Chronic Kidney Disease, Mineral Bone Disorder: Review and Appraisal

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ABSTRACT

To review available literature on mineral and bone disorders in patients with chronic kidney disease with the aim of promoting better understanding of the concepts of divalent ions bone disorders . It also aims to highlight new trends in the definition and management, with emphasis on recent treatment strategies focusing on molecular targets. as well as the emerging knowledge of this condition in our local practice. A literature search was done on chronic kidney disease–mineral bone disease, pathogenesis and treatment strategies using the electronic database; MEDLINE, EMBASE, OVID, Google Internet search engines (for local websites and medical journals) and relevant textbooks. Mineral bone disorder is one of the major complications in patients with chronic kidney disease. Normally in people with healthy kidneys, normal serum levels of phosphorus and calcium are maintained through the interaction of parathyroid hormones(PTH) and 1,25 $(OH)_2D_3$ (calcitriol), the active metabolite of vitamin D_3. However in Chronic Kidney Disease, this interaction is deranged . This could result in various types of bone diseases viz high turnover bone disease (osteitis fibrosa cystica) , low bone turnover disease or a mixed variety. The clinical features could be asymptomatic initially, but could later manifest as myopathy and bone pains with increased risk of fractures and metastatic calcification of soft tissues including lungs, kidneys and joints. Cardiovascular complications are among the common causes of morbidity and mortality.

In Nigeria, It was formerly thought to be rare due to the tropical diet and also the fact that due to lack of renal replacement therapy, patients with CKD did not live long enough to develop mineral bone disease. However, with more centers offering renal replacement therapy and more patients on long term haemodialytic support and the attendant better chances of survival, cases of CKD-MBD are increasingly being seen in our practice. Mineral bone disorders are a major complication of chronic kidney disease and the incidence with its attendant complications is increasing globally. Early recognition and detection and aggressive treatment with prescribed diets and medications must be pursued.

Keywords: *Mineral bone disease, chronic kidney disease*

INTRODUCTION

Chronic Kidney Disease (CKD) – Mineral Bone Disorder (MBD) is defined as a systemic disorder of mineral and bone metabolism due to CKD manifested by one or a combination of the following:

(i) abnormalities of calcium, phosphorus, PTH or vitamin D metabolism,

(ii) abnormalities of bone turnover, mineralization, volume, linear growth or strength and / or

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(iii) vascular or other soft tissue calcification.

It also encompasses renal osteodystrophy which is described as an alteration in bone morphology in patients with CKD[1].

The link between renal failure and bone disorders was first described by Lucas in 1883 when he reported an association between albuminuria and late rickets [2]. Sixty years later, the term renal osteodystrophy was coined to describe an interplay between vitamin D, parathormone and divalent ions in patients with chronic renal failure[3]. In the 70s, and 80s, osteomalacia was identified as a major cause of mineral bone disease especially the presence of aluminium in dialysis water and its use as phosphate binders[4]. Over the last two decades, there have been a renewed interest in the knowledge of metabolic bone disorders especially the identification of calcium sensing receptors (CaSR) and their cloning[5], changing bone patterns, the identification of newer vitamin D (third generation) analogues and vitamin D receptors[6] and lately the implications of mineral metabolism in cardiovascular disorders[7].

This new interest is also due to the increasing incidence especially in post renal transplantation patients and the consequent newer guidelines by associations such as NKF/DOQI and the British Renal Association (by way of dietary regime guide and medications)[1, 8, 9].

Normal Homeostasis of Calcium, Phosphorus, Vitamin D and Parathormone Calcium Homeostasis

The main sources of calcium in the diet include; milk, cheese, eggs, meats, peas, dried fruits and nuts. Calcium is absorbed actively from jejunum and passively from the ileum. Intake of vitamin D, acidic PH and presence of proteins in the food favour absorption.

The total body content of calcium is 1200g in an adult. This is present in the skeleton, teeth, plasma and in all tissues of the total body calcium. Ninety eight percent of the total body calcium is in bones as calcium phosphate (hydroxyapatite) held in a protein matrix (osteoid). In the plasma, 50% of the circulating calcium is in ionized form i.e. free calcium, 40% is protein bound and 10% is complexed with citrate and phosphate ions. Calcium gives the strength and rigidity to the skeleton. In the plasma, calcium is present as the free ions, albumin bound form and as complexes which are diffusible. In health, serum calcium level ranges from 9.0 – 10.5mg% (2.25-2.6mmol/L). Note that a decrease in serum albumin of 1g/dl is usually associated with a decrease of 0.8mg/dl in total calcium concentration. Calcium and phosphorus levels also vary inversely with each other and the Calcium **x** Phosphate product is almost constant around $40mg^2/dl^2$

Corrected serum calcium is calculated as; measured serum calcium + (0.8 x (4 - serum albumin in g/dl)). Calcium regulation involves three tissues, namely the bone, kidney and intestine. It also involves three hormones, PTH, calcitonin and activated vitamin D.

