polycystic Kidney Disease	3	1.4
TB kidney	3	1.4
Rheumatoid Arthritis	2	0.9
Glomerulonephritis	1	0.5

At presentation, the mean body weight was 64.182±12.32 kg , males were significantly heavier, mean 67.30(±12.09)kg compared to females 61.46(±11.91)kg, $p < 0.001$(Student's t test).

The mean Systolic Blood Pressure (SBP) was140±30.64mmHg and Diastolic Blood Pressure (DBP) was 88.11 ±16.46mmHg. Table 4 illustrates the clinical findings of the study population.

Table 4: Clinical Characteristics of the study population

Parameter	*Mean in Males(n=100)*	*Mean in females(n=114)*	*Overall mean*	*P-value*
Age in yrs	54.35(±16.51)	47.75(±16.82)	50.64 ±17.00	**0.004**
Age in yrs(Diabetic)	58.86±15.998	57.14±11.714	46.68(±17.10)	
Age in yrs(Non-diabetic)	51.09±16.229	43.41±17.098	58.06(±14.12)	
Body Weight (kg)	67.30(±12.09)	61.46(±11.91)	64.182±12.32	**0.000**
SBP mmHg	142.42±30.159	139.62±31.131	140.93 ±30.64	0.507
DBP mmHg	87.23±15.72	88.88±17.12	88.11 ±16.46	0.465

The estimated glomerular filtration rate (eGFR) was 31.342 ±24.66 ml per min per 1.73 m^2 and the mean intact PTH level 52.02 ±99.02 pg/ml. The females recorded a significantly higher mean iPTH levels of 68.46(±123.78) pg/ml, twice as much, compared to males with a mean iPTH of 33.28(±54.24) pg/ml, $p < 0.01$(Students t test).

Median serum creatinine level was 264.00µmol. The mean phosphorus was 1.65 µmol. Table 5 illustrates the mean levels of laboratory findings, parameters within the normal range, of the study population with gender comparison.

Table 5:Laboratory parameters of study population with gender comparison.

Parameter	*Mean in Males(n=100)*	*Mean in female(n=114)*	*Overall Mean*	*p-value*
eGFR ml per min per 1.73 m^2[90-120]	33.66(±24.65)	29.31(±24.60)	31.342 ±24.66	0.199
Serum intact PTH pg/ml	33.28(±54.24)	68.46(±123.78)	52.02 ±99.02	**0.007**
Serum Creatinine [60-130µmol/]	228.5(median)	276.00(median)	264.00(median)	0.933
Serum Phosphorus mmol/l [0.81-1.62 µmol]	1.67(±0.76)	1.63(±0.67)	1.65 ±0.71	0.617

The mean albumin was 33.29±10.03g/l. The mean calcium was 1.78±0.43µmol, below the lower limit of normal and mean alkaline phosphotase was 245.07±161.65 U/L which was above the upper limit of normal. The mean heamoglobin level was 10.05g/dl±2.03g/dl which was below the lower limit of normal. There was no significant difference in means between males and females. Table 6 below illustrates the mean summary of laboratory findings, of the study population.

Table 6: Laboratory parameters of study population with gender comparison

Parameter	*Mean in Males(n=100)*	*Mean in female(n=114)*	*Overall Mean(n=214)*	*p-value*
Serum albumin g/l [35 -54 g/l]	33.78±10.42	32.87±9.708	33.29±10.03	0.509
Serum Calcium mmol/l	1.62 (±0.49)	1.67(±0.46512)	1.65±0.47	0.488
Corrected Calcium mmol/ [2.02-2.65µmol]	1.75±.42	1.81±.4291	1.78 ±0.43	0.306
Alkaline Phosphotase IU/L [42-141U/L]	234.84±146.086	254.04±174.306	245.07 ±161.65	0.387
Haemoglobin level g/dl	10.47 (±2.92)	9.66(±2.69)	10.05(±2.82)	0.151

Normal Reference Range

Serum intact PTH (15-65pg/ml)

Serum creatinine 60-130µmol/l

Serum calcium 2.02-2.65µmol

Serum phosphorous 0.81-1.62 µmol

Serum alkaline phosphotase 42-141IU/L

Heamoglobin male: 13-15g/dl female: 11-13g/dl

Serum albumin 35 -54 g/l

Intact PTH

This study evaluated the mean levels of iPTH in each NFK-K/DOQI stage of CKD and found that mean iPTH levels gradually increased as renal function declined.

The mean iPTH levels in CKD stages 1, 2 and 3 recorded levels within the normal reference range and no inter-gender differences were observed. However, in stage 4, the mean iPTH level was found to be elevated more than two times higher in females at 59.28(±61.10) pg/ml than the males 26.45(±33.52) pg/ml, $p < 0.05$. In CKD stage 5the mean difference in iPTH levels is maintained and the mean iPTH levels in females of 121.85(±176.80)pg/ml double than the mean value of males' 58.52(±79.83)pg/ml, $p < 0.05$. Table 7 shows the trend of mean iPTH levels for each CKD stage in both males and females.

Table 7: Mean levels for serum intact PTH (iPTH) for each CKD stage

NFK-K/DOQI CKD Stage	Frequency of males	Male mean iPTH pg/ml	Frequency of females	Female mean iPTH)pg/ml	P Value
Stage 1(≥90ml/min/1.73m2)	4	25.90(±18.78)	3	20.49±28.63	0.773
Stage 2 (60 - 89ml/min/1.73m2)	11	18.68(±22.26)	10	11.77±16.63	0.434
Stage 3(30 - 59ml/min/1.73m2)	37	21.26(±38.55)	33	25.48±46.68	0.680
Stage 4(15 - 29ml/min/1.73m2)	18	26.45(±33.52)	24	59.28±61.10	**0.032**
Stage 5(< 15ml/min/1.73m2)	30	58.52(±79.83)	44	121.85±176.80	**0.041**
Total	100	33.27±54.24	114	68.46±123.79	

In males iPTH levels shows a gradual rise as renal function declines, such that there does not seem to be distinct differences between the CKD stages but the overall mean difference is significant $p<0.05$ ($F = 2.512$) with a significant rise in mean iPTH in stage 5 disease compared to stage 1. Fig 2 displays the trend of increase in mean iPTH for each CKD stage in males.

