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Comprehensive Review of CKD-MBD: From Diagnosis to Therapeutic Interventions

Vankodoth Sireesha[1], P. Ramya Sri[2], Asiya Sultana[2], Ayesha Mateen[2], M. Shiva Kumar[3]

[1]Department of Pharm D, CMR College of Pharmacy, Kandlakoya, Hyderabad, Telangana, India – 501401.
[2]Department of Pharm D, CMR College of pharmacy, Kandlakoya, Hyderabad, Telangana, India – 501401.

Corresponding Author: V. Sireesha

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ABSTRACT

Globally, one of the most common diseases is chronic kidney disease, which is complex and varied. One of the complications associated with the advancement of chronic kidney disease is mineral bone disorders, which include biochemical and hormonal dysregulation. A number of biomarkers, including Fibroblast Growth Factor-23, klotho, phosphate, calcium, vitamin D, and PTH, have abnormal serum level variations that are central to the pathophysiology of chronic kidney disease-Mineral Bone Disorders. Biomarkers for essential elements and functionaries of chronic kidney disease-Mineral Bone Disorders include inorganic phosphate, fibroblast growth factor 23, parathyroid hormone, and calciprotein particles. A number of management strategies are used with patients with chronic kidney disease-Mineral Bone Disorders, including the use of calcimimetic agents, vitamin D and its analogues, bisphosphonates or denosumab, calcitriol, and specific treatments acting on chronic kidney disease to prevent and treat the complications associated with secondary hyperparathyroidism. This condition is highly prevalent among dialysis patients, and appropriate treatment is crucial to improving their outcomes.

Keywords: chronic kidney disease-mineral bone disorders, hemodialysis, phosphate, calcium, mortality, parathyroid hormone, vitamin D.

1. INTRODUCTION

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) refers to a condition that affects individuals with CKD and involves abnormalities in mineral metabolism. These abnormalities are frequently accompanied by rapid calcification of the arteries and tissues, as well as abnormalities in bone remodelling. In order to treat chronic kidney disease-Mineral Bone Disorder (CKD-MBD), clinical judgment and biochemical parameter measurement are crucial.[1] The complicated illness known as chronic kidney disease-mineral bone disorder (CKD-MBD) is characterised by abnormalities in the levels of calcium, phosphate, parathyroid hormone (PTH), vitamin D, and fibroblast growth factor-23 (FGF23). Changes in bone morphology and systemic implications result from these changes, with higher death rates predominantly from cardiovascular problems. Certain factors, such as the loss of the transmembrane protein Klotho, increased FGF23 production, lower rates of bone synthesis, and vascular calcification, frequently take place before abnormal biochemical markers show symptoms when

the glomerular filtration rate (GFR) drops below 40 mL/min.[2] CKD-MBD biomarkers include the fibroblast growth factor-23, α-Klotho, sclerostin and serum calcification propensity testing and their respective management strategies in CKD-MBD.[1] CKD-MBD biomarkers and the risk for kidney failure is well-characterized in stage 2–5 CKD patients.[3]

2. ETIOLOGY:

Impaired kidney function, dysregulated calcium, phosphate, and vitamin D homeostasis, and dysregulated renal function are the main etiological factors contributing to the development of CKD-MBD. abnormal control of PTH, Secondary hyperparathyroidism: This disorder is caused by a number of events that begin and sustain excessive PTH secretion. The symptoms of this illness include: phosphate retention, Reduced levels of free ionized calcium, reduced levels of calcitriol, and increased levels of FGF23, vitamin D receptors, and FGF receptors in the parathyroid glands. The etiological factors of CKD-MBD include-Itchy skin, Bone pain, Weak bones that break easily, Blocked blood vessels, Heart problems, Anaemia, Nerve problems, Difficulty fighting off germs or infections.[3]

3. PATHOPHYSIOLOGY:

The pathophysiology of CKD-MBD can be divided into different components based on the varied condition.

Skeletal Abnormalities in CKD-MBD (Renal Osteodystrophy)

Renal osteodystrophy, the skeletal manifestation of CKD-MBD is histologically classified into high or low bone turnover states.

High bone turnover: Higher rates of bone resorption and production are indicative of high bone turnover conditions. When parathyroid gland adenomas secrete PTH on their own, it can result in tertiary hyperparathyroidism, which is characterized by accelerated bone turnover as a result of secondary hyperparathyroidism.

Low bone turnover: Osteomalacia and adynamic bone disease are the two main conditions associated with low bone turnover. Osteomalacia: Intoxication with heavy metals, particularly aluminum, can cause osteoblasts and osteoclasts to malfunction. An overabundance of bone matrix accumulates and bone mineralization is impaired as a result of dysfunctional osteoblasts. Adynamic bone disease: Without the excessive osteoid accumulation found in osteomalacia, adynamic bone disease is predominantly caused by reduced PTH levels, which lead to limited bone turnover and inadequate bone mineralization.