Phosphorus Homeostasis

The total body content of phosphorus is 800-900g and most of it in the body is present in the bones and teeth. In all tissues, this element is present intracellularly as phosphates. In the plasma, it occurs as inorganic phosphates at a concentration of 2.8 – 4.5mg/dl (0.81-1.45mmol/l). Around 88% of phosphorus is in ionic form and the rest is present in the protein bound form. Phosphorus is contained abundantly in eggs, cereals, meat and diary products. Normal diet supplies 800 – 1400mg/day while absorption from the gut is passive with 60 – 80% absorbed. The serum level is controlled mainly by the renal excretory mechanism. Around 85% of filtered phosphate is absorbed at the proximal tubule and only 10 – 15% is lost in urine. Negative phosphate balance is usually caused by the abnormalities of renal clearance of 1, 25 $(OH)_2$ D_3 which promotes absorption.

Apart from its role in stimulating the parathyroid gland and thus contributing to hyperparathyroidism, hyperphosphatemia (serum phosphates above 6.5mg/dl) represents an independent risk factor for death in patients treated with HD and death from cardiovascular causes account for the excess mortality [10]. A strong relationship has been found between cardiac deaths and factors that favour metastatic calcification (i.e hyperphosphatemia and increased ca **x** phosphate product)[11]. Serum phosphate has been found to stimulate the phenotypic transformation of vascular smooth muscle cells into osteoblasts capable of producing a 'promineralisation milieu'. In this circumstance, the supersaturation of extracellular calcium and phosphorus tend to accelerate the development of medial wall calcification which is associated with an increase in

arterial stiffness , left ventricular size and all cause mortality in patients on haemodialysis[10, 11].

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Homeostasis of Parathyroid Hormone

Parathyroid hormone (parathormone) is secreted by the chief cells of the parathyroid gland which are situated normally posterior to the thyroid gland. It is a single chain polypeptide having 84 amino acids encoded by a gene on the short arm of chromosome 11. It is secreted as a pre-prohormone with 115 amino acid residues and is further converted into a prohormone containing 90 amino acid residues. The active hormone contains 84 amino acid residues.

In circulation, PTH is a mixture of polypeptide chains of different biological activity. The secretion of PTH is controlled by several factors. Circulating ionized calcium exerts the major control of PTH secretion and release. A fall in ionized serum calcium stimulates PTH secretion while a rise in serum phosphate stimulates PTH secretion indirectly by decreasing calcium levels detected by specific calcium sensing receptors on the membranes of the parathyroid cells. PTH can be estimated by radioimmunoassay (RIA). Parathyroid hormone levels estimated by this method may not reflect true biological activity since a part of the estimated hormone may not be biologically active .It has a very short half life (2-4 minute) and the normal range of the intact PTH assay is 10-65pg/ml while the recommended target range for CKD stages 3, 4 and 5 are 35-70pg/ml, 70- 110pg/ml and 150-300pg/ml respectively(fig 1).

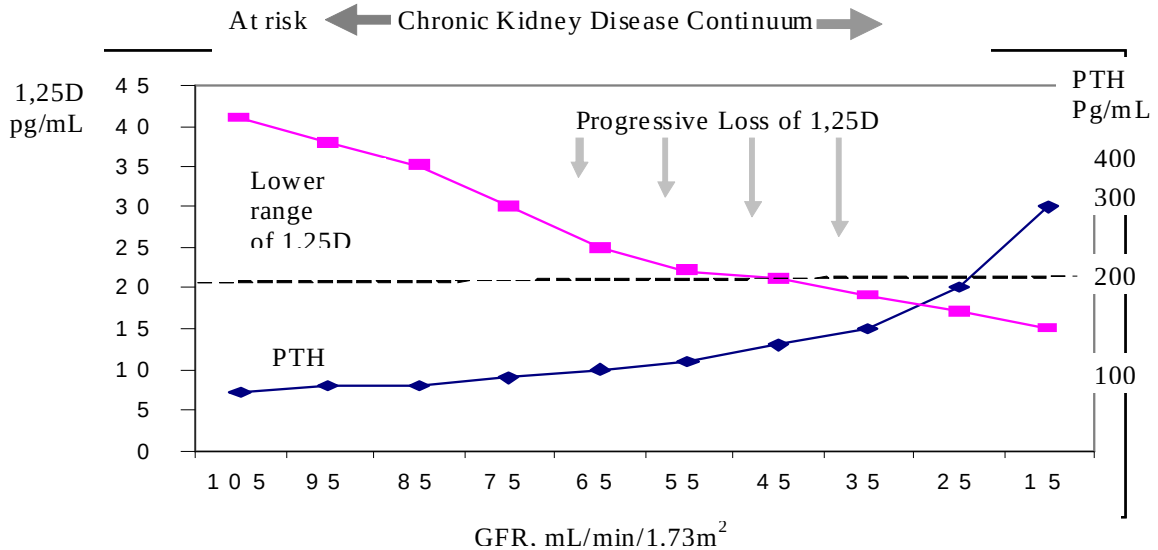
The ultimate effect of PTH is to conserve body calcium and increase its level in extracellular fluid. It exerts its functions in several ways and most of these are receptor mediated. These include increased distal tubular reabsorption of calcium, increased absorption of calcium from the intestine, increased renal excretion of phosphate and hydroxylproline resulting in decreased plasma phosphate. It also increases calcium resorption from bone, and raises serum calcium.