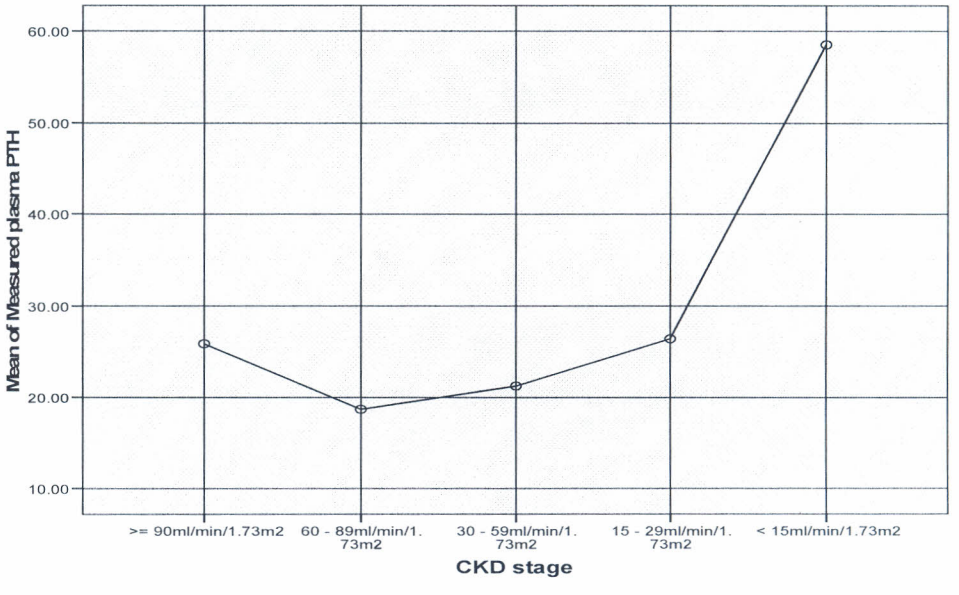


Fig 2 Mean levels of serum iPTH for each K/ODQI CKD stage in males

In the women also, serum iPTH increases with decline in kidney function but much more distinct in stage 4 compared to stages 1,2 and 3 followed by a very significant rise in serum iPTH in stage 5 twice above the mean level in stage 4. There is a very significant overall difference in means of iPTH levels between the different CKD stages in the women $p <0.001$ ($F=4.121$). Fig 3 shows the mean levels of serum iPTH for each K/DOQI CKD stage in females.

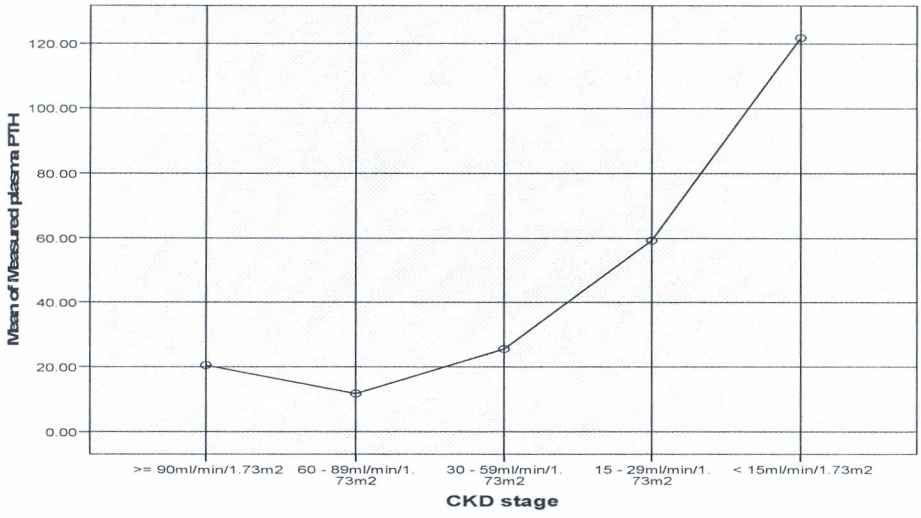


Fig 3 Mean levels of serum iPTH for each K/DOQI CKD stage in females

Serum intact PTH was categorized according to the levels above, below and within the normal limits. Normal levels of iPTH were considered if between 15-65pg/ml, iPTH levels were considered to be low if less than 15pg/ml and high if above 65pg/ml.

Elevated serum intact PTH was found in 22.4% (n=48) of the study patients. Majority of the study patients were found to have intactPTH below the lower limit of normal 50.5%(n=108 patients), 27.1% (n=58)had intactPTH levels within the normal(15-65pg/ml) range.

In the group with iPTH levels below the lower limit of normal, 41.7% (n=45) were diabetic, while 58.3% (n=63) were non-diabetic.

In the group with elevated iPTH 27.1% (n=13) were diabetic while 72.9% (n=35) were non-diabetic. Table 8 illustrates the distribution of diabetic and non-diabetics, according to categories low, normal and high intact PTH levels.

Table 8: Distribution of diabetic and non-diabetic population for each category of serum intact PTH

Parameter	Low Intact PTHN{iPTH<15pg/ml}	Normal Intact PTH {iPTH 15- 65pg/ml}	High Intact PTH {iPTH>65pg/ml}
Diabetic (%) N=78	45(41.7)	20(35.5)	13(27.1)
Non-diabetic(%) N=136	63(58.3)	38(65.5)	35(72.9)
Total N=214	108(100)	58(100)	48(100)

There was, however, no significant association between presence of diabetes and intact PTH levels, p=0.204 (χ^2=1.176). Table 9 illustrates the distribution of mean iPTH leves for each stage of CKD for categories diabetics and non-diabetics.

Table 9: Distribution of mean iPTH levels for each stage of CKD

NFK-K/DOQI CKD stage	No of Diabetic N=78	Mean serum iPTH pg/ml	No of Non-diabetic	Mean serum iPTH pg/ml	Student's t test
Stage 1>= 90ml/min/1.73m2	3	31.30(±22.81)	4	17.79(±21.55)	0.459
Stage 2 60 - 89ml/min/1.73m2	11	6.84(±12.87)	10	24.79(±21.97)	**0.032**
Stage 330 - 59ml/min/1.73m2	26	28.58(±58.68)	44	20.10(±29.05)	0.496
Stage 4(15 - 29ml/min/1.73m2)	19	37.71(±55.76)	23	51.40(±51.39)	0.413
Stage 5(< 15ml/min/1.73m2)	19	84.70(±137.87)	55	100.13(±152.45)	0.698
Total	78	41.51(±83.78)	136	58.04(±106.61)	0.241

Patients with iPTH levels above the upper limit of normal appeared to be younger with a mean age of 45.94±16.23 years compared to those with iPTH levels within the normal limit of normal mean age 54.67±16.79 years, with $p<0.00$. Table 10 below illustrates the mean age for each category of intact PTH level.

Table 10 Distribution of Serum Intact PTH and mean age in years

PTH level Categories	N	Percentage%	Mean Age
Low(iPTH<15pg/ml)	108	50.5	50.94±16.96
Normal(iPTH 15- 65pg/ml)	58	27.1	54.67±16.79
High(iPTH>65pg/ml)	48	22.4	45.94±16.23
Total	214	100	50.83±16.96

Majority, 56.3%(n=27), of the patients observed to have hyperparathyroidism had an Intact PTH level elevated more than 2 times above the upper limit of normal, 27%(n=13) had mild elevation with a level less than 1.5 times above the upper limit of normal and 16.7%(n=8) had moderate elevation with levels between 1.5 to 2 times the upper limit of normal. Table 11 demonstrates the patterns of distribution of iPTH levels above the upper limit of normal (Hyperparathyroidism) in the study population

Table 11 Patterns of distribution of iPTH levels above upper limit of normal (hyperparathyroidism) in the study population.

