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Chronic Kidney Disease in Bone and Mineral Disorder

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Abstract: ***The patient with Chorine Kidney Disease (CKD) represents on entreme model for arteriosclerosis . Vascular calcification and bone disorders, all of which are also associated with ageing in the general population. As the GFR loss aggavates, the disturbed mineral metabolism worsens the bone microstructure and remodelling - scenario, which is known as CKD-Mineral bone disease (MBD). CKD-MBD is characterized by: (1) abnormal metabolism of calcium, phosphorus, parathyroid hormone (PTH), or Vitamin D, (2) abnormalities in bone turnover, mineralization, volume linear growth or strength, (3) soft-tissue calcifications, either vascular or extra-osseous. CKD should be regarded as an atypical disease in which both traditional and novel cardiovascular risk factors have effects on outcome. But CKD can also be viewed conceptually as an accelerator of traditional cardiovascular risk factors. Findings from research into mineral bone disorder associated with CKD (CKD-MBD) could help the medical community to better understand the vascular actions of certain molecules such as phosphates, fibroblast growth factor 23, parathyroid hormone, sclerostin, or vitamin D and their relevance to the management of different pathologies in the general population. Thus, achieving a better understanding of CKD-MBDs could provide substantial insight into future treatment for arteriosclerosis and osteoporosis, which are strongly associated with ageing and morbidity in the general population.***

Keywords: Chronic kidney disease- mineral and bone disorder, update pathogenesis, emerging trends, management

1. Introduction

Chronic Kidney Disease- Mineral Bone Disease (CKD-MBD) is a term coined in 2005 by KDIGO-Kidney Disease: Improving Global Outcomes, to highlight that disorders of calcium, phosphorus, parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF-23) metabolism could generate the systemic condition where the outcome, if untreated, may lead to derangements in bone metabolism (renal osteodystrophy), vascular calcification, and cardiovascular (CV) death.

Chronic Kidney Disease (CKD) is a worldwide health problem affecting 5-10% of the world's population and the majority of these patients are at an increased risk of developing distrubances of bone and minerals metabolism. Mineral and bone disorders are common in patients with CKD and contribute to the large burden of cardiovascular and bone disease characteristic of CKD.

Healthy kidney plays many important roles. They removes wastes and extra fluid from body, help to make red blood cells, and help to keep none strong. They also help to keep the right amount of minerals in blood. Minerals are nutrients that body needs to stay healthy. When kidney disease occurs, kidney cannot do these important function well. As a result, may develop mineral and bone disored. It is a common problem in people with kidney disease and it affects almost everyone receiving dialysis.

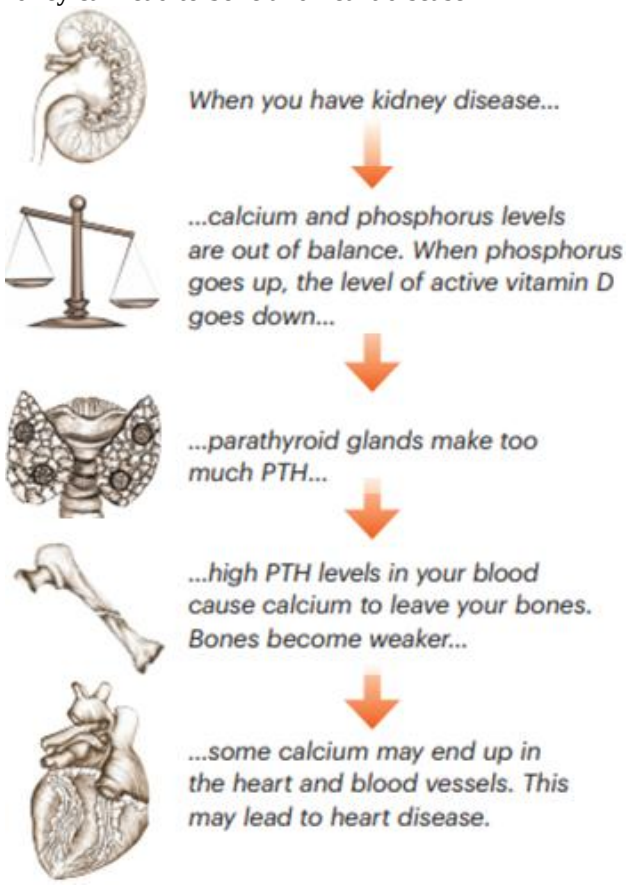
At the onset of chronic kidney diseeasee (CKD), th systemic mineral metabolism and bone composition starts to change along with glomerular filtration rate (GFR) loss. As the GFR loss aggravates, the disturbed mineral metabolism worsens the bone microstructure and remodelling scenario that is known as CKD- Mineral bone disease (MBD). The kidney are the major source of the anti-ageing protein klotho, and CKD is a state of klotho deficiency. The patients with renal disease show decreased klotho expression as early as CKD stage 1 – klotho deficiency being one of the first mineral and bone disorder that occurs in the setting of CKD. As CKD progresses, klotho concentration continue to decline, causing FGF23 resistance and therefore leading to large increase in serum concentration FGF23 and parathyroid hormone, as well as decrease in vitamin D concentration. Many of these changes predispose patient to develop vascular calcifications and their sequelae. Increasing evidence is including that klotho deficiency could contribute to salt-sensitive hypertension, aberrant cardiac remodelling, vascular calcification, bone loss, neurodegenerative disease, and renal fibrosis.

Collectively, these alterations have been termed CKD-Mineral and bone disorders (CKD-MBDs). The additional health risk imposd by CKD-MBDs on CKD risk factors such as systemic hypertension, hypercholesterolaemia, left ventricular hypertrophy, coronary heart disease, and diabetes, could provide an opportunity for improved risk management beyond controlling traditional factors.

What is mineral and bone disorder?
Kidney disease and kidney failure can cause important minerals in blood stream, such as calcium phosphorus, to get out of balance. Mineals are nutrients that body needs. As a result, bone may lose calcium and become weak over time. Some calcium and phosphorus may end up in parts of body where they do not belong, like heart and blood vessels. This can lead to heart disease.

Mineral and bone disorder connected to heart problems?
The some problems that weaken bones may also cause minerals like calcium and phosphorus to build-up in heart and blood vessels. As a result, heart and blood vessels can become shift and narrow. This increases risk of heart failure, heart attack, and several other problems.

Kidney can lead to bone and heart disease



What happens when you have mineral and bone disorder?

When you have and mineral disorder, if affects how body releases importat hormones that help to keep bone strong. It also affects how body balance two important miinerals – calcium and phosphorus. Body needs calcium to build bones, control blood pressure, and keep a normal heart beat. Calcium comes into body when eat foods with calcium, like milk and other dairy products. Most of the body's calcium is in bones and teeth. Healthy kidney helps to keep the right level of calcium in body.

Phosphorus is another important mineral in body. Phosphorus has many functions. It helps with growth and energy. Phosphorus gets from food. In adults, most of the body's phosphorus is in the bones. Healthy kidneys get rid of the phosphorus don't need.

A body also has problems releasing certain hormones, like "active" vitamin D and parathyroid hormone (PTH). "Active" vitamin D helps your kidneys, bones, and intestine balance phosphorus and calcium. Healthy kidney change vitamin D get from sunlight and the food into "active" vitamin D. But with mineral and bone disorder, kidneys can't changes vitamin D into "active" vitamin D. Without vitamin D, people with mineral and bone disorder can't keep the right balance of calcium and phosphorus in the body. Calcium will be too low and phosphorus will be too high.

Parathyroid hormone (PTH) is another hormone that helps to keep the right balance of calcium in the bone and in the blood. When the level of phosphorus in the blood goes up and level of "active" vitamin D goes down, body makes to much PTH. High PTH causes calcium to leave bone and go into blood. As more and more calcium bones, they become weaker, more brittle and may break more easily.

Characteristics of mineral and hormonal disruption in CKD:

As the GFR falls, free serum calcium levels fall and serum phosphorus increases. Because of GFR loss, compensatory production of fibroblast growth factor 23 (FGF23) decrease level of sodium – dependent phosphate transport protein (Npt)2a and Npt2c in the kidney, resulting in increased urinary excretion of phosphate. In response, the parathyroid glands increase the production of PTH, which decrease the abundance of Npt2a and Npt2c in the proximal tubule, leading to increased urinary Pi excretion that in turn lowers serum Pi levels. FGF23 also inhibits the production of 1, 25 (OH) 2D and therefore decreases intestinal Pi absorption, further decreasing serum Pi levels. The decreased 1, 25 (OH) 2D induceds hypocalcaemia and then stimulated PTH production persists, which ensure secondary hyperparathyroidism (SPHT). As GFR continues to fall, however, these compensatory mechanisms fail, leading to hyperphosphatemia, hyperthyroidism, and higher serum FGF23 concentration. The SPHT and uremic toxin accumulation accelerate bone turnover by activating osteoclastogenesis and increase the release of calcium and phosphate from bone. Under physiological condition, FGF23 decreases the PTH from gland. As progressive GFR loss, PTH was resistance to the suppression by FGF23 and sequential nodular parathyroid hyperplasia formed. On the aspect of vascular health, hyperphosphatemia, SPHT, and hypovitaminosis were strongly associated with increased cardiovascular morbidity and mortality and increased the risk of calciphylaxis. Therefore, the treatment on (i) phosphate restriction, (ii) calcimimetics and, (iii) vitamin D analogues supplement.

Hyperphosphatemia is associated with higher mortality in CKD / end-stage renal disease (ESRD) patient, and phosphate restriction is mandatory in treating SHPT, and both dietary restriction and oral phosphate binders are important strategies. Among the phosphate binders, calcium – based phosphate binders hindered the effect of vitamin D because of the risk of hypercalcemia. Calcium – free phosphate binders such as sevelamer or lanthanum decreases the intestinal calcium loading, and it provided the benefit in mortality in contrast to the cakcium – based phosphate binder. The calcium – sensing receptor (CaSR) important in regulating PTH secretion and therefore, this target offers the potential to suppress PTH secretion by complementory mechanism to vitamin D analogues. Calcimimetics allosterically enhance the sensitivity of CaSR in the parathyroid gland to calcium. As it direct suppression on PTH, the serum calcium and phosphate concentration could be controlled. Current studies involving the use of cinacalcet include ADVANCE and Evaluation of Cinacalcet HCL Therapy to Lower Cardiovascular Events (EVOLVE) studies, and the use of calcimimetics provided the benefits on controlling Vascular Calcification (VC) in subgroup analysis.

Role of Klotho in CKD – MBD

Klotho is transmembrane protein that confers tissue specificity of FGF23. The importance of this co-receptor was demonstrated in klotho null mice showing a phenotype similar to that of FGF23 null mice, with features of premature aging, vascular calcification, altered calcium / phosphate metabolism with hyperphosphatemia, and shortened lifespan. Diordered FGF23 has been shown to be an early feature of CKD. Klotho plays a fundamental role in mineral homeostasis through an interplay with other markers of CKD – MBD (parathyroid hormone, phosphate, fibroblast growth factor-23, and 1, 25-[OH]2 vitamin D3). The loss of ability of FGF23 to normalize phosphate levels through its phosphaturic effect and regulate PTH secretion was evidenced in dialysis patients where higher levels of FGF23 corresponded to the highest PTH levels. This dysregulated compensatory mechanism by FGF23 was largely attributed to klotho deficiency in CKD, which is characterised by low expression of klotho and FGF23 receptor 1 in the parathyroid gland. Klotho is responsible for converting FGFR1 (IIIC) into a specific receptor for FGF23. In addition, klotho is also termed a Calciophospho regulatory protein as demonstrated in its ability to enhance phosphaturia and prevent urinary calcium loss. Thus, klotho deficiency will lead to a constellation of disordered mineral metabolism, secondary hyperparathyroidism, vascular calcification, and cardiac hypertrophy, while exogenous administration of klotho may ameliorate or prevent the development of CKD – MBD.

Renal Osteodystrophy

The prevalence of osteoporosis varies according to CKD stages. Fractures in early-stage CKD patients (stage1-3A CKD) are more resemblance as traditional osteoporosis rather than CKD – MBD. However, most patients in stage 4 or 5 CKD exhibit certain degree of decreased bone mineral density (BMD) and/or certain level of CKD – MBD. At the time of dialysis initiation as many as up to half of the patients, might have experienced a fracture. Together, vitamin D deficiency, poor nutrition, inactivity, myopathy, and peripheral neuropathy pay a role in muscle weakness and falls. Since vitamin D is crucial for bone health, and vitamin D supplement is protective in fracture prevention in CKD, the role of vitamin D should be stratified.

Diagnosis of CKD – MBD

In 1983, *Sherald et al* proposed a classification for renal ostesdystrophy based on bone histomorphometry findings, namely high turnover disease, low turnover and mixed uremic osteodystrophy. The emphasis on this classification was on bone turnover; however sine a bone biopsy is not routinely used for monitoring patients there is a need for reliable biomarkers for assessing and monitoring patients with CKD – MBD. Therefore, the KIDGO guideline recommended the use of serum PTH in conjunction with total or bone-specific alkaline phosphate (b-ALP) since high or low levels of these markers correlated with underlying bone turnover. To further support the diagnostic utility of these various biochemical markers of mineral bone disorders, the KIDGO group conducted one of the largest bone biopsy studies involving 492 dialysis patients.In their multivariate analysis, both intact PTH and whole PTH were found to remain significantly predictive in differentiating high from non-high bone turnover. In addition to PTH, they also assessed the additive value of bone specific alkaline phosphatase and the amino-terminal propetide of type I procollagen (PINP) in providing diagnostic accuracy. Surprisingly, the inclusion of specific b-ALP level added only non-statistically significant value to PTH while PINP did not. However, due to limited serum samples, they could not assess the diagnostic utility of FGF23, 25-OH vitamin D and other newer biomarkers of CKD – MBD.

How is mineral and bone disorder treated?

Once mineral and bone disorder is found, diet and certain medications may help slow down the loss of bone and the buildup of mineral in blood vessels and the heart. Treatment will be based on the results of test and how quickly the results are changing.

If the results change over time, treatment may change,

- Diet is important for controlling minerals.
- Vitamins, supplements, and medicines may be prescribed.

Also, treatment to control parathyroid hormone (PTH) may be needed. The goal is to slow down overactive parathyroid gland that make too much PTH. These glands can be made less active with medicine. In some cases, surgery may be needed if other treatments are not effective. This surgery (Parathyroidectomy) removes the parathyroid glands that make PTH.

Medicines prescribed in mineral and bone disorders

- **Phosphate binders:** If a lower – phosphorus diet does not control blood phosphorus, may need a medicine called a phosphate binder.
- **Active vitamin D:** If vitamin D level is low, may need a prescription form of active vitamin D.
- **Calcimimetics:** Healthcare provider may prescribe another medicine called a calcimimetics to help to control mineral and bone disorder. It works differently from phosphate binders and vitamin D. It is often used when PTH, calcium and phosphorus levels are too high.
- **Calcium supplements:** Healthcare provider will decide if you need calcium supplements. Do not take them an your own. If patient receiving dialysis, it's important to know that the dialysis fluid contains calcium. Your healthcare provider will look at all the medicines you are taking for bone and mineral disorder to decide if changing the amount of calcium in dialysis fluid could help you.
- **Osteoporosis medicines:** Some patients have both mineral and bone disorder and the bone disease osteoporosis. Osteoporosis medicines are not always prescribed for people with kidney disease, but they may help some people.

Which medicine replaces active vitamin D?

Synthetic forms of active vitamin D are available as pills aoijections. These are several types that might be used. Do not substitute for what your healthcare provider orders. Because each type of vitamin D is a little different, your healthcare provider will decide which type is best for you. If you have kidney failure and are receiving hemodialysis,

your vitamin D may be given to you during dialysis treatment.

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