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A REVIEW ON RISK FACTORS OF LOW BONE MINERAL DENSITY IN CHRONIC KIDNEY DISEASE

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ABSTRACT
Osteoporosis, fragility fractures, and mineral bone disorder (MBD) are all linked to chronic kidney disease (CKD). Higher fracture risk, higher morbidity, and increased mortality are among the effects of CKD-MBD. Abnormalities in calcium, phosphorus, PTH, and/or vitamin D are included in CKD-MBD, as are abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and/or calcification of arteries or other soft tissues. In order to improve both short- and long-term results, it is imperative to comprehend the intricate pathophysiology of CKD-MBD. Treatment solutions for mineral bone disorder (MBD) associated with chronic kidney disease (CKD) should be patient-centered. The pathogenetic or risk factors, diagnosis, and treatment of patients with CKD-MBD are the main topics of this review. To examine the underlying pathophysiology and risk factors in greater depth as well as to evaluate the safety and effectiveness of treatments for CKD-MBD, more research is necessary.

KEYWORDS: Chronic kidney disease, mineral bone disorder, osteoporosis, dialysis, fractures.

INTRODUCTION

Chronic kidney disease (CKD) is a widespread issue in public health around the world. If a person has kidney damage or a glomerular filtration rate (GFR) of 60 ml/min/1.73 m2 for three months or longer, they are said to have the disease. Since patients with different stages of the illness have varying prognoses and physical states, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) has advocated categorising CKD into several stages based on GFR and albuminuria.[1]

The systemic regulation of mineral metabolism includes a significant contribution from the kidneys. Chronic kidney disease (CKD) patients' declining renal function results in the systemic syndrome of CKD-mineral bone abnormalities (CKD-MBDs). Patients who have CKD frequently get bone fractures. Low bone mass and damage to the bone tissue microenvironment are two symptoms of osteoporosis (OP), a systemic skeletal disease.

Osteoporosis in the presence of chronic renal disease is challenging to diagnose (CKD). This is especially true for the elderly population, which is more prone to fragility fractures, a decreased glomerular filtration rate (GFR), and poor bone mineral density (BMD).

A systemic disorder known as CKD-MBD is generally defined as having one or more of the following characteristics:

- Disturbances in the metabolism of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D;
- Vascular or other soft tissues calcification and/or
- Irregularities in bone turnover, mineralization, or strength.[2,3]

Pathogenisis of CKD-MBD

This condition has a complicated pathogenesis that includes several feedback loops connecting the kidney, bone, gut, parathyroid glands, and the vasculature. The maintenance of calcium and phosphorus balance is the primary objective of this system, frequently at the price of anomalies in other parts of the system.

- Imbalances in the metabolism of calcium, phosphorus, PTH, and vitamin D
- Disruptions in Volume Linear Growth, Mineralization, or Strength Of Bone.
- Extra skeletal calcification

Despite adequate levels of vitamin D, calcium, and PO4 as well as parathyroid hormone (PTH), early CKD is characterised by a lack of anabolism that alters the nascent hormonal systems, resulting in cardiovascular

disease and stunted growth. The two newly identified hormonal systems are osteocalcin and FGF23. Renal damage reduces the amount of the rapidly exchangeable phosphate and calcium pools, which serves as an early trigger for secondary hyperparathyroidism. The hematopoietic stem cell niche is formed by osteoblasts, and maintaining haematopoiesis requires adaptation to the osteoblast function loss in CKD. Hyperparathyroidism as a secondary adaptation.

The hematopoietic stem cell niche is regulated by three (family of) factors: PTH, wingless/ints proteins (Wnts), and bone morphogenetic proteins (BMP). Due to the diminished effect of either BMPs or Wnts on osteoblast activity after renal injury, hyperparathyroidism may represent the adaptation required to maintain endosteal and bone marrow microenvironments, including the hematopoietic stem cell (HSC) niche. High PTH levels and a greater impact of secondary hyperparathyroidism on bone remodelling are compromised in order to adapt to preserve the niche size.