There are three molecular targets regulating parathyroid gland function. These are (i) the G protein-coupled calcium-sensing receptor (CaSR) which in conjunction with calcium is the major regulator of PTH transcription, secretion, and parathyroid gland hyperplasia; (ii) Vitamin D receptor (VDR) located in the parathyroid glands which is acted upon by calcitriol to suppress PTH transcription only and (iii) extracellular phosphate sensors which have direct effects on parathyroid production through the regulation of PTH message stability.

Homeostasis of Vitamin D

Vitamin D is obtained from the diet or produced in the skin as cholecalciferol (vitamin D_3) by sunlight photoactivation of 7-dehydrocholesterol. The latter is the primary source of vitamin D metabolites. Vitamin D_3 is transported to the liver via a Vitamin D-binding-protein (DBP) where it is converted by microsomal and mitochondrial hydroxylases to 25-

Figure 1 showing relationship of GFR to the PTH



Above illustration culled and modified from Nephrol Dial Transplant; 1996 (Suppl 3): 22-28.(with permission).

OHD_3 the major circulating form of Vitamin D. This is further transported via DBP to the kidney where it is converted to either the active vitamin D metabolite 1, 25 $(OH)_2D_3$. or to the less active form 24, 25 $(OH)_2D_3$. The enzymes responsible for these conversions are the cytochrome P_{450}-dependent 25-hydroxy 1α and 24 hydroxylases respectively. They are located in the proximal tubule and are responsive to PTH and to plasma phosphate concentration. Production of 1,25 $(OH)_2D_3$ is favoured by hypocalcemia, high PTH and low phosphate and its metabolism is tightly regulated and mediated via changes in serum calcium, phosphate and parathyroid hormone (PTH). 1, 25 $(OH)_2D_3$ has a variety of biological actions in the kidneys, bones and in the gut. It stimulates absorption of calcium and phosphate from the gastrointestinal tract via increase in the production of a specific calcium binding protein by duodenal and ileal cells where they increase active calcium transport. Phosphate absorption is also stimulated by 1, 25 $(OH)_2D_3$ This occurs in the duodenum and is independent of the Vitamin D induced effect on calcium absorption.

In the bone, 1, 25 $(OH)_2D_3$ is effective in promoting mineralization of osteoid, while it also has a role with PTH in promoting bone remodeling via resorption and remineralization i.e. facilitates deposition of calcium in bone. In healthy subjects, total vitamin D level is 35.0 ± 3.4mg/ml, while $25(0H)D_3$ and 1,25 $(OH)_2D_3$ are 28.5±2.0mg/ml and 35.0 ± 3 pg/ml respectively. In chronic kidney disease, circulating levels of $1,25(OH)D_3$ are low.(fig.2).

Pathogenesis of Mineral Bone Disorder in Chronic Kidney Disease

Normally the parathyroid hormones in conjunction with other phosphaturic hormones like phosphatonins and its derivatives like fibroblast growth factor 23 (FGF23) have an innate phosphaturic action by decreasing activity of the sodium phosphate cotransporter in the proximal renal tubule and facilitating the excretion of phosphates. However as early as stage II chronic kidney disease, when the GFR reduces, this phosphaturic action is blunted and the serum phosphate begins to rise (fig 2).

Vitamin D_3 is also reduced in chronic kidney disease owing to reduced 1α hydroxylation of vitamin D which occurs as a result of the reduced renal mass. Reduced vit D_3 leads to lower intestinal calcium absorption and ultimately low serum calcium. The low serum calcium stimulates parathyroid hormone synthesis.

Also as a result of this low serum calcium, the increased parathyroid hormone tries to normalize the serum calcium levels by acting on the bone by promoting phosphate excretion, hence a new steady state is achieved at the expense of hyperparathyroidism .A major characteristic of secondary hyperparathyroidism is increased parathyroid cell proliferation, as CKD progresses, this increase in cell proliferation results in diffuse parathyroid gland hyperplasia. Both hypocalcemia and hyperphosphatemia stimulate parathyroid gland proliferation and hyperplasia which also result in a decline in calcium sensing receptors CaR expression (a characteristic of actively proliferating cells of the parathyroid gland). (fig 2).