Vascular calcification: The process of vascular calcification involves complex interactions between calci protein particles (CPPs), the extracellular matrix, and vascular smooth muscle cells. It was formerly thought to be a passive byproduct of degenerative aging. CPPs can cause extracellular matrix calcification, apoptosis in smooth muscle cells, and inflammatory reactions.

Cardiac abnormalities: Cardiovascular events are linked to elevated levels of FGF23 and PTH. FGF23 is associated with diseases like atrial fibrillation and cardiomyocyte hypertrophy and raises the risk of volume overload. Lower concentrations of Klotho, a protein that is depleted in chronic kidney disease, may provide cardioprotective benefits.

Neurological events: Elevated levels of FGF23 have been connected to neurological events such cognitive decline, dementia, and minor cerebral vascular disease. Patients receiving haemodialysis demonstrated that brain ischemia occurrences were linked to hypophosphatemia and brain haemorrhage, respectively. An increased risk of myocardial infarction and haemorrhagic stroke has been linked to elevated PTH levels. The conditions hyperphosphatemia and hypercalcemia have been associated with a higher risk of brain haemorrhage.

Gastrointestinal effects: Gastrointestinal effects associated with CKD-MBD include

constipation, liver inflammation, and alterations in the intestinal microbiome. Hyperphosphatemia, dietary restrictions, phosphate binders, and uremic toxins can impact natural intestinal bacteria.

Infections: Infections are the second-leading cause of death in patients on hemodialysis, and indicates a relationship between CKD-MBD and infection-related mortality. Elevated levels of PTH and FGF23 can hinder leukocyte recruitment and impair the host immune response.

Malnutrition: Malnutrition is prevalent in patients with end-stage renal disease due to factors such as uremic toxins, chronic inflammation, protein loss during dialysis, and dietary constraints, elevated FGF23 levels correlate with increased inflammatory markers and C-reactive protein levels.[4]

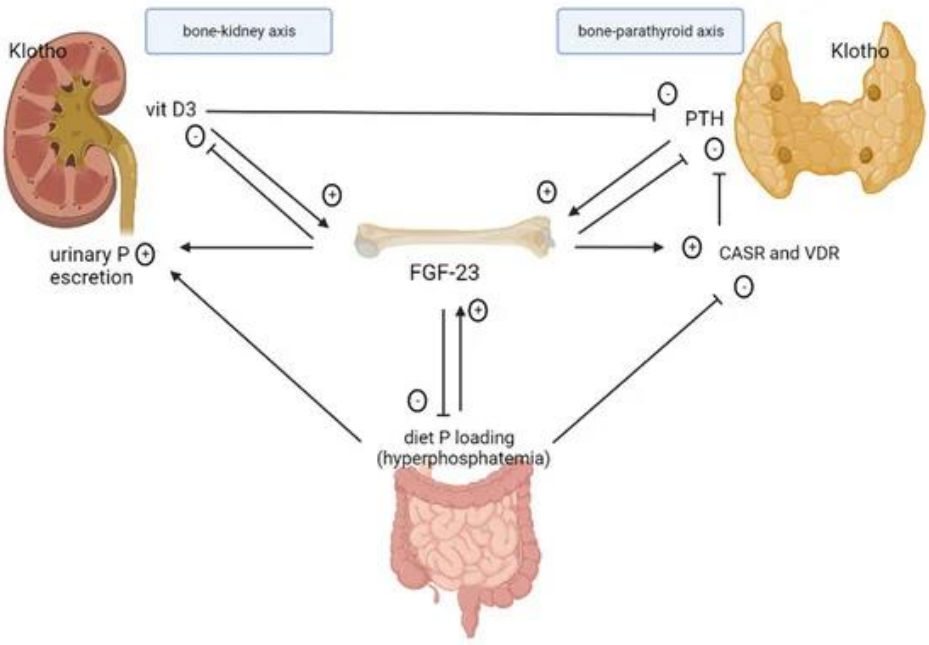

Fig 1: Pathophysiology involved in CKD-MBD patients [5]

4. DIAGNOSTIC APPROACHES FOR CKD-MBD:

Most patients with CKD-MBD are asymptomatic at the onset of the disorder, an investigation should be performed whenever clinical suspicion is high. Although a bone biopsy is the gold standard for diagnosis, it is not always feasible due to its invasiveness. However, blood tests for markers of bone metabolism, combined with radiological imaging, can help narrow down the differential diagnosis in patients.[4] Imaging by X-ray to assess subperiosteal bone erosion, linear osteosclerosis of the spine. Ultrasound examination (US) is very useful in detecting PTG hyperplasia and to distinguish diffuse and nodular hyperplasia. Computed tomography (CT) and magnetic resonance imaging (MRI) of the skeleton are another tool for diagnosis of CKD-MBD. Bone densitometry (DEXA scan) could be done, but its results should also be interpreted carefully as it cannot distinguish between osteoporosis and CKD-MBD. Bone biopsy.[6]

5. BIOMARKERS IN CKD-MBD:

Table 1: Biomarkers of CKD-MBD [7]