After a relatively mild decline in glomerular filtration rate (between 60 and 90 ml/min/ 1.73m2, stage 2 CKD), and before abnormalities of mineral homeostasis are detectable by serum assays of calcium, inorganic phosphorus (Pi), calcitriol, and PTH, the earliest immunohistochemical abnormalities of bone in the CKD-MBD are observed. Elevated FGF-23 and PTH levels are seen in these early stages of CKD before increases in serum phosphorus, calcitriol, or calcium are apparent, but the latter is seen less commonly.

Numerous variables, such as hypocalcemia, low calcitriol levels, hyperphosphatemia, and others, directly boost PTH release as renal failure progresses. These serve the additional objectives of striving to maintain the homeostasis of calcium, calcitriol, and phosphorus. They are additive to the initial stimulation created by renal damage, boosting the strength of the adaptation. When calcium homeostasis is maintained, hyperparathyroidism stimulates bone resorption to release Ca and Pi from the storage reservoir, but this blocks the reservoir from absorbing too much phosphorus when the latter's balance shifts to a positive value.[4,5,6]

Pathogenetic Factors/Risk Factors for CKD-MBD

Phenotypic loss in smooth muscles

Loss of smooth muscle terminal differentiation results from early CKD. Systolic hypertension is caused by vascular stiffness caused by CKD, a newly identified early symptom of the CKD-MBD that is particularly significant in children.

Fibroblast growth factor-23

The first phosphatonin, or hormone that regulates phosphate excretion, was identified in research on autosomal dominant hypophosphatemia rickets and oncogenic osteomalacia. Gradually rising FGF-23 levels are seen during CKD. It is well recognised that the primary producers of FGF-23 are osteocytes and osteoblasts, and that a reduction in bone growth serves as the stimulation for its synthesis. As a result, FGF23 serves as a skeletal signal that more Pi needs to be excreted because it is not being deposited. In the multiorgan system implicated in the CKD-MBD, FGF-23 represents a direct bone-kidney relationship.

Osteocalcin

During the process of making bones, osteoblasts release osteocalcin. While osteocalcin is a well-known calcium-binding matrix protein exclusive to osteoblasts, its uncarboxylated version is a recently discovered hormone that controls energy generation and consumption.. Osteocalcin is lowered and energy synthesis/utilization is decreased as a result of the early loss of bone growth in CKD.[6,7]

Calcitriol deficiency

Increased FGF-23 synthesis results directly in decreased calcitriol production. These declines are noticeable early on in CKD as alterations within the normal range. Proximal tubular 25- hydroxycholecalciferol 1-hydroxylase activity causes calcitriol shortage as CKD progresses because it causes a decrease in the mass of working nephrons, which, when combined with an increase in phosphate load in the remaining nephrons, causes calcitriol insufficiency. In consequence, a calcitriol shortage reduces the intestinal absorption of calcium, which results in hypocalcemia. In situations of advanced renal failure, it also lowers the tissue levels of vitamin D receptors (VDR), particularly the VDR found in the cells of the parathyroid gland. Because the main cell VDR inhibits the development of pre-pro-PTH mRNA, patients with ESKD have lower levels of circulating calcitriol and fewer vitamin D receptors.

Hyperparathyroidism

PTH is produced more often and the parathyroid glands develop nodular hyperplasia in CKD as a result of all the mechanisms mentioned above. The fundamental cause of the gradual rise in parathyroid gland size during CKD is diffuse cellular hyperplasia; in dialyzed CKD patients, this size increase is positively linked with rising serum PTH levels. Additionally, monoclonal chief cell proliferation occurs, which leads to the development of nodules. Nodular hyperplastic glands are more resistant to calcitriol and calcium than diffusely hyperplastic glands because they contain fewer calcium- and vitamin D-sensing receptors. While adaptive to maintaining osteoblast surfaces, persistently elevated PTH levels result in an aberrant phenotype of osteoblast function that produces more RANKL ligand than anabolic osteoblasts and relatively less type 1 collagen.