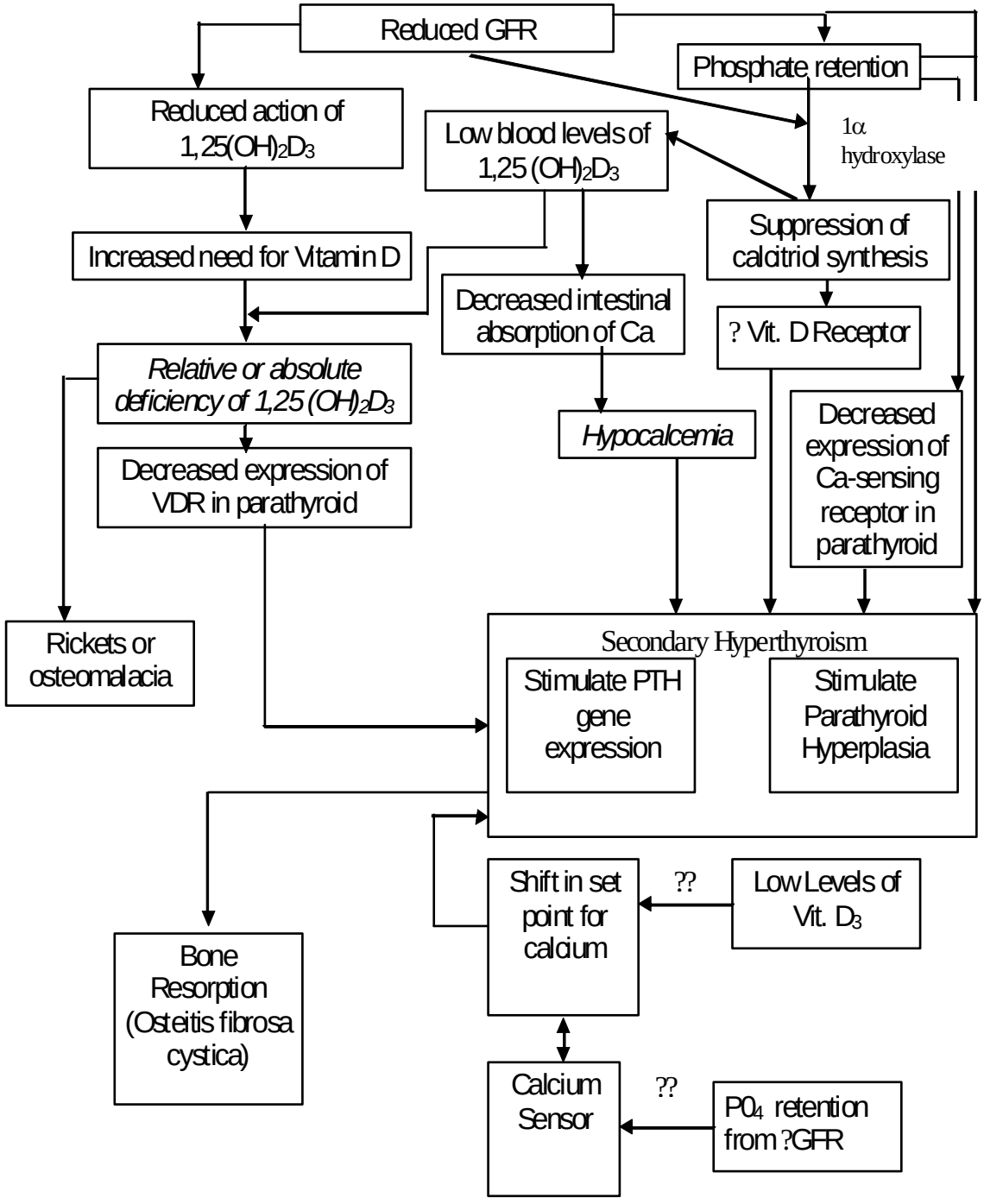
In summary, hyperparathyroidism in chronic kidney disease is as a result of a number of reasons viz; hyperphosphatemia resulting from reduced phosphate excretion which inactivates 1α hydroxylase leading to low vitamin D_3 synthesis; and low vitamin D_3 which reduces intestinal absorption of calcium. With the elevated phosphates, the serum calcium level goes down to achieve a constant solubility product. Low vitamin D_3 leads to reduced vitamin D_3 expression on the parathyroid, with the ameliorating effect on the normal inhibition of PTH secretion. Low serum calcium also inactivates Calcium sensing receptors on the parathyroid leading to enhanced PTH secretion, and when prolonged leads to hyperplasia. Elevated phosphates also stimulate PTH gene expression directly as a result of the increased parathyroid hormone.

Histological Classification of Bone Disease Associated with Chronic Kidney Disease

Bone disease associated with CKD has traditionally been classified according to specific histological types being due to different degree of bone turn over and impaired mineralization at the matrix. The high bone turnover type is osteitis fibrosa cystica while the low bone turnover types include osteomalacia and adynamic bone disease. It could also be a mixed variety i.e combination of high and low bone turnover [1].

I-PTH levels above 300pg/ml are associated with the high turn over type while the low turn over variety is suggestive in those with less than 150pg/ml

Pathogenesis of Abnormalities in Mineral Metabolism and Bone Disease in CKD



Modified from Pathogenesis of Abnormalities in mineral Metabolism and Bone Disease in CKD. From NKF/DOQI guideline, Handbook on bone metabolism and disease in chronic kidney Disease(CKD Stages 3-4)

Fig. 2: Showing the relationship between serum calcium, phosphates, vitamin D and hyperparathyroidism

[1]. Other markers of differentiating them include bone specific alkaline phosphatase levels, serum tartrate- resistant acid phosphatase-5b, osteocalcin and osteoprotegerin amongst others[12].