Hyperparathyroid Category	Frequency	Percentage%
Mild Elevation (>65 - ≤1.5x65pg/ml)	13	27%
Moderate (1.5x65 -2x65pg/ml)	8	16.7%
Severe (> 2x65pg/ml)	27	56.3%
Total	48	22.4

Out of 78 diabetic patients recruited in this study, 16.7% (n=13) had serum iPTH levels above the upper limit of normal. Diabetics with hyperparathyroidism were 27.1%. Most, 76.9% (n=10), of the diabetic population with hyperparathyroidism, had severe elevation of the serum iPTH of more than two times above the upper limit of normal. Mild and moderate elevation of the serum iPTH was observed in 15.4% (n=2) and 7.7% (n=1) respectively.

In the non-diabetic population recruited in the study, 72.9 %(n=35) were found to have hyperparathyroidism. 48% (n=17) of the non-diabetics had severe elevation, 31.4% (n=11) with mild elevation and 20% (n=7) with moderate elevation of serum iPTH. Table 12 illustrates the distribution of iPTH levels above upper limit of normal (hyperparathyroidism) in diabetics and non-diabetics.

Table 12 Distribution of the CKD patients with hyperparathyroidism

Parameter	No of Patients	Mild(>65 - ≤1.5x65pg/ml)	Moderate(1.5x65 - 2x65pg/ml)	Severe(> 2x65pg/ml)	Total within group(%)
Diabetic	78	2(15.4)	1(7.7)	10(76.9)	13(27.1)
Non-Diabetic	136	11(31.4)	7(20.0)	17(48.)	35(72.9)
Total within category		13	8	27	48(100)

In this study, each stage of CKD observed hyperparathyroidism. In Stages one and two 4.2% had hyperparathyroidism one male was found with severe elevation of serum iPTH while in stage 2 disease, one male had mild elevation of iPTH. No female in stages 1 and 2 disease had hyperparathyroidism.

In Stage 3 CKD, 12.5% (n=6) had hyperparathyroidism, 5 cases (3 male and 2 female), with severe elevation of serum iPTH and 1(female) case with mild elevation. There was no statistical difference s between gender, $p = 0.500$.

Stage 4 CKD, 27.1% (n=13) had hyperparathyroidism, 6 cases had mild, 4 had moderate and 3cases (all females) had severe, elevation of serum iPTH.

Stage 5 CKD had majority of the cases with hyperparathyroidism, 56.3%. 5 had mild elevation of serum iPTH, 4 had moderate elevation and 18 cases, 13 of which female, had serum iPTH elevated more than 2 times the upper limit of normal.

This study showed a trend to more women registering high iPTH levels 66.7% compared to males 33.7% Tables 13 illustrate the distribution of hyperparathyroidism f or each stage of CKD, while table 14 illustrates the male and female distribution for each category of iPTH elevation.

Table13:Distribution of the hyperparathyroidism for each stage of CKD

CKD stage	% with Hyperparathyroidsim
Stage 1 &2(n=2)	4.2
Stage 3(n=6)	12.5
Stage 4(n=13)	27.1
Stage 5(n=27)	56.3
Total	(100%)

Table 14 Distribution by gender for each category of serum iPTH elevation for each stage of CKD

NFK-K/DOQI CKD Stage	Mild Elevation (>65 - ≤1.5x65pg/ml)		Moderate (1.5x65 - 2x65pg/ml)		Severe (> 2x65pg/ml)		Total
	Male	Female	Male	Female	Male	Female	
Stage 1(≥90ml/min/1.73 m2)	-	-	-	-	1	-	1(2.1)
Stage 2 (60 - 89ml/min/1.73m2)	1	-	-	-	-	-	1(2.1)
Stage 3(30 - 59ml/min/1.73m2)	-	1	-	-	3	2	6 (12.5)
Stage 4(15 - 29ml/min/1.73m2)	2	4	1	3	-	3	13(27.1)
Stage 5(< 15ml/min/1.73m2)	2	3	1	3	5	13	27(56.3)
Total	5	8	2	6	9	18	48
	(38.5%)	(61.5%)	(25%)	(75%)	(33.3%)	(66.7%)	(100%)

Biochemical Evidence of Bone Disease

The prevalence of biochemical mineral bone disease was observed in 65% (n=139) of the total patient population. There was significantly more low turn-over bone disease observed in 50.9%(n= 109) of the patients, with biochemical evidence of mineral bone disease, than the high turn-over disease observed in only 14.0%(n=30) patients. Normal turn-over was documented in 35%(n=75) . Fig 4 and Table 15 below illustrate the distribution of biochemical bone turn-over in the study population

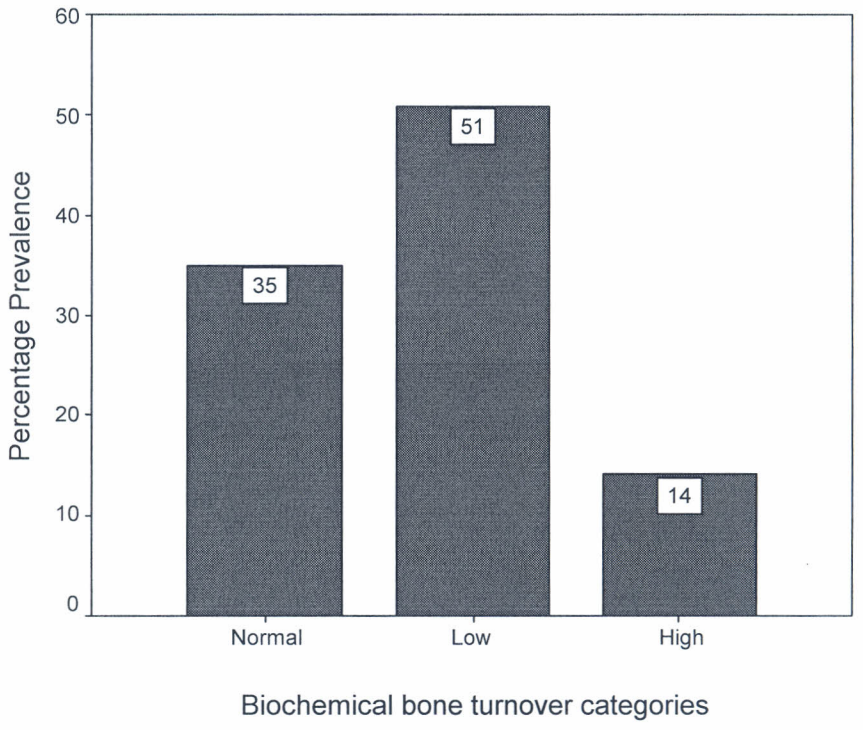


Fig 4 Biochemical Mineral Bone turn-over categories

Table 12 Distribution of Biochemical Mineral Bone Turn-over in CKD patients

Biochemical bone turn-over	Number	Percent
High turn-over (ALP >200IU + iPTH >1.5x65pg/ml=97.5pg/ml)	30	14.0%
Low turn-over(ALP <82.5+ iPTH ≤65pg/ml)	109	50.9%
Normal turn-over(ALP>82.5IU/L iPTH≤65pg/ml)	75	35.0%
Total	214	100.0%

The distribution of biochemical evidence of CKD- mineral bone disease (CKD-MBD) was as follows:

CKD stage 1: the distribution biochemical low turn-over bone disease was equal amongs males and females, no evidence of high turn-over bone disease was noted.