Hyperphosphatemia

The stimulus to hyperphosphatemia caused by a drop in filtered phosphate is reversed as renal damage reduces the number of nephrons through PTH- and FGF-23-mediated declines in tubular epithelial phosphate

transport. In exchange for greater levels of PTH and FGF-23, the increase in phosphate excretion by the remaining nephrons maintains normal phosphate excretion. Hyperphosphatemia becomes fixed in stage IV and stage V CKD due to insufficient renal excretion despite high levels of PTH and FGF-23 when renal damage is severe enough to cause the glomerular filtration rate to fall below 30% of normal.Finally, in CKD and ESKD, hyperphosphatemia is a signalling pathway that induces heterotopic vascular mineralization.[8,9]

Hypocalcemia

Hypocalcemia develops as CKD worsens as a result of decreased intestinal Ca absorption. PTH secretion is stimulated by low blood levels of ionised calcium and suppressed by high calcium levels. Through a calcium sensor, a G-protein-coupled plasma membrane receptor (CASR) expressed in chief cells, kidney tubular epithelia, and, at lower levels, broadly distributed throughout the body, calcium acts on parathyroid gland chief cells. Low calcium causes PTH bundled in granules to be exocytosed, which stimulates PTH secretion over the short term, and increases the number of PTH-secreting cells over the long run. A secondary storage pool is mobilised and intracellular PTH breakdown alterations are brought on by longer-lasting hypocalcemia.

Inflammatory mediators

Inflammatory CKD is well-known for having high levels of inflammatory cytokines, chemokines, and their receptors. For instance, interleukin-8 (IL-8) levels are increased in CKD, which helps to produce PTH. The pathogenesis of ROD is aided by the central inflammatory cytokine IL-6, which is a direct indicator of inflammation in CKD. Inflammatory mediators' crucial functions in the CDK-MBD, however, are still unknown.

Leptin

The stimulation of leptin production from adipose tissue is one of the functions of inflammatory mediators in the CKD-MBD. Small anorexigenic hormone leptin reduces appetite by acting directly on the hypothalamus. Additionally, leptin inhibits osteoblast function by binding to melanocortin receptor 4 and activating -adrenergic neurotransmission. Increased leptin levels in CKD are linked to cachexia brought on by uremia. Kidney illness slows its metabolism by reducing proximal tubular metabolism. Its function as a pathogenic component in the adynamic bone condition is yet not completely understood.

Acidosis

The capacity to replenish the bicarbonate used to buffer metabolic acids is reduced as nephron mass decreases in CKD. Metabolic acidosis is therefore a consistent observation in stage 4/5 CKD. In this situation, bone plays a crucial role as a buffer against acid generation in people with ESKD. In order to achieve a negative bone balance, metabolic acidosis induces bone resorption while suppressing bone formation, which plays a crucial role in the pathophysiology of CKD-MBD.

Aluminium

The buildup of aluminium (Al^{3+}) in bone and other organs, like the parathyroid glands, can happen in dialysis patients or even before the start of the procedure. PTH secretion is reduced as a result of aluminium buildup in the parathyroid glands, which also suppresses bone turnover. The activity of the enzyme 25-hydroxycholecalciferol 1-hydroxylase is also inhibited by aluminium, which may further contribute to lower levels of calcitriol.[10,11,12]

Hypertension

Hypertension is a significant contributing factor to the cardiovascular symptoms of CKD- MBD. Automatic blood pressure monitoring-based assessments of hypertensive phenotypes show that CKD, especially paediatric CKD, is mostly responsible for these findings. Early research indicates that phosphate contributes to vascular stiffness in CKD, and this suggests that the CKD-MBD is a component of unknown importance in hypertension and possibly cardiac function in CKD.

Clinical Manifestations

Clinical symptoms of CKD BMD could include:

- Bone soreness and/or a higher risk of fractures.
- Weak muscles.
- Worsening hyperphosphatemia
- Subsequent hyperparathyroidism (results from retained phosphorus, low levels of vitamin D, and a reduction in serum calcium).
- Possibility of calcium excess.
- Stinging (due to increased phosphorous or PTH levels).
- Calcification of the peripheral and coronary blood vessels.
- Bloodshot eyes (due to capillary deposition of minerals).
- Calcifications in the subcutaneous tissues, muscles, and skin.[13,14,15]

Complications

The consequences of mineral and bone disorders.