Clinicopathological Features

(i) High bone turnover disease-; this is typified by osteitis fibrosa cystica. It is caused by excess parathyroid hormone and it is characterized by increased bone turnover as evident by excessive proliferation and increase in size of the osteoclasts and osteoblasts, there is increased number of resorption lacunae with scalloped trabeculae. There is increased in the bone formation rate (BFR) with peritrabeculae fibrosis. The mineralization lag time is the mean time interval between osteoid deposition and its mineralization.

(ii) Low bone turnover disease; this could either be osteomalacia or adynamic bone disease [14]. Osteomalacia; this is caused by the accumulation of aluminium or other metals (strontium, iron) or diefficiency of 25 (OH) cholecalciferol or phosphate depletion. There is reduced bone turnover i.e. reduced osteoblastic / osteoclastic activity with increased mineralization lag time of more than 100 days relative to the normal time of 35days. The bone volume is low to medium. Aplastic/ Adynamic bone disease; this is caused by aluminium deposition. It may also be caused by parathyroid suppression and other factors such as deficiency of bone growth factors or increased suppression of bone remodeling. It may be associated with increased or reduced aluminium.It is seen more frequently in patients on long term peritoneal dialysis, diabetes mellitus and older patients. Histology shows more of osteoid tissues [14, 15].

(iii) Mixed disease; This is caused by a combination of secondary hyperparathyroidism and aluminium deposition or in some instances, the cause is unknown. The bone volume is normal; the turnover is increase, while the mineralization lag time is abnormal.

(iv) Aluminium related bone disease (ARBD); this may be caused by reduced renal excretion of aluminium, intake of aluminium salts as phosphate binders or dialysate aluminium concentration above 2-3mg/litre. There is extensive accumulation of aluminium at the mineralization front and this is diagnostic if it covers more than 15% of the trabecular surface and bone formation rate is reduced to less than the lower limit of normal (< 220mm^2/mm^2/day). Other features include reduced osteoblasts and increased osteoid volume [16]. Aluminium related bone disease could however be seen in any of the following:

(a.) Vitamin D resistant osteomalacia;

(b.) Specific adynamic bone disease; this is caused by excessive suppression of parathormone by 1, 25 dihydroxy cholecalciferol.

(c.) Mixed bone disease; this is characterized by a defect in matrix synthesis caused by PTH suppression and aluminium toxicity.

Clinical features of ARBD include severe diffuse bone pains, muscle weakness (especially in the upper limb), spontaneous fracture, neurological syndromes or microcystic anemia.

Diagnosis of ARBD is by detection of increased amount of aluminium in the serum > 50ug/ litre, slightly elevated calcium (which may increase with vitamin D dosing) and a normal serum alkaline phosphatase.

Early recognition of ARBD requires a desferrioxamine (DFO) test in combination with a serum iPTH measurement. DFO is a chelating compound that will liberate aluminium from the body stores, resulting in the formation of Aluminium –DFO complex (Aluminioxamine) to enter the bloodcompartment. A low dose of 5mg/kg is administered and aluminium estimation is done before and forty eight hours after the DFO challenge with a DC plasma emission spectrophotometer. An increase in serum aluminium after the DFO administration suggests the presence of ARBD. It is a useful test to differentiate patients with ARBD from those with an increased risk of aluminium toxicity and aluminium overload [16].

ARBD is prevented by avoiding aluminium in high risk patients (diabetics and children), avoiding concomitant administration of citrates in patients on

aluminium and reducing aluminium in dialysis solutions to less than 2-3ug/lit.

CKD MBD in Nigeria

Renal bone disease a few decades ago was initially thought to be rare in Nigeria and in the tropics for several reasons. The nature of the diet in the tropics was said to be protective partly due to limited intake of diary products; consumption of vegetables which contain phytates which mop up phosphates, food processing habits which encourage the use of large amount of water which is often decanted intermittently during cooking and by this the amount of phosphates is reduced; exposure to abundant sunlight which is thought to enhance the availability of vitamin D; and most of the patients do not live long enough for full establishment of the clinical symptoms of renal bone disease partly due to rapid progression for the disorder to manifest and lack of renal replacement therapy.

However, due to the increasing availability of renal replacement therapy in the country and improved management strategies, the lifespan of our end stage kidney disease patients is prolonging and the problem of renal bone disease may become obvious.

A few local studies done in Nigerians have been reported and these were mainly radiological and clinico-pathological studies[17, 18,19]. Limitations were the lack of parathyroid hormone estimation and vitamin D assay in these studies coupled with limited bone histology samples and reports.

Odenigbo *et al* in 2001 reported on the radiological prevalence of renal osteodystrophy in 90 patients studied and concluded that osteitis fibrosa cystica was the commonest form and this was more prevalent in female patients [17]. This finding was also confirmed in another work done in Nigeria which also showed that osteitis fibrosa cystica was common among the patients seen. The histology of the bone biopsies done in 10 patients were confirmatory. Hypocalcemia was further seen in 71% and hyperphosphatemia in 79% [18].