CKD stage 2: 46.7% of females compared to 53.3% males have low turn-over disease while no evidence of high turn-over bone disease is noted.

CKD stage 3: 53.5% of females compared to 46.5% in males have low turn-over disease. High turn-over disease is observed in an equal proportion between males and females.

CKD stage 4:52.4% males compared to 47.6% of females have evidence of low turn-over disease and 71.4% females compared to 28.6% males have high turn-over bone disease.

CKD stage 5: 46.2% of males compared to53.6% females have biochemical evidence of low turn-over disease while 58.8% in females compared to 42.1% in males have high turn-over disease.

There seemed to be a trend towards women having more biochemical high turn-over bone disease compared to men in stages 4 and 5, however the difference did not reach statistical significance. Table 16 illustrates the distribution of biochemical bone disease for each stage of CKD.

Table 16 Distribution of biochemical evidence of bone disease for each stage of CKD

NFK-K/DOQI staging of Chronic Kidney Disease	**Low turn-over (iPTH≤65pg/ml , ALP<82.5 IU/L)**		**High turn-over (iPTH>97.5pg/ml, ALP>200 IU/l)**		**Chi square**
	Male (%)	**Female (%)**	**Male (%)**	**Female (%)**	
Stage 1(≥90ml/min/1.73m2)	50	50	0	0	
Stage 2 (60 - 89ml/min/1.73m2)	46.7	53.3	0	0	
Stage 3(30 - 59ml/min/1.73m2)	53.5	46.5	50	50	0.367
Stage 4(15 - 29ml/min/1.73m2)	52.4	47.6	28.6	71.4	0.438
Stage 5(< 15ml/min/1.73m2)	46.2	53.6	42.1	58.8	0.715
Total(139)	55(100%)	54(100%)	12(100%)	18(100%)	

This study compared the mean iPTH levels for stages 3 to 5 according to the NFK-K/DOQI 2003 guidelines and found that 9.1%(n=17) of the study population, in stages 3 to 5, within the recommended guideline.

In stage 3 of CKD 10% (n=7), stage 4 2.4%(n=1) and Stage 5 12.2%(n=9) were within K/DOQI target levels. Majority of the patients 81.8%(n=151) were below target levels while 10.2%(n=19) where above the K/DOQI target levels. Table 17 demonstrates the distribution of iPTH levels in comparison to K/DOQI recommendations

Table 17 Comparison of the levels of iPTH for each stage of CKD with K/DOQI guidelines

CKD stage	**Serum iPTH pg/ml as per K/DOQI guidelines**	**No within guidelines**	**%within guidelines**	**No above guidelines**	**% above guidelines**	**No below guidelines**	**% below guidelines**
Stage 3(N=70)	30-70	7	**10**	5	7	58	83
Stage 4 (N=42)	80-100	1	**2.4**	7	16.6	34	81
Stage 5(N=74)	150-300	9	**12.2**	7	9.4	59	78.4
Total		17	**9.14**	19	**10.21**	151	**81.8**

Other Laboratory parameters

Mean levels of serum phosphorus progressively increased from stages 1 to 5. When the relationship between serum levels of phosphorus and levels serum iPTH was evaluated, there was a very significant positive association between serum phosphorous and iPTH, $r^2 = 0.069$, $p < 0.001$.

The mean serum alkaline phosphatase levels were all above the upper limit of normal for all stages of CKD and no difference between females and males was established

There was, however, no significant association between serum alkaline phosphotase and level of elevation of serum iPTH $r^2 = 0.012$, $p = 0.112$.

The mean corrected calcium levels were all below the lower limit of normal in both females and males.

There was no association between the corrected serum calcium and iPTH, $r^2 = 0.004$, $p = 0.404$.

Table 18 illustrates the mean levels of alkaline phophotase, calcium, phosphorous for each stage of CKD and the significance of association with serum iPTH.

Table 18 Mean levels of calcium, phosphorous and alkaline phosphotase in for each stage of CKD and association with serum iPTH

Parameter	Stage 1 (n=7)	Stage 2 (n=21)	Stage 3 (n=70)	Stage 4 (n=42)	Stage 5 (n=72)	P value
Mean Corrected Calcium	1.76±0.54	1.80±0.35	1.78±0.44	1.74±0.49	1.74±0.49	0.11
Mean Phosphorous	1.08±0.59	1.07±0.30	1.33±0.44	1.51±0.47	2.24±0.73	**0.00**
Mean Alkaline Phosphotase(ALP)	184.57±114.12	178.67±86.67	235.04±130.35	277.95±205.51	260.46±175.37	0.40

Normal Reference ranges

Serum calcium 2.02-2.65μmol

Serum phosphorous 0.81-1.62 μmol

Serum alkaline phosphotase 42-141IU/L

Heamoglobin and CKD

Heamoglobin levels were recorded in 99 patients and the mean heamoglobin level significantly decreased with decreasing eGFR, as the stage of disease worsened, from a mean heamoglobin level in CKD stage 1of 12.7g/dl to a mean heamoglobin of 8.24g/dl in CKD stage 5. Table 19 illustrates the mean heamoglobin levels for each stage of CKD.

Table 19 Mean levels of haemoglobin for each stage of CKD

K-K/DOQI KD Stage	Number (%)	Total	Males		Females		
		Mean Hb g/dl	No	Mean Hb level g/dl	No.	Mean Hb level g/dl	Student's t test
tage 1(>= 90ml/min/1.73m2)	3(3.0)	12.7	1	11.3	2	13.4(1.83)	0.522
tage 2(60 - 89ml/min/1.73m2)	8(8.1)	11.74	2	11.46(±4.03)	6	11.84(±1.82)	0.378
tage 3(30 - 59ml/min/1.73m2)	32(32.2)	11.62	20	11.58(±3.08)	12	11.67(±1.20)	0.921
tage 4(15 - 29ml/min/1.73m2)	17(17.2)	9.94	8	10.16(±2.37)	9	9.75(±1.73)	0.684
tage 5(< 15ml/min/1.73m2)	39(39.4)	8.24	16	9.07(±2.52)	23	7.68(±2.01)	0.063
otal	99(100)		47		52		

Serum PTH and musculoskeletal system

History of musculoskeletal complaints were observed in 74.7% of the study population, muscle pain was the most common complaint 33.6%(n=72) , followed by bone pain 31.3%(n=67) and 9.8%(n=21) of these patients had history of previous fractures.

There was a significant association between iPTH and history of muscle pain, p=0.048. Those with high iPTH tended to have had muscle pain for longer duration.

There was no association, however, between history of bone pain and previous fractures.

