Chapter 5

Mineral Bone Diseases and Osteoporosis in Chronic Kidney Disease

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Abstract

Mineral bone disease (MBD) is a common complication of chronic kidney disease (CKD) and is characterized by abnormalities in bone and mineral metabolism. Chronic kidney disease- Mineral bone disease (CKD-MBD) encompasses a spectrum of disorders ranging from bone abnormalities such as osteoporosis and osteomalacia to soft tissue calcification, which can lead to cardiovascular disease. The underlying mechanisms of CKD-MBD are primarily linked to deviations in the serum levels of multiple biomarkers, including Fibroblast Growth Factor 23 (FGF-23), phosphate, klotho, vitamin D, calcium, and parathyroid hormone (PTH).

Osteoporosis is a particularly significant concern for individuals with CKD as they are at an increased risk of fractures due to alterations in calcium and phosphate metabolism. These changes can lead to bone loss, bone pain, and fractures. Osteoporosis is often asymptomatic until a fracture occurs, which is why screening for bone mineral density is critical.

Treatment options for CKD-MBD and osteoporosis may include dietary modifications, medications, and dialysis. Maintaining adequate levels of calcium, phosphate, and vitamin D is crucial to preventing CKD-MBD. Medications such as bisphosphonates, calcimimetics, and vitamin D analogs may be used to prevent bone loss and reduce the risk of fractures. In patients with advanced CKD, dialysis may be necessary to control hyperphosphatemia and secondary hyperparathyroidism (SHPT).

Prevention is key to managing MBD and osteoporosis in CKD. Patients with CKD should undergo regular monitoring of their bone mineral density and bone metabolism markers. Making changes to one's lifestyle, such as engaging in weight-bearing physical activity, quitting smoking, and moderating alcohol consumption, can be effective in decreasing the likelihood of developing osteoporosis. Overall, early recognition and intervention are essential in managing MBD and osteoporosis in individuals with CKD.

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Introduction

CKD is a progressive condition that can lead to a range of complications, including MBD and osteoporosis (1). The kidneys play a crucial role in regulating mineral and bone metabolism by controlling the levels of calcium, phosphate, and vitamin D in the body (1). However, as kidney function declines in CKD, the kidneys are no longer able to properly regulate these levels, leading to an imbalance in mineral and bone metabolism (2). As per the 2006 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, CKD-MBD is classified as a systemic disorder that affects the metabolism of bones and minerals due to CKD. It is characterized by the presence of irregularities in calcium, phosphorus, PTH, or vitamin D metabolism, abnormalities in bone turnover, mineralization, volume, linear growth, or strength, or calcification of vascular or other soft tissues (3). Therefore, CKD-MBD involves intricate interconnections among the kidneys, parathyroid glands, bone, and intestine (4). (figure 1).

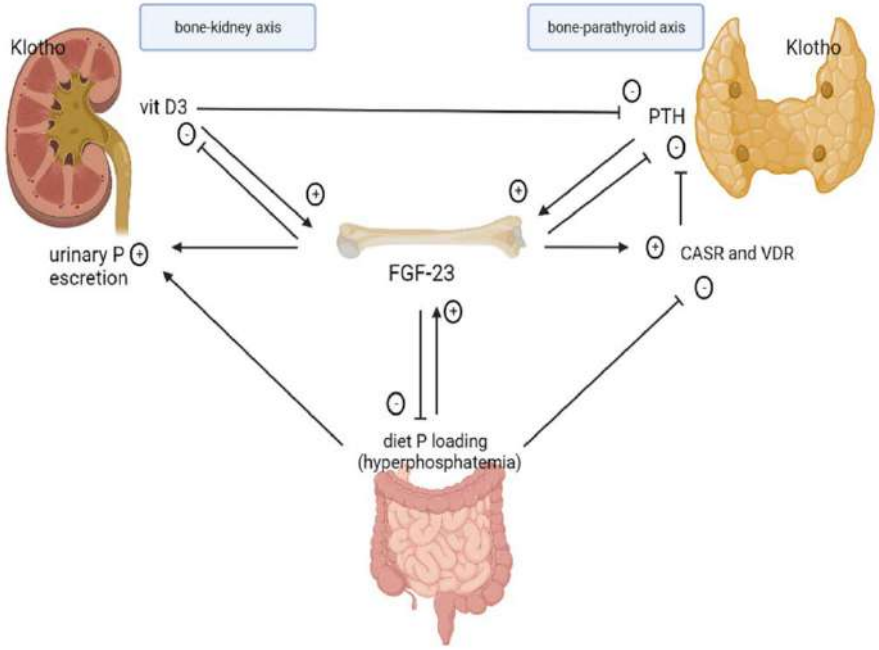

Figure 1. In CKD, there is a complex interplay between various factors, including FGF-23, PTH, vitamin D3, and phosphorus. When there are increased levels of PTH, 1,25(OH)D3, and phosphorus from diet loading, the secretion of FGF-23 is stimulated. However, FGF-23 then inhibits PTH secretion and reduces levels of 1,25(OH)D3. FGF-23 also reduces intestinal