Sanusi *et al* in a prospective study of 40 patients in 2009 reported the increased prevalence of mineral and bone disorders especially the low turnover variety and it was said to be common in males. Hypocalcemia was present in 59.3%, hyperphosphatemia in 75%, low vitamin D was found in 83.3%. 18% of the patients had hyperparathyroidism while 42.9% of the patients had increased alkaline phosphatase. Majority of the patients wereasymptomatic[19]. Radiological features of osteitis fibrosa were seen in 23%, unlike 3.35% and 2.2% reported in the other two studies. In all these studies, there was paucity of clinical features of bone disease in the patients.

Clinical Manifestations of Bone Diseases Associated with CKD

Most patients with CKD and mildly elevated circulating PTH are asymptomatic. When present, the clinical features of bone disease may manifest with musculoskeletal features which include fractures**,** tendon rupture, bone pains and weakness around the low back, hips and legs aggravated by weight bearing, bone deformities, muscle pain/weakness**,** periarticular pains and hip fractures. The latter is clinically significant and it is high among stage 5 CKD patients. It is particularly associated with an increased risk for death.

Extraskeletal manifestation is mainly pruritus which is seen in advanced chronic kidney disease especially patients on HD, and it is possibly related to the deposition of calcium and phosphorus in the skin.

Cardiovascular Complications

This accounts for half of all deaths in haemodialysis patients [7, 8, 20]. Calcium is deposited on heart valves especially the mitral and aortic valves and in the myocardium causing arrhythmias, left ventricular dysfunctions, aortic and mitral stenosis, ischemia, congestive cardiac failure and death. An association has also been described between left ventricular hypertrophy and parathyroid hormone levels in CKD patients with secondary hyperparathyroidism. Hypertrophied growth of cardiomyocytes and smooth muscles cells due to activation of cardiomyocyte protein kinnase have been reported.[21].

Coronary artery and vascular calcifications also occur frequently in majority of patients on renal replacement therapy and this is probably due to excessive use of calcium containing phosphate binders and vitamin D analogues. Coronary artery calcification is detected by non-invasive electron-beam computed tomography (EBCT) [20]

Calciphylaxis/ calcific uremic arteriolopathy(CUA). This is a vascular disorder characterized by systemic medial calcification of the small arterioles and resulting in ischaemic necrosis of skin and soft tissues. It is often complicated by

capillary thrombosis and recanalisation and it is seen primarily in CKD stage 5 and occurs in 1-4% of maintenance haemodialysis patients [22]. Although less frequently seen, it may be a feature of the cardiovascular complication of Chronic Kidney Disease-MBD. Calcification could be of proximal or distal types. Proximal calcification presents with painful lesions over the thigh, abdomen and buttocks and it is seen commonly in pre-dialytic CKD patients. Risk factors include; White race, female gender, morbid obesity and poor nutrition. Distal calcification is seen in the lower extremity especially in patients on long term HD with hyperparathyroidism and high Calcium x Phosphate product (mg^2/dl^2). It is more commonly found at local trauma areas of injections especially insulin, heparin and iron dextran infusions [22, 23].

Patients manifest with non healing ulceration of the skin and gangrene resistant to medical therapy and this often leads to amputation and death. There is high mortality due to uncontrollable sepsis[23].

Diagnosis is by a general evaluation of the clinical features clinical ,skin biopsy or three phase technetium 99m methylene diphosphate bone scintigraphy. This reveals calcifications in subcutaneous nodules or non-ulcerating lesions in viable tissues.

Specific management of CUA includes stoppage of oral calcium and usage of non-calcium containing binders, control serum phosphates to <6mg/dl, wound debridement and parathyroidectomy(if PTH levels are above 600pg/ml).

Mechanism of Calcification

Under the influence of uraemia and hyperphosphataemia ,the smooth muscle gene expression is down regulated in preference for osteoblastic differentiation**.** Promoters of vascular calcification like bone morphometric protein-4 (BMP-4) and osteopontin expressions are also increased, while low levels of inhibitors of vascular calcification like 2-Herman Schmid glycoprotein, Fetuin-A and matrix –GLA protein have been demonstrated in uremic patients[7, 23]. Fetuin A is a serum glycol-protein that binds calcium and phosphorus in circulation and forms "calciprotein particles" in order to clear the circulation of excess calcium and phosphorus . It is a major systemic and circulating inhibitor of calcification synthesized in the liver. Matrix glycoprotein A is synthesized by vascular smooth muscle and chondrocytes and may be responsible for inhibiting calcification of arteries and cartilage as has been demonstrated experimentally[23].

Amyloidosis

This is a musculoskeletal abnormality seen in patients on maintenance heamodialysis for more than 7 years[23]. It is not related to disordered calcium and phosphate homeostasis but there is osteoarticular B_2-microglobulin amyloid deposition. It manifests as erosive cystic changes, carpal tunnel syndrome and as a destructive spondyloathropathy in the cervical and lumbar spine ultimately leading to spinal instability and neurologic compression and pathological fractures . There is no effective treatment except kidney transplant. Prevention is through the use of high flux dialysers such as polysulfone or polyacrylonitrile (AN69) that enhance β_2M excretion [23].