Table 20 illustrates the number of musculoskeletal complaints recorded amongst the study population

Table 20 Major Musculoskeletal Complaints of study patients

Parameter	Frequency	Percentage
Muscle pain	72	33.6
Bone pain	67	31.3
Fractures	21	9.8
Total	160	74.7

Musculoskeletal abnormalities were observed in 61.8% of the study patients on physical exam, most common finding was restricted joint movement 44.9%, followed by lumbosacral spine tenderness16.4%. There was no association between iPTH levels and restricted joint movements, however there was a significant association between level of iPTH and presence of spinal pain. Those with lumber pain were found to have longer durations of pain compared to those with iPTH levels below the lower limit of normal, 31.4% compared to those with levels above the upper limit of normal. Table 21 shows the various musculoskeletal abnormalities found in the study population.

Table 21 Major Musculoskeletal abnormalities in study patients

Parameter	**Frequency**	**Percentage**
Restricted joint movement	96	44.9
Lumbar tenderness	35	16.4
Proximal weakness	1	0.5
Total	132	61.8

Serum PTH and the Cardiovascular System

About half of the study population had cardiovascular abnormalities, 50.4%, with probable LVH, defined by displacement of the apex beat 1.5-2 cm to the left of the mid-clavicular line (MCL),being the predominant abnormality observed in 37.9%. Table 22 shows the distribution of cardiovascular abnormalities found in the study patients

Table 22 Major Cardiovascular abnormalities in study patients

Parameter	Frequency	Percentage
Probable LVH(displaced apex beat 1.5-2 cm to left of MCL)	84	37.9
CCF(increased jvp, basal creps, peripheral oedema)	15	7.6
Gallop rhythm	8	4.2
Other(bradycardia, absent brachial pulse)	2	0.7
Total	109	50.4

A Fluid overloaded state was the observed in more than half(52.1%) of the study population. Pulmonary oedema being the commonest finding 20.7%. peripheral odema was seen in form of ascites18.3% and pedal oedema13.1%. Table 23 illustrates the distribution of fluid-overload related symptoms in the study population.

Table 23: Distribution of fluid-overload related symptoms in the study population

Parameter	Frequency	Percentage
Pulmonary oedema	44	20.7
Ascites	39	18.3
Pedal oedema	28	13.1
Total	111	52.1

Serum PTH and the Central nervous system

Only 12.7% of the study population had signs of central nervous system disturbance. The commonest was slowed mentation, 4.3% had hemi-paresis. 1.4% had peripheral neuropathy and 1.0% other disturbances. Table 24 illustrates the central nervous system abnormalities found in the study population.

Table 24 Major Central Nervous System abnormalities in the study population

Parameter	**Frequency**	**Percentage**
Slowed mentation	13	6.0
Residual hemiparesis (stroke)	9	4.3
Peripheral neuropathy	3	1.4
Other(visual loss, tremors)	2	1.0
Total	28	12.7

Discussion

Secondary Hyperparathyroidism develops early and shows a progressive worsening during the course of CKD. Higher PTH levels have been associated with multiple complications, including bone disease, uremic pruritus, cognitive and sexual dysfunction, as well as higher cardiovascular morbidity and mortality [19].

This study demonstrates a number of key findings, some of which corroborate previous work, and some of which are novel.

As per K/DOQI staging of chronic kidney disease, this study found, majority of the study patients were in CKD stage 3, 4 and 5 comprising n=70(32.7%), n=42 (19.6%) and 34.6%(n=74) respectively with the highest numbers being observed in stage 5.

This study provides a description of patterns and prevalence of hyperparathyroidism , specifically elevated levels of serum iPTH and biochemical bone turn-over, from stages 1 to 5, in a cohort of 214 pre-dialysis patients in a single centre, the Kenyatta National hospital renal clinic

Analysis shows the overall prevalence of hyperparathyroidism is 22.4%. This prevalence, of hyperparathyroidism, increases as renal function, eGFR, declines.

This finding is not a surprising finding as with a 50% reduction in GFR, abnormalities of mineral metabolism begin to occur and hyperparathyroidism develops as an adaptive mechanism to maintain calcium and phosphrous homeostasis. Hyperparathyroidism worsens as the kidney function deteriorates

and may progress ultimately to an advanced stage that is refractory to medical treatment.

Prevalence for each stage of CKD was 2.1% in CKD stages 1 and 2 respectively, 12.5% in stage 3, 27.1% in stage 4 and 56.3% in stage 5.

Levin et al (SEEK study) studied the prevalence of abnormal vit D, calcium, phosphorous and in 153 US centres. The study cohort comprised of 1860 pre-dialysis patients over 40yrs of age. SEEK study showed prevalance of elevated iPTH to be 12% in stage 1,17% in stage 2, 21% in stage 3 and 56%in stage 4 and 5.[9]

This study shows lower prevalence compared to the SEEK study. This could be attributed to the fact that our patient population was younger, the overall mean age being 51yrs compared to 70yrs in the SEEK study.

The smaller sample size in this study, 214 compared to 1860 in the SEEK , may also mask the true prevalence rates.

Rahmian et al, studied the prevalence of hyperparathyroidism in 80 hemodialysis patients in Iran and found a prevalence of 45%[87]

In comparison to Rahmian et al, this study had a much larger sample size of 214 compared to 80. He however studied exclusively stage 5 disease, hemodialysis patient, and therefore the prevalence of 56.3% in stage 5 disease in our population is comparable.

For the various patterns of serum iPTH elevation, this study showed lower prevalence, compared to what has been observed worldwide, of mild and moderate categories of iPTH elevation 27.1 % and16.7% respectively. However, this study found higher prevalence in the severe category of iPTH elevation 56.3% compared to western statistics. DOPPS (Dialysis Outcomes and Practice Patterns Study) is one of the largest observational studies to describe the state and consequences of mineral metabolism for representative

samples of hemodialysis facilities, from 7 countries(France, Germany, Italy, Spain, UK, US and Japan) described prevalence for various catergories to be 52% in mild, 21% for moderate and 25% had severe elevation[10]. The fact that DOPPs was carried out in dialysis population, unlike this study carried out in a pre-dialysis population, may explain the difference.

Gutiérrez et al studied 1860 patient, the SEEK cohort, to determine the severity of disorded mineral metabolism in blacks. The black population was 227, and found more severe iPTH elevation of 65%, higher than non blacks who had 38%. This is in keeping with our study that showed 56.3% in the severe elevation category.[9]

The study showed that there was more low turn-over bone disease observed in 50.9%(n= 109) high turn-over disease 14.0%(n=30) patients while normal turn-over was documented in 35%(n=75).

Patel et al, sought to determine the clinical, biochemical evidence of renal ostoedystrophy in 41 renal failure and included both a pre-dialysis and on dialysis population[26].

Patel found 60% high turn-over disease using iPTH ,this study is in contast with Patel's study. However, Patel included patients already on heamodialysis , in stage 5 disease, and her sample size was much smaller than this study 41 compared to 214.