absorption of phosphorus and inhibits phosphorus reabsorption in the proximal tubule, leading to increased urinary excretion. In addition, 1,25(OH) D3 suppresses PTH, while hyperphosphatemia reduces the sensitivity of the calcium-sensing receptor (CASR), directly affecting PTH synthesis.

According to data obtained from the National Health and Nutrition Examination Survey (NHANES), there is a high prevalence of both CKD and osteoporosis (5,6). Individuals with an eGFR<60 ml/min were found to be twice as likely to have osteoporosis compared to those with an eGFR>60 ml/min, among NHANES III participants (6). According to a study, among women diagnosed with osteoporosis, more than 80% had a Cockcroft-Gault creatinine clearance of less than 35 ml/min. In men diagnosed with osteoporosis, more than 50% had a Cockcroft-Gault creatinine clearance of less than 35 ml/min (5). In patients with predialysis CKD, the likelihood of hip fracture was more than double in those with a history of osteoporosis compared to the general population (6). Generally, the incidence of fractures was reported to be 2 to 100 fold higher in individuals with CKD compared to age-matched individuals without CKD (6,7), and patients with CKD were found to have more than three times greater mortality rates after fracture compared to those without CKD (8).

Patients with CKD often suffer from a variety of mineral bone disorders, including renal osteodystrophy, Adynamic Bone Disease (ABD), and osteomalacia. These conditions can lead to decreased bone density, increased fracture risk, and other complications that have a significant impact on the quality of life of CKD patients (1,2). Patients with CKD are at a higher risk of developing osteoporosis due to disturbances in mineral and bone metabolism (2). Osteomalacia occurs when osteoid, the unmineralized bone matrix, is not properly mineralized due to a deficiency of calcium and/or phosphate. Historically, osteomalacia was observed in patients treated with aluminum-containing phosphate binders or dialysates for a long period. However, aluminum-induced bone diseases, including osteomalacia, are now rare due to the use of aluminum-free phosphate binders and dialysates (9).

A decrease in bone cell activity, including osteoclasts and osteoblasts, without an excess of osteoid accumulation, characterizes ABD (10). This condition is commonly observed in dialysis patients and those with diabetes mellitus (11). Skeletal resistance to PTH or iatrogenic PTH suppression underlies the pathogenesis. Excessive use of calcium-containing phosphate binders and/or vitamin D analogues can cause over-suppressed PTH levels (12). Despite exhibiting PTH levels above the upper limit of the normal reference range, patients with ABD often display skeletal resistance to the

effects of PTH, which results from chronically elevated PTH levels down-regulating PTH receptors on osteoblasts (13).

Osteitis fibrosa cystica is a condition characterized by high bone turnover, resulting from SHPT. SHPT occurs due to the accumulation of phosphate, a deficiency of vitamin D, and a decrease in the activity of 1-alpha hydroxylase associated with declining renal function (14). At the onset, the increase in PTH levels is appropriate as it aids in increasing phosphate excretion by the kidneys, calcium absorption in the intestine, stimulating bone resorption, and increasing the activity of 1-alpha hydroxylase to correct developing hypocalcemia (15). FGF-23 has more recently been identified to have a vital role in this process.

The use of immunosuppressant drugs, particularly glucocorticoids (GCs), increases the risk of metabolic bone disorders, especially osteoporosis. Loop diuretics that are commonly prescribed for CKD patients can also contribute to hypercalciuria and negative calcium balance, which are additional risk factors for impaired mineralization (16).

Preventing and treating MBD and osteoporosis in CKD patients requires careful management of mineral and bone metabolism, as well as regular monitoring of bone density and other markers of bone health (1). Treatment options may include medications, dietary changes, and lifestyle modifications (2).

Overall, MBD and osteoporosis are common complications in patients with CKD, and careful management and monitoring are essential to minimize their impact on patients' health and quality of life (1,2).

General Aspects and Pathophysiology

MBD and osteoporosis are common complications in CKD patients, and their pathophysiology is complex and multifactorial (1,2). CKD is characterized by a progressive decline in kidney function, which results in an impaired ability of the kidneys to maintain mineral and bone homeostasis (1).