Diagnosis of CKD – MBD

1. *Biochemical parameters*

PTH levels; The normal range of the intact PTH assay is 10-65pg/ml in normal individuals. While the recommended target range, (using the K/DOQI guideline) for serum iPTH for stage 3 is 35-70pg/ml, stage 4 , 70-110pg/ml and stage 5, 150-300pg/ml [8].

Biochemical serum markers of bone turnover; These includes Total alkaline phosphatase, osteocalcin, procollagen -1-propertide and parathormone which are all elevated in high turn over bone disease.

2. *Imaging*

There is increased osteoblastic activity with associated increased trabeculae bone volume which accounts for the sclerotic changes i.e. rugger jersey spine pattern seen on the X ray . Other features seen on spine and hand roetgenogram include; subperiosteal erosions which are best seen at the distal end of the phalanges, erosion of the distal extremities of the clavicles and at the sacroiliac joints. Mottled appearance are seen on the skull while expansile lytic lesions (Brown tumors) can be seen in severe osteitis fibrosis . Pseudofractures show up as wide radiolucent bands perpendicular to the bone long axis(e.g looser's zone) as seen in osteomalacia.

3. *Bone biopsy*

The gold standard for diagnosing renal osteodystrophy is by Jamshidi needle aided trans illiac bone biopsy after double labeling with two doses of tetracycline two weeks apart, prior to biopsy[24]. The KDIGO recommends that bone biopsies in patients with CKD should be further characterized bydetermining the bone turnover (histomorphometric), mineralization and volume as it provides information on type and severity of MBD[1, 23].

MANAGEMENT OF MBD – CKD

The goals of management are to maintaining blood levels of Calcium and Phosphorus to as close to normal; to prevent/ treat abnormally elevated levels of parathyroid hormone early; to prevent parathyroid hyperplasia; to prevent extra skeletal calcification and to avoid the over-suppression of PTH secretion by vitamin D_3.[23]

The various options for treating 2^O HPTH and hyperphosphatemia include; dietary phosphorus restriction, calcium and non-calcium based phosphate binders, calcitriol or other active Vitamin D analogues, calcimimetics and parathyroidectomy.

Controlling Serum Phosphorus

Foods such as diary products, nuts, certain vegetables, chocolates and colas should be restricted for patients with CKD in especially for those in stages 4 and 5 because they contain high phosphate levels.KDOQI guidelines recommends that dietary phosphorus intake be restricted to 800 – 1000mg especially if serum phosphate concentrations is >4.6mg/dl at stage 3 and 4 of CKD and > 5.5mg/dl(1.78mmol/L) in patients with CKD stage 5. Serum phosphates concentrations should also be monitored every month after the start of dietary phosphate restrictions.

Phosphate Binders

They combine with dietary phosphates in the gastrointestinal tract to form an insoluble complex that is excreted in the stool. Indications include; elevated phosphate concentration despite compliance with dietary phosphate restrictions and elevated blood PTH concentrations after dietary phosphorus restrictions.

TYPES

This could either be aluminium containing binders, calcium based binders, non calcium based binders or non calcium, non aluminium based binders

Aluminium Based Binders.

This forms insoluble and non absorbable aluminium phosphates which precipitate in the intestinal lumen. They are effective binders which are eliminated in the kidney and there is gradual tissue accumulation of absorbed Aluminium with resultant toxicity. They were previously used in the last 3 decades to treat renal osteodystrophy but went out of favour due to the side effects..These manifest majorly in the bone, skeletal muscle and the CNS, leading to low bone turn over osteomalacia and adynamic bone disease, refractory microcytic anemia, myopathies and dementia [25]. These binders are known to have comparable better phosphate control without any increase in the serum calcium levels.

K/DOQI guidelines recommend the use of Aluminium binders only in patients with serum phosphorus>7.0mg/dl(2.26mmol/l), i.e. one course short term therapy for less than 4 weeks only and to be replaced thereafter by other phosphate binders.

Calcium Based Phosphate Binders (Calcium carbonate/calcium acetate)

These include calcium carbonate, calcium acetate, calcium citrate and calcium ketoglutarate and they are often recommended as an initial therapy. Calcium carbonate has been widely used, although calcium acetate is a more effective phosphate binder as it dissolves in both acid and alkaline medium [26]. They are most effective when taken with meals as it binds dietary phosphorus and therefore leaves less free calcium available for absorption. There is an increased risk of hypercalcaemia and metastatic calcifications which are associated with cardiovascular mortality [10, 11, 27]. To avoid the above complications, the K/DOQI guidelines suggest that the total dose of elemental calcium (including dietary sources) should not exceed 2000mg.