The study showed that there was significantly more low turn-over bone disease observed in 50.9%(n= 109) of the patients, with biochemical evidence of bone disease, compared to high turn-over disease observed in only 14.0%(n=30) patients, while normal turn-over was documented in 35%(n=75) .

Barreto *et al* studied 97 patients for one year to assess, in a cohort of patients undergoing intermittent hemodialysis in São Paulo, Brazil, to what extent the intact PTH range of 150-300 pg/ml reflected normal bone turnover. They obtained a bone biopsy in each of them at baseline and a repeat biopsy in 64 of them 12 months later. Barreto et al found two-thirds of those subjects whose baseline PTH was in K/DOQI range had low-turnover bone disease on the basis of bone histomorphometry .*[88]*

Ferreira *et al* (Portugal) in a randomized open-label study comparing the effects on bone histology of sevelamer hydrochloride with those of calcium carbonate at baseline, and again after one year of follow-up,found prevalence of low-turnover bone disease despite well-controlled serum calcium, phosphorus, and intact PTH levels.[88]

Barreto et al and Ferreira et al showed high prevalence of low turn-over disease in brazillian and pourtuguese populations, this is a similar finding to this study.

One could speculate, firstly that the reference ranges for dynamic parameters of bone turn-over that were established in a control population of North America, with possibly a higher degree of vitamin D insufficiency and higher serum PTH levels than in the general population of Brazil, Portugal and possibly Kenya.

Secondly, factors other than PTH play a role in the regulation of bone formation and resorption. This may include age, diabetes, growth factors, cytokines and diet.

Thirdly, that there exists ethnic differences in bone turn-over.

This study showed a trend to more women registering high iPTH levels 66.7% compared to males 33.7%.

The mean age of women in this study, however, was 47.75yrs. Most of these woment would be assumed to be peri-menopusaul or menopausal conditions known to be associated with higher bone resorption.

Rahimain et al, who studied prevalence of hyperparathyroidism in 80 patients, from Iran, found no significant relationship between level of serum iPTH elevation and age, p=0.89 or gender, p=0.87. [86]

This finding of gender difference was also in contrast to study done by Guiterrez et al. Gutiérrez et al who studied 1860 patient, the SEEK cohort, to determine the severity disorded mineral metabolism in blacks and non blacks,227 of whom were black, did multivariable linear regression models adjusted for age, gender, and found no significant association with iPTH levels[9].

There was, a trend towards lower mean levels of iPTH, in diabetics. The diabetic population with hyperparathyroidism were fewer 27.1% compared to non-diabetics 72.9%. However, no significant association between presence of diabetes and intact PTH elevation was found, p=0.204(t=1.176).

Inaba et al in Japan carried out a study on 197 male patients, to determine whether PTH secrection might be impaired in diabetic patients on dialysis compared to non-diabetics and found that mean serum PTH was significantly lower in diabetic patients 136±129.0pg/ml comapared to those without 260.5±231.6 ,$p<0.05$.[91]

This study was in keeping with findings of Inaba et al, the possible explanation being firstly, that increased amounts of advanced glycemic end products may interfere with PTH secretion. Lower levels of insulin growth like factor, reduced

osteoblastic life span have also been postulated as another factor in diabetics compared to non-diabetic population[92].

This study found patients with iPTH levels above the upper limit of normal appeared to be younger with a mean age of 45.94±16.23 compared to those with iPTH levels within the normal limit of normal mean age 54.67±16.79,$p<0.00$.
This association with age was in contrast Gutiérrez et al studied 1860 patient, the SEEK cohort, to determine the severity disorded mineral metabolism in blacks and non blacks,227 of whom were black did and found no significant association[9].
Similarly, Rahimain et al, who studied prevalence of hyperparathyroidism in 80 patients, from Iran, found no significant relationship between level of serum iPTH elevation and age,$p=0.89$[86].

This study compared the mean iPTH levels for stages 3 to 5 according to the NFK-K/DOQI 2003 guidelines and found that 24.6% of the study population within the recommended guideline.
In stage 3 of CKD 10%, stage 4 CKD 2.4% and Stage 5 CKD 9% were within K/DOQI target levels. Majority of the patients 81.8% were below target levels while 10.2% where above the K/DOQI.
This study is in keeping with Sankarasubbaiyan's et al study, a descriptional study to determine the spectrum of biochemical abnormalities in HD patients in South India. Study population was115 patients, found that two thirds of the study population had serum iPTH levels lower than the upper limit of normal compared to the K/DOQI target levels [90].

NFK-K/DOQI guidelines were made on evidence in the 1990s when second generation assays were used to determine iPTH, these assays recognize PTH

fragments other than only large C-PTH fragments and may therefore exaggerate the level of elevation[85,86].

NF-K/DOQI guidelines were made based on studies carried out in European and American centres and one could speculate that there exists ethnic differences in deficiencies of vitamin substrate being more in the western poupulations or vice versa.

Serum phosphorus shows there is a slight decrease at stages 2 and 3 with respect to stage 1 and a progressive increase in stages 4 and 5. There was a very significant association between serum phosphorous and iPTH, r^2=0.069, p=0.000.

This was an expected finding because as the number of functioning nephrons decrease, the failing kidneys are unable to excrete phosphorus and a progressive increase in serum phosphorus levels ensues.[47-55]

The SEEK study showed, multivariable linear regression models adjusted for age, gender, diabetes, body mass index, and eGFR, Black, race was independently associated with increased log phosphorus (β = 0.11, P = 0.04), that is a 4% higher phosphorous level than non blacks.[9]

There was no a significant association between serum alkaline phosphotase and iPTH r^2=0.012, p=0.112. The mean serum alkaline phosphatase levels, however, were above the upper limit of normal and no difference between females and males was established.

Baradarani et al studied the correlation of serum PTH with hypertension in 78 Iranian patients on HD and found a significant positive correlation between serum PTH and serum ALP r2=0.302,p=0.005. However, Barandani et al had a much smaller sample size of 78 compared to 214in this study.[95]

The SEEK study showed, in a multivariable linear regression models adjusted for age, gender, diabetes, body mass index, and eGFR, that black, race was

independently associated with increased log alkaline phosphatase (β = 0.12, P<0.01, that is a 14% higher alkaline phosphatase compared to non-blacks. [9]

There was no association between the corrected serum calcium and iPTH, r^2=0.004, p=0.404. However, the mean corrected calcium levels below the lower limit of normal in both females and males.

This was an unepected finding as hypocalcemia causes inactivation of the CaRs on the parathyroid glands and results in an increase in PTH secretion. PTH, in turn, stimulates the release of calcium and phosphorus from the bone and increased activation of vitamin D, resulting in increased intestinal absorption of calcium as the body attempts to maintain normal calcium homeostasis[42-45].

This study found that haemoglobin level significantly decreased with decreasing eGFR, as the stage of disease worsened, from a mean haemoglobin level in CKD stage 1of 12.7g/dl to a mean haemoglobin of 8.24g/dl in CKD stage 5

High PTH levels may contribute to anemia by directly inhibiting the production of red blood cells and increasing their fragility, thereby shortening cell survival. Secondary HPT can also cause marrow fibrosis, further decreasing the production of red blood cells. Data indicate that the response to Erythropoetin alfa therapy in these patients depends largely on the extent of bone marrow fibrosis [96].