Biomarker	Role of the biomarker
PTH	bone metabolism regulator. Test standardization issues and substantial biological variability are two of PTH's drawbacks. Patients with chronic kidney disease (CKD) may also experience hypo responsiveness, or decreased skeletal sensitivity.
Bone-specific alkaline phosphatase (bALP)	Osteoblasts that express this enzyme. This enzyme inhibits mineralization by hydrolysing inorganic pyrophosphate (PPi). which is a sign for formation of bones
Osteocalcin	It affects the mineralization of osteoid binding to hydroxyapatite and is the primary non-collagen Gla protein of bone. It is the indicator for the development of bones
Intact-Procollagen type 1 N-terminal propeptide (Intact P1NP or trimeric P1NP)	fragment released during the process of bone formation when type 1 collagen is placed in the bone matrix. indicator of the development of bones.
Procollagen type 1 C-terminal propeptide (P1CP)	When type 1 collagen is deposited in the bone matrix during the process of bone formation, a fragment is liberated. indicator of the growth of bones.
Carboxy-terminal cross-linking telopeptide of type 1 collagen (CTX) Amino-terminal cross-linking telopeptide of type 1 collagen (NTX)	During bone resorption, cathepsin-K breaks apart fragments of type 1 collagen. indicator of bone resorption markers.
Artrate-resistant acid phosphatase isoform 5b (TRAP-5b)	This is an isoform of acid phosphatase. It breaks up type 1 collagen into pieces and is found in osteoclasts. An indication of bone resorption.
Sclerostin	It controls the metabolism of bone. It is an inhibitor of the β-catenin/Wnt signalling pathway, which prevents the production of new bone. It increases the genesis of osteoclasts and decreases the osteoblast genesis.

6. MANAGEMENT:

The treatment for patients with CKD-MBD varies according to the prevailing metabolic abnormality, the severity of the underlying kidney impairment, and the characteristic bone disease. Management of this condition revolves around strict control of phosphate, calcium, vitamin D, and PTH levels.

Treatment for Adult Dialysis Patients

The following therapeutic goals are advised for dialysis patients: For dialysis patients, the ideal range for phosphate levels is 3.5-2.55 mg/dL (1.13-1.78 mmol/L). It is preferable to keep serum calcium levels below 9.5 mg/dL, or less than 2.37 mmol/L. PTH levels are to be kept between two and nine times the assay's upper limit.

Phosphate: For individuals whose serum phosphate level is greater than 5.5 mg/dL (1.78 mmol/L), phosphate management is essential. Phosphate binders and phosphate restriction are common first treatments. Treatment should start as soon as serum phosphate level reaches this level. Calcium-containing and non-calcium-containing phosphate binders are the two categories into which they fall. Acetate and carbonate are examples of binders that contain calcium, while lanthanum and sevelamer are examples of binders that do not contain calcium.

Calcium: Maintaining calcium levels below 9.5 mg/dL (2.37 mmol/L) is essential. Asymptomatic and mild hypocalcaemia does not require treatment due to the risk of

hypercalcemia. In dialysis patients, calcium levels are maintained near the upper end of the normal range by adjusting the calcium concentration in the dialysate.

Vitamin D: Correcting vitamin D deficiency is crucial, as low vitamin D levels have been associated with increased mortality among haemodialysis patients. Both cholecalciferol and ergocalciferol are effective in correcting vitamin D levels.

Hyperparathyroidism: Calcimimetics, calcitriol, synthetic vitamin D analogues, and a mix of the two are used to lower PTH levels in the treatment of hyperparathyroidism. If phosphate levels are more than 5.5 mg/dL or calcium levels are more than 10.2 mg/dL, calcitriol or synthetic vitamin D analogues are stopped or given at a reduced dose. The possibility of reaching goal PTH levels without developing hyperphosphatemia or hypercalcemia is increased when calcimimetics are used in conjunction with continuous calcitriol or vitamin D analogues and phosphate binders.[8]

7. CONCLUSION

Mineral and bone disorders are complex abnormalities that cause morbidity and decreased quality of life in patients with CKD. Chronic kidney disease–mineral and bone disorder (CKD-MBD) is characterized by bone abnormalities, vascular calcification, and an array of laboratory abnormalities, it also includes disturbances in the parathyroid hormone, vitamin D metabolism. fibroblast growth factor 23 (FGF23) and klotho which has also have been identified as important regulators of mineral metabolism. Klotho deficiency and high circulating FGF23 levels results in secondary hyperparathyroidism in CKD patients. Levels of FGF23 and parathyroid hormone increase along the progression of CKD to maintain mineral homeostasis and to overcome end stage renal disease. CKD-MBD is associated with adverse outcomes including cardiovascular disease and mortality. This review summarizes the outlines of laboratory abnormalities and representing biomarkers of the disease severity. These markers provide insight into mineral metabolism and its dysfunction in CKD-MBD patients.[9]

Declaration by Authors

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