Non calcium Based, Non aluminium Based Phosphorus Binders

Sevelamer Hydrochloride; This is a cross linked poly-allylamine hydrochloride exchange resin which binds phosphorus and releases chloride. They are moderate phosphorus binders[24]. Dosage is 800-1600mg with

major meals to a maximum of 4800mg/day.They reduce serum phosphates and calcium –phosphorus product with a potency almost equivalent to that observed with calcium acetate therapy but with less risk of hypercalcemia They also attenuate the progression of coronary calcification(a predictor of all cause mortality) as compared to calcium acetate in both the *Prevalent [treat to goal trials][28]* and *Incident [renagel in new dialysis]* trials[29,30].

They lower lipids and uric acid levels, reduce inflammation and oxidative stress, increases fetuin A levels and ultimately improving bone health. They are not selective for phosphorus ions only, as it can bind other negatively charged ions such as chloride and bicarbonates. Major side effect is reduction in serum bicarbonate level.

Lanthanum Carbonate

This is a relatively effective and practical non aluminium/non- calcium based phosphate binder. They are trivalent metallic cations with ability to chelate dietary phosphates. They bind phosphate effectively across the physiological pH range of the upper GIT hence has low systemic absorption. They also reduce PTH concentrations and calcium-phosphate product in CKD patients[31, 32]. They have no detrimental effects on calcium/vitamin D metabolism and are well tolerated however, commonly reported adverse effects are nausea,peripheral oedema and myalgia. The dose is 250-500mg (maximum of 1500mg) and effects are seen within 3 weeks of treatment.

Vitamin D

These could be classified as Vitamin D precursor, active vitamin D compounds and Vitamin D analogues ,. as first, second and third generation compounds or as nutritional vitamin D (ergocalciferol and cholecalciferol), vitamin D receptor activators (calcitriol, alphacalcidiol, doxercalciferol) and D – mimetics (paricalcitol, maxacalcitol).

Ergocalciferol (Vitamin D_2) is a vitamin D precursor. It requires hydroxylation within the liver to calcifediol and a second hydroxylation within the kidney to form active vitamin D compound. It is of limited value in the latter stages of Chronic Kidney Disease. Dose is 400 – 50,000I.U. orally or intravenously.

Calcitriol (1,25 dihydroxyvitamin D) is a first generation active Vitamin D. It does not require any further activation and has been shown to effectively suppress parathyroid hormone secretion. The dose is between 0.25 – 5mcg, orally daily or thrice a week.

Doxercalciferol(1α- dihydroxy vitamin D_2) is a second generation vitamin D analog, like all second generation analogues, they have a side chain modification of the vitamin D molecule to minimize calcium and phosphorus absorption, but still requires activation and conversion to its active form of 1α-25 dihydroxyvitamin D_2 in the liver. Dose is 5–20mcg (orally) or 2 – 8mcg (IV), thrice weekly[33].

Paricalcitol (19-nor- 1,25- dihydroxy vitamin D_2) is a third generation Vitamin D analog with a high affinity for the Vitamin D receptor. The chemical modification to the vitamin D ring structure makes paricalcitol have less calcaemic and phosphatemic effect than calcitriol. Dose is 1 – 4mcg thrice daily orally or 2.5 -15mcg intravenously thrice weekly[34, 35]. It could suppress PTH to dangerous levels.

Generally Vitamin D sterols reduce the transcription of the parathyroid hormone gene and hormone synthesis over a period of several days.

Calcimimetics (Cinacalcet HCl, AMG-073)

This is a novel approach to treating secondary hyperparathyroidism without raising serum calcium or using active Vitamin. D analogues. These agents mimick the effects of blood ionised calcium on the parathyroid. They also stimulate caR (calcium sensing receptors) found in the parathyroid and C thyroid glands as well as renal tubular cells, they reduce PTH secretion and also control hyperplasia[36]. Activation of this receptor by calcimimetics increases intracellular calcium concentration, which causes rapid reduction in PTH secretion(within a few hours after administration), serum phosphorus levels, and the calcium **x** Phosphorus product, which remain suppressed for up to 3 years[37]. Oral dose is 30-180mg once daily.

Parathyroid Intervention Therapy

This could either be surgical or medical. Surgical treatment is via parathyroidectomy while the medical treatment is by percutaneous direct injection therapy. Indications for parathyroidectomy include; persistently elevated intact PTH (<800pg/ml) which is associated with hypercalcemia and/or hyperphosphatemia despite medical management, mass on imaging > 0.5-1g, calciphylaxis (with increased iPTH), severe bone pains/ fractures in the presence of elevated intact PTH level and severe pruritus refractory to medical

management[33]. It could either be via subtotal parathyroidectomy or total parathyroidectomy in which there is no re-implantation of parathyroid tissue in the forearm as done in metastatic calcification while re-implantation is often performed in some other instances particularly to avoid hyperparathyroidism especially after renal transplantation[38,39].

Percutaneous ethanol injection therapy

This is an alternative procedure to surgical parathyroidectomy. Side effect is mainly recurrent laryngeal nerve injury. However this have been replaced by calcitriol preparation for percutaneous injection into parathyroid gland or percutaneous calcitriol analogue injection therapy (22-oxacalcitriol) which has shown suppressive effects on PTH level as well as reduction in the size of the enlarged glands [23].

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