Goiccoechea et al studied the effect of calcitarol in decreasing the need for erythropoietin; found that an increase in hemoglobin level, in response to calcitorol therapy, was associated with decrease in PTH levels [97].

Limitations of the study

- The study was performed in a single renal clinic, localised at K.N.H (Nairobi) and the results may not be generalizable to the CKD population in Kenya.
- PTH levels were used as surrogate markers for bone turnover instead of bone biopsies (tetracycline labelled) to confirm the pattern of bone disease. Biopsies were not carried out due to logistical and financial constraints.
- This study was unable to rule out primary parathyroid disease.

Conclusion

This study demonstrated that hyperparathyroidism develops and progressively worsens as glomerular function declines.

However, the overall prevalence of hyperparathyroidism in CKD patients attending renal clinic at the Kenyatta National hospital was observed to be lower than it is worldwide.

This study showed a trend towards more women registering higher iPTH levels than the males. Biochemical high turn-over mineral bone disease was observed more in women, with CKD, than the men.

In comparison to statistics from western countries, there seems to be more biochemical low turn-over mineral bone disease in our patients as opposed to more high turn-over mineral bone disease in the western populations.

Recommendations:

- Serum PTH levels should be sought early especially in CKD stages 3 to 5.
- Serum PTH should be done on all dialysis patients to allow for adequate therapeutic management.
- Studies should be carried out to determine whether there exists a gender predilection towards high PTH levels.
- Larger multicentre study should be carried out to compare whether there is indeed a lower prevalence of hyperpathyroidism in our population.
- A study should be carried out, using tetracycline labelled bone biopsies, to establish the actual bone turn-over in these patients with biochemical evidence of bone disease.

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APPENDIX 1
Statement of Information Form

PREVALENCE AND PATTERNS OF HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE PATIENTS AT THE KENYATTA HOSPITAL

Statement of Information for Patients Participating in the Study

Purpose of the Study

I, Dr. Anne Mugera, am undertaking a study to learn about the prevalence and patterns hyperparathyroidism and mineral bone disease in patients diagnosed to have chronic Kidney disease at Kenyatta National hospital. Parathyroid hormone is one of the proteins in the body that helps regulate calcium. The study is being conducted at this hospital with cooperation from the staff and permission from the hospital administration.

Procedures

You are being asked to participate in a survey that will take between 45 and 60 minutes. If you agree to participate, I will ask you the questions and note your responses in writing. I will then examine you and may send you to the laboratory for blood tests. I will inform you of the test results. I will then, enroll you into clinical care the same day. All the results will remain confidential. The purpose of this consent form is to ask your permission to do so. If you agree to participate, I shall ask you to sign the consent form. However, this form will not be linked to your answers. Your individual responses will be seen only by the researchers, and will be stored in a locked place under their control.

The risks to you as a participant in this study include:

- Pain in the cubital region on your arm upon venepuncture
- Swelling at the venepuncture site may appear, this collection of blood under the skin(haematoma).

  NB: Should any of the above happen to you, feel free to contact Dr Anne Mugera for examination and management.

The benefits to you as a participant in this study include:

- Free evaluation of your current kidney function tests
- Free estimation of your Glomerular filtration Rate
- Free evaluation of the level of your parathyroid hormone(protein which helps with control of the calcium metabolism in the body)
- Free evaluation of any biochemical evidence of bone abnormalities
- A free copy of your results will be availed to you upon request
- The findings of this study may identify ways of delaying the progression of complications of kidney disease.

Right to Refuse or Withdraw

Your participation in this research is voluntary. You do not have to participate. If you do choose to participate, but prefer not to answer certain questions, you are free to do so. You are also free to terminate the interview and withdraw from the study at any time.

You are free to ask questions before signing the consent form. If you agree to participate in the study, please sign on the consent form.

Appendix 2

CONSENT FORM

I, _____ consent to participate in the study on prevalence and patterns of hyperparathyroidism in chronic kidney disease patients at the Kenyatta hospital. I do this with the full understanding of the purposes of the study and the procedures involved which include filling out a study questionnaire and having laboratory tests, all of which have been explained to me by Dr. Mugera/ her assistant.

Signature of patient _____

Signature of witness _____

Date _____

If you have questions during the course of the study, you may contact the following:

Dr. Anne Mugera

Mobile Phone: 0722- 747-695

OR

The Chairman of Ethical and Review Committee

Kenyatta National Hospital

Tel:020-2726300/0722-829500/0733-606400 Ext :44102

IDHINI

Nambari ya hospitali..... Umri.....

Mimi.....
natoa idhini mwenyewe bila aina yoyote ya kushurutishwa au kulazimishwa kushiriki katika utafiti uliotajwa hapa kuhusu utafiti wa kiwango cha hormoni inioitwa "parathyroid" na ugonjwa wa mifupa kati ya wagonjwa wa figo. Nimeelezwa kikamilifu kuhusu madhumuni na hali yake na naelewa kuwa nitaulizwa maswali kadha na nipimwe damu. Pia naelewa kuwa naweza kujiondoa wakati wowote iwapo nitabadilisha mawazo.

Sahihi ya mshiriki _____

Sahihi ya Shahidi _____

Tarehe _____

Ukiwa na swali au jambo lolote unaitaji kuelezwa zaidi tafadhali wasiliana na Dkt. Anne Mugera kwa nambari ya simu ifuatayo: 0722 747 695.

Asante

INVESTIGATOR'S STATEMENT.

I the investigator have educated the research participant on the purpose and implications of this study.

Signed..... Date.....

Appendix 3

SCREENING QUESTIONAIRE

PREVALENCE AND PATTERNS OF HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE PATIENTS AT THE KENYATTA HOSPITAL

SCREENING NUMBER | 0 | | | |

Date ____/____/_____

Weight Kg

Previous Serum Creatine (micromol)

Calculated GFR ml/min/1.73m2

2 Are You Known To Have (BE)/Been On Any Of The Following?

YES = 1 NO=2

Question	Yes=1	No=2
GFR >60ml/min/1.73m2 =1 **GFR<60ml/min/1.73m2=2**		
Dialysis sessions		
Diabetes Mellitus		
Menopausal (stopped experinecing monthly periods)		
Contraceptives/Steroids/ Thiazide		

Diuretics/AED (antiepileptic drugs)		
Thyroid(Goitre)/Parathyroid Disease		
Cancer Of Any Kind		
Bedridden For any reason		
SUM TOTAL		

ABSOLUTE TOTAL= [ ]

The study is interested in persons with none, with exclusion of Diabetes Mellitus, of the above. Therefore:

If total 14 to 16 Recruit into study and issue Study Number | **0** | | | |

If total<=8 Do Not Recruit

ELIGIBILTY

Are you willing to participate in the study prevalence and patterns of hyperparathyroidism in chronic kidney disease patients at the Kenyatta Hospital?

YES=1 N0=2 [ ]

APPENDIX 4

STUDY QUESTIONAIRE

PREVALENCE AND PATTERNS OF HYPERPARATHYROIDISM IN CHRONIC KIDNEY DISEASE PATIENTS AT THE KENYATTA HOSPITAL

PATIENT RECORD FORM

I. GENERAL DATA

Study number | 0 | | | |

Hospital number | 0 | | | | | | | | |

Date of first visit | | | | | | | Study Date | | | | | | |

Day Month Year Day Month Year

NAME: | | | | | | | | | | | | | | | | | | |

Last name First name Middle Name

SEX: | | 1=Male 2=Female

DATE of Birth: | | | | | | Day Month Year

Kenyan Resident 1=Yes 2=No | | If No Specify _____

Physical address: (District/Estate/Village/Location) _____

_____

Telephone number: _____

Civil status: [ ]

1= Married 2= Single 3= Widowed 4= Separated 5= Other

Highest educational attainment: [ ]

1= No formal education 2= Primary 3= High school 4= College/University

Present occupation: [ ]

1= Employed 2=Self Employed 3= Retired 4=Other

II. MEDICAL HISTORY

Any complaints: **YES=1 NO=2** [ ] If yes specify

History of present illness

Do you have any of the following: **YES=1 NO=2 (** Tick Me **)**

Reduced Urine Output [ ] (0-3months [ ] 3-6months [ ]
6-12months [ ] >12 months [ ])

Blood in Urine [ ] (0-3months [ ] 3-6months [ ]
6-12months [ ] >12 months [ ])

Facial Swelling [ ] (0-3months [ ] 3-6months [ ]
6-12months [ ] >12 months [ ])

Bone Pain [ ] (0-3months [ ] 3-6months [ ]
6-12months [ ] >12 months [ ])

Location: Lumbar ☐ Hip ☐ Wrist ☐ Forearm ☐

Other_____

Muscle Pain (myalgia) ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Location: Lumbar ☐ Arms ☐ Hips ☐

Fractures ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Lumbar ☐ Hip ☐ Wrist ☐ Forearm ☐

Other_____

PAST MEDICAL HISTORY

Have you ever had any of the following? **YES=1 NO= (** Tick Me **)**

Diabetes Mellitus ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Hypertension ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Nephrotic Syndrome ☐ 0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Glomerulonephritis ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

SLE ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Rheumatoid Arthritis ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Hepatitis B ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Obstructive Nephropathy ☐ (0-3month ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Polycystic Kidney Disease ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

HIV(optional) ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

CURRENT MEDICATION

Are you on any of the following? **YES=1 NO=2(** Tick Me **)**

Drugs to lower blood pressure ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Drugs to lower blood sugar ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Drugs to lower calcium ☐ (0-3months ☐ 3-6months ☐

6-12months ☐ >12 months ☐)

Previous Laboratory results if any **YES=1 NO=2**(include date of examination)

UE/CR ☐ ☐☐☐☐☐☐

CALCIUM ☐ ☐☐☐☐☐☐

PHOSPHOROUS ☐ ☐☐☐☐☐☐

ALBUMIN ☐ ☐☐☐☐☐☐

PARATHYROID HORMONE ☐☐☐ ☐☐☐☐☐☐

III. PHYSICAL EXAMINATION

Weight (Kg) ☐☐☐ Height (cm) ☐☐☐

VITAL SIGNS:SBP(mmHg) ☐☐☐ DBPmmHg ☐☐☐

HR ☐☐☐ /min RR ☐☐ /min

TEMPERATURE ☐☐ ^{0}C

MUSCULOSKELETAL:

	Appearance Abnormal=1 Normal=2	**Movement** Abnormal=1 Normal=2	**Pain/Tenderness** Yes=1No=2
Gait			
Spine			
Arms			
Wrist			
Elbows			
Legs			
Hip			
Knee			

If any abnormality describe _____

HEAD EAR, NOSE THROAT:

Thyroid Enlargement ☐ Yes=1 No=2

Lymphadenopathy ☐ Yes=1 No=2 if any describe

System	Abnormality 1=Yes 2=No	If any Abnormality Describe
Cardiovascular		
Respiratory		
Gastrointestinal(Abdomen)		
Central Nervous System		

ASSESSMENT/ DIAGNOSIS [Tick Me]

[ ] definitive [ ] presumptive [ ] negative [ ] unknown.

Recommendations/Mangement _____

_____

_____

Interviewer:

_____

Signature over printed name/position

Appendix 5

LABORATORY PARAMETERS

BIOCHEMICAL PARAMETERS (MEASURED/CACULATED)

LAB EXAM	RESULT	Date	
Plasma intact PTH(pmol/L)			
Serum Creatinine (mmol/L)			
Calculated(GFR) creatinine clearance(ml/min/1.73m2)			
Serum Calcium (mmol/l)			
Serum albumin			
Corrected serum calcium(mmol/L)			
Serum Phosphorus(mmol/L)			
Serum Alkaline Phosphotase(IU/L)			
CKD(KDOQI) STAGE(2/3/4/5)		**BONE TURNOVER High/Low**	

APPENDIX 6

Criteria for Classification of Mineral Bone Disease and Patterns of Hyperparathyroidism

Mineral Bone Disease

TYPE OF BONE TURN-OVER	IntactPTH LEVELS(pg/ml)	ALKALINE PHOSPHOTASE LEVEL u/L
NORMALTURN-OVER	10 -65pg/ml	30-125 U/L
HIGH TURN-OVER	≥x1.5 normal iPTH	≥200U/L
LOW TURN-OVER	≤10pg/ml/or btw10-65pg/ml	≤82.5U/L

Patterns of Hyperparathyroidism

Pattern of Hyperparthyroidism	Intact PTH level (Normal intact PTH 15-65pg/ml)
Mild	Intact PTH{>65pg/ml to 1.5X upper limit of normal iPTH}
Moderate	IntactPTH {>1.5 to 2 X upper limit of normal iPTH}
Severe	Intact PTH >2 X upper limit of normal iPTH

KENYATTA NATIONAL HOSPITAL
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Email: KNHplan@Ken.Healthnet.org

Ref: KNH/UON-ERC/ A/121

11th December 2008

Dr. Anne N.N. Mugera
Dept. of Clinical Medicine & Therapeutics
School of Medicine
University of Nairobi

Dear Dr. Mugera

RESEARCH PROPOSAL: "PATTERNS AND PREVALENCE OF HYPERPARATHYROIDISM AND MINERAL BONE DISEASE IN PATIENTS WIT CHRONIC KIDNEY DISEASE AT THE K.N.H" (P308/11/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above cited research proposal for the period 11th December 2008 – 10th December 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. Prof. K.M. Bhatt, Chairperson, KNH-ERC
The Deputy Director CS, KNH
The Dean, School of Medicine, UON
The Chairman, Dept. of Clinical Medicine & Therapeutics, UON
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