The pathophysiology of MBD and osteoporosis in CKD involves a variety of mechanisms, including alterations in calcium, phosphate, vitamin D, and PTH metabolism, as well as changes in bone turnover and remodeling (10).

As the kidney function deteriorates in CKD, the active vitamin D production decreases, resulting in reduced calcium absorption from the intestines (1). Consequently, there is a decrease in the serum calcium levels, which trig-

gers the secretion of PTH from the parathyroid gland (1,2). PTH, in turn, stimulates bone resorption and the release of calcium into the bloodstream (1,2).

In addition to changes in calcium metabolism, there are also alterations in phosphate metabolism in CKD (1,2). As kidney function declines in CKD, there is a decrease in the excretion of phosphate, which can lead to an increase in serum phosphate levels (1,2). High levels of serum phosphate can further stimulate the secretion of PTH, which can result in increased bone resorption and decreased bone formation (1,2).

Moreover, CKD patients often experience a state of low bone turnover, where bone formation and resorption are decreased (2,4). This can result in the development of ABD, which is characterized by low bone turnover and reduced bone strength (2).

Overall, the pathophysiology of MBD and osteoporosis in CKD involves complex interactions between calcium, phosphate, vitamin D, and PTH metabolism, as well as changes in bone turnover and remodeling (4).

Pathophysiology of FGF-23

FGF-23 is created mostly by bone cells in response to increased levels of certain hormones, including 1,25-dihydroxyvitamin D3, PTH, and oral phosphate. Other factors such as calcium, iron, the Renin Angiotensin Aldosteron System (RAAS), oxidative stress, and inflammation can also regulate FGF-23 production (17).

FGF-23 acts on different organs in the body through its receptors, which require the presence of αKlotho to increase their affinity to FGF-23. In the kidneys, FGF-23 decreases phosphate reabsorption and increases urinary excretion of phosphate by reducing the expression of certain transporters (18). In the distal tubule of the kidney, FGF-23 increases the reabsorption of calcium and sodium by upregulating the expression of certain channels and transporters (19,20).

In the early stages of CKD, FGF-23 helps maintain normal levels of phosphate in the body by prompting necessary adjustments. Therefore, it can be used as an indicator of abnormal phosphate regulation (17). Research by Isakova et al. found that FGF-23 levels increase before serum PTH levels in CKD patients. Additionally, a study of individuals with mild-to-moderate CKD found that higher levels of FGF-23 in the blood predicted a faster progression to end-stage kidney disease (ESKD) (21).

FGF-23 inhibits the production and secretion of PTH in the parathyroid glands, while also increasing the expression of certain receptors (22). In the intestine, FGF-23 reduces the absorption of phosphorus from food by inhibiting the activity of certain transporters and reducing the serum concentration of 1,25-dihydroxyvitamin D3, leading to a negative phosphate balance (23-25).

Elevated FGF-23 levels in CKD patients contribute to the reduction of hyperphosphatemia, suppression of active vitamin D levels, and inhibition of PTH synthesis and secretion.

Diagnosis

MBD and osteoporosis are common complications of CKD. MBD refers to a wide range of disorders that affect bone and mineral metabolism, including abnormalities in bone turnover and mineralization, as well as vascular calcification. Osteoporosis, on the other hand, is a specific type of MBD that is characterized by low bone mass and increased risk of fractures.

Diagnosis of MBD and osteoporosis in CKD can be challenging due to the complex interactions between bone and mineral metabolism. Therefore, a combination of laboratory tests and imaging studies are typically used to diagnose and monitor these conditions.

Laboratory tests commonly used to diagnose MBD and osteoporosis in CKD include measurements of serum calcium, phosphorus, and PTH levels. Examining bone turnover markers could be advantageous in determining metabolic bone disease in the overall populace, but their effectiveness is hindered when assessing CKD. CTX, a marker of bone resorption, is eliminated through glomerular filtration, and its accumulation in patients with CKD can lead to falsely elevated readings (26). Therefore, markers of bone formation such as procollagen type 1 N-terminal propeptide (P1NP) and bone-specific alkaline phosphatase (BSAP), which are not eliminated through the kidneys, may be more reliable indicators of bone turnover. In CKD patients, high levels of serum phosphorus and PTH are associated with an increased risk of bone loss and fractures (23). Other biomarkers such as BSAP, tartrate-resistant acid phosphatase 5b (TRACP5b), and osteocalcin can provide additional information on bone turnover and help identify patients at higher risk of fractures (27).

Alternative imaging techniques, such as Trabecular Bone Score (TBS) or microindentation methods, have shown promising results in predicting fractures in the general population. However, their effectiveness in the context

of CKD is still being studied, and these techniques are not yet widely available. Dual-energy X-ray absorptiometry (DXA) and quantitative computed tomography (QCT) are imaging studies that can be used to diagnose and monitor osteoporosis in CKD patients. DXA is the gold standard for measuring bone mineral density (BMD) and is recommended for CKD patients at high risk for fractures (24). QCT is a more detailed assessment of bone density and can differentiate between cortical and trabecular bone (28).

Clinical Presentation

MBD are a common complication of CKD, and can manifest in a variety of ways, including osteoporosis. In CKD, MBD is characterized by abnormalities in bone and mineral metabolism, such as changes in calcium, phosphate, and vitamin D levels. These abnormalities can lead to bone loss and increased fracture risk, as well as soft tissue calcification and cardiovascular complications.

The clinical presentation of MBD in CKD can vary depending on the severity of the disease. Early stages of MBD may be asymptomatic, while more advanced cases may present with a variety of symptoms, including bone pain, muscle weakness, fractures, and even renal osteodystrophy, a form of bone disease specific to CKD patients.

MBD can negatively impact the quality of life of patients with CKD, leading to increased hospitalizations, reduced mobility, and decreased ability to perform daily activities.

Several studies have investigated the clinical presentation of MBD and osteoporosis in CKD patients. One study found that CKD patients with MBD had a higher incidence of fractures and hospitalizations compared to those without MBD (2). A study reported that CKD patients with osteoporosis exhibited higher levels of bone turnover markers and lower bone mineral density in comparison to healthy individuals (25). Identifying and treating MBD and osteoporosis in CKD patients promptly is essential to prevent potential complications and improve clinical outcomes. Treatment approaches may involve lifestyle modifications such as dietary alterations and increased physical activity, as well as medication-based therapies like bisphosphonates, calcimimetics, and vitamin D analogues.

Management

The management of MBD and osteoporosis in CKD involves a multidisciplinary approach that includes dietary and lifestyle modifications, as well as pharmacological interventions.

Dietary modifications include reducing phosphorus intake by avoiding high phosphorus foods and using phosphorus binders to reduce the absorption of dietary phosphorus. Additionally, a low-protein diet may slow the progression of CKD and reduce the risk of bone fractures (6). To keep bones healthy and reduce the risk of fractures in CKD patients, it is important to consume sufficient amounts of calcium and vitamin D as part of a balanced diet (Table 1).

Engaging in weight-bearing exercises can also help improve bone density and lower the risk of fractures. Quitting smoking is also advised since smoking is associated with decreased bone density and increased fracture risk (28).

Pharmacological interventions for MBD and osteoporosis in CKD include calcium and vitamin D supplementation, which are recommended for all CKD patients to maintain bone health and prevent fractures (27). Bisphosphonates, teriparatide, and denosumab are effective treatments for osteoporosis in CKD patients (26). However, the use of these medications in CKD patients may require dose adjustment or close monitoring due to altered drug metabolism and potential adverse effects on kidney function (29).

In addition to pharmacological interventions, management of MBD and osteoporosis in CKD should also address cardiovascular risk factors, as vascular calcification is a common complication of these conditions. Control of hypertension and dyslipidemia, as well as glycemic control in patients with diabetes, is essential to reduce cardiovascular risk in CKD patients (30). Several studies have shown that individuals with CKD have an elevated risk of cardiovascular mortality, which increases as renal function declines. This increased risk is due to both traditional risk factors like hypertension, diabetes, dyslipidemia, smoking, and age, as well as non-traditional risk factors including anemia, chronic inflammation, and mineral metabolism abnormalities. CKD-MBD is characterized by fluctuations in the levels of various biomarkers, including calcium, phosphorus, vitamin D, PTH, FGF23, and Klotho, which can cause calcium-phosphate deposits in vascular tissues. Vascular calcification can occur in the intima layer of the vessel wall, which is common in dyslipidemia patients, or in the tunica media of vessels, which

is more prevalent in CKD-MBD. Previously, this process was considered a passive deposition of salts in blood vessels, cardiac valves, and heart; however, recent studies have revealed that several pathways contribute to the pathophysiology of this phenomenon.

Table 1: Management Algorithm for MBD and Osteoporosis in CKD

Step	Description
1	Screen all CKD patients for MBD and osteoporosis using laboratory tests, such as serum calcium, phosphorus, PTH, vitamin D, and alkaline phosphatase, and bone density testing, such as DEXA scan.
2	Limit dietary intake of phosphorus and use phosphate binders, such as calcium carbonate or sevelamer, to lower serum phosphorus levels.
3	Control serum PTH levels with vitamin D supplements or active vitamin D analogues, such as calcitriol or paricalcitol, and consider surgical intervention for patients with refractory SHPT.
4	Use bone-targeted therapies, such as bisphosphonates, denosumab, or teriparatide, to prevent and treat osteoporosis. Consider referral to a specialist for evaluation and management of osteoporosis.
5	Regularly monitor serum levels of calcium, phosphorus, PTH, vitamin D, and alkaline phosphatase, and adjust treatment as necessary to achieve target levels and prevent complications of MBD and osteoporosis.
6	Manage coexisting medical conditions that may contribute to MBD or osteoporosis, such as diabetes, hypertension, and autoimmune diseases.
7	Encourage physical activity, a healthy diet, and avoidance of smoking and excessive alcohol consumption. Ensure adequate intake of calcium and vitamin D through diet or supplements.
8	Schedule regular follow-up visits to monitor disease progression, adjust treatment, and address any new concerns.

Treatment

The treatment of MBD and osteoporosis in CKD involves a combination of dietary and lifestyle modifications, as well as pharmacological interventions.

Dietary modifications include reducing phosphorus intake by avoiding high phosphorus foods and using phosphorus binders to reduce the absorption of dietary phosphorus. Moreover, a diet low in protein may help in slowing down the advancement of CKD and lower the likelihood of bone fractures (34). Sufficient consumption of calcium and vitamin D is essential for maintaining good bone health and preventing fractures.

Engaging in weight-bearing exercise can also improve bone density and minimize the risk of fractures. Quitting smoking is also recommended as smoking has been found to be associated with reduced bone density and an increased risk of fractures (35).

Pharmacological interventions for MBD and osteoporosis in CKD include calcium and vitamin D supplementation, which are recommended for all CKD patients to maintain bone health and prevent fractures (31). Bisphosphonates, teriparatide, and denosumab are effective treatments for osteoporosis in CKD patients (32). However, the use of these medications in CKD patients may require dose adjustment or close monitoring due to altered drug metabolism and potential adverse effects on kidney function (36).

In addition to pharmacological interventions, If medical treatments prove ineffective, parathyroidectomy - a surgical intervention - is a crucial therapeutic approach that should be taken into account (36).

It is important to note that the treatment of MBD and osteoporosis in CKD should be individualized, taking into consideration the patient's stage of CKD, comorbidities, and other medications. Close monitoring of bone health, kidney function, and adverse effects of medications is essential for optimal management.

In conclusion, the treatment of MBD and osteoporosis in CKD requires a comprehensive approach that includes dietary and lifestyle modifications, as well as pharmacological interventions. Close monitoring and individualized treatment plans are essential to optimize bone health and reduce the risk of fractures in CKD patients.

Prognosis

The prognosis for MBD and osteoporosis in CKD can vary depending on the severity of the disease and the effectiveness of treatment. If left untreated, MBD and osteoporosis can lead to significant morbidity and mortality, including increased risk of fractures, hospitalizations, and cardiovascular events.

Several studies have investigated the long-term outcomes of MBD and osteoporosis in CKD patients. In a study by Block GA and colleagues, it was found that CKD patients with MBD had an increased risk of death from all causes compared to those without MBD, and the risk increased with the severity of the disease (37). In another study by Nickolas TL and colleagues, CKD patients with osteoporosis were found to have a higher risk of hip fracture and death compared to healthy controls (27).

However, with appropriate treatment and management, the prognosis for MBD and osteoporosis in CKD can be improved. A study of CKD patients with osteoporosis found that treatment with bisphosphonates was associated with a decreased risk of fractures and mortality (38).

It is important for CKD patients to receive regular monitoring and treatment for MBD and osteoporosis in order to improve their long-term outcomes.

Conclusion

In conclusion, MBD and osteoporosis are common complications of CKD that can lead to significant morbidity and mortality. CKD patients with MBD and osteoporosis may present with a variety of clinical manifestations, including bone pain, fractures, and vascular calcifications. Diagnosis of MBD and osteoporosis in CKD patients involves laboratory testing and imaging studies to assess bone mineral density and bone turnover.

Management of MBD and osteoporosis in CKD patients includes lifestyle modifications, such as adequate nutrition and physical activity, as well as pharmacologic interventions, such as