- Decelerated bone growth and abnormalities
- Broken bones
- Cardiovascular problems

Decelerated bone growth and abnormalities

Kidney damage makes it more difficult for them to remove phosphorus from your body. Less calcium in your blood and the release of PTH by your parathyroid glands are linked to phosphorus buildup. Calcium leaves bones and enters blood as a result of PTH. One or more of the following complications could occur: slower bone growth, which could result in short height that lasts into adulthood; a condition known as "renal rickets" in which

the legs flex inward or outward; and an increased risk of bone fractures.

Broken bones

If you have a mineral and bone issue as an adult and the condition is left untreated, your bones will eventually deteriorate and become weak. Joints and bones may start to hurt, the likelihood of getting osteoporosis, also known as low bone mineral content, rises. Your risk of fractures or shattered bones may increase if your osteoporosis is severe.

Cardiovascular problems

- High blood calcium levels can harm your blood vessels and cause cardiac issues.
- Your blood vessels may calcify as a result of high phosphorus levels in your body.
- Even if your calcium level is within permissible range, could lead to improper hormone regulation.
- PTH and FGF23, another hormone produced in the bones, can both damage your bones and your heart and blood vessels.[16,17]

Diagnosis

The primary evaluations utilised in the usual diagnosis of CKD-MBD are based on biochemical, radiographic, and bone biopsy results, followed by pathological evaluation.

Biochemical parameters

According to KDIGO recommendations, screening for Ca, P, alkaline phosphatase (ALP), and PTH is strongly advised. Early CKD "stage III" should include routine monitoring of these parameters. Regular checks should be made on total calcium. Serum Ca, however, is not a reliable indicator of the underlying CKD-MBD. P should only be measured carefully. The P level varies during the day and after meals. As a result, checking should be done while fasting. An additional bone marker is total ALP. An immunoassay for bone specific ALP is a superior marker for bone turnover even if it is not currently used in clinical trials.

Radiological tests

1. Imaging via X-ray to assess phalangeal tufts, subperiosteal bone degradation, linear osteosclerosis of the spine, and lucent regions of the long bones are among the common radiological tests employed in the diagnosis of CKD-MBD.
2. PTG hyperplasia can be detected and diffuse from nodular hyperplasia can be distinguished using ultrasound examination (US).
3. Other methods for CKD-MBD diagnosis include magnetic resonance imaging (MRI) of the skeleton and computed tomography (CT).
4. Bone densitometry (DEXA scan) may be used, but the results must be carefully interpreted because it cannot differentiate between osteoporosis and CKD-MBD.

Dual-energy X-ray absorptiometry is used to determine bone density (DEXA). DEXA is a quick and painless imaging test that uses X-rays to detect whether you have healthy bones, osteopenia, or osteoporosis. It gives a result known as a T-score:

- Normal bone density is between +1 and -1.
- Low bone mass is indicated by a value of -1 to -2.5.
- Osteoporosis is indicated by a score of -2.5 or less.[18,19]

Management

Preventing the negative effects linked to secondary hyperparathyroidism is at the heart of CKD-MBD therapy. As a result, the management of secondary hyperthyroidism depends on detectable surrogate signs of disturbed mineral bone metabolism. 88 These indicators include 25-hydroxyvitamin D, intact parathyroid hormone, blood calcium, and phosphate levels. As a result, the current KDIGO recommendation suggests a course of treatment based on the serial patterns of these biochemical markers.

Controlling hyperphosphatemia

Hypercalcemia is a potential adverse effect of the Ca-based P binders that are required for patients with hyperphophatemia. Sevelamer carbonate is an effective non-Ca-based P binder that has the potential to lower low-density lipoprotein cholesterol levels, making it essential to manage using non-Ca-based P binder. Although lanthanum carbonate is likewise a powerful P binder, it is currently not widely available. P binders ought to be consumed with each meal. One of the main causes of CKD patients' poor adherence is a high tablet burden.[20]

Management of altered Ca level

There are various benefits of using magnesium carbonate and calcium acetate together. The risk of soft tissue calcification can be decreased by magnesium. The use of bisphosphonates as a therapy for osteoporosis and malignant bone disease has become routine practise. Due to the fact that they are only removed by the kidneys, the majority are contraindicated in cases of severe renal insufficiency.

Management of altered vitamin D level

In order to prevent and treat SHPT in CKD patients, vitamin D or vitamin D analogues are frequently administered. For many years, calcitrol was the most often applied substance. The usage of paricalcitol, a selective VDR activator and vitamin D analogue, has increased in recent years.[21]

Management of secondary hyperparathyroidism

According to the revised KDIGO recommendations, the only traditional treatment for SHPT in CKD patients is the use of calcitrol, a vitamin D analogue, or dietary P binders to restore normal levels of Ca, P, and PTH. However, delivery of a vitamin D analogue raises serum levels of calcium and phosphorus; as a result, HPT

treatments that can effectively reduce PTH levels without causing hypercalcemia are required.[22]

Teriparatide

Osteoporosis is treated with an anabolic substance that is a PTH analogue. Teriparatide increased BMD and decreased fracture risk in patients with mild to moderate CKD who had normal serum PTH levels. Teriparatide is contraindicated for usage in PTH-related conditions, including CKD, hence it would seem unwise to take this medication in CKD.[23]

Management of aluminum toxicity

Al toxicity has been significantly reduced with the use of HD water free of Al and P binders without Al. Oral P binders that contain Al should be replaced with ones that don't, like calcium carbonate and magnesium hydroxide. Al must be removed from the dialysate solution during dialysis. Al concentrations in dialysis fluid should ideally be lower than 0.2 mmol/l. Given that more than 80% of Al is strongly linked to protein, HD has not been successful in lowering the body's load of the metal. Desferrioxamine is an iron chelating drug that, after being infused into patients, allows HD to remove a significant amount of Al.[24]

Hormone replacement therapy

Postmenopausal women receiving dialysis may also be at risk for osteoporosis. Due to the pharmacokinetics of estradiol in renal failure, hormone replacement therapy (HRT) may have positive advantages as well as potentially substantial dangers, especially in uremic women. In non-uremic women, therapeutic alternatives such selective oestrogen receptor modulators (SERMs) have demonstrated that oestrogen has positive effects on bone and serum lipid levels without having negative effects on the breast and endometrial. Raloxifene and other SERMs may therefore be an effective HRT substitute for postmenopausal uremic women.[25]

Denosumab

Denosumab is an effective RANK-L antagonist that has anti-resorptive properties. It is a monoclonal antibody that blocks the growth and proliferation of osteoclasts by binding to the receptor activator of NFkB ligand. Since denosumab is not cleared by the kidney like bisphosphonates are, there is no concern of excessively reducing bone turnover due to drug buildup in CKD.[26]

Cinacalcet

Cinacalcet, a calcimimetic, lowers PTH levels right away after injection by raising the sensitivity of the calcium-sensing receptor to extracellular calcium ions. This reduces the release of parathyroid hormone. Following dialysis, parenteral cinacalcet (Etelcalcetide) is administered three times per week at a starting dose of 30 mg and is increased based on response. Regular monitoring of serum calcium and phosphate levels is advised due to the side effect of cinacalcet, hypocalcemia.[27,28]

CONCLUSION

Considered an underlying disease, CKD-mineral and bone disorder (CKD-MBD) is linked to fracture, cardiovascular disease, and mortality. It is linked to improper control of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) due to disturbances in bone and mineral metabolism. With regard to its aetiology, diagnosis, unfavourable clinical consequences, and therapy, CKD-MBD has undergone continuous evolution over time. This condition deteriorates as CKD advances. But despite the extensive research on CKD-MBD, there are still information gaps, which calls for additional RCTs to help with CKD-MBD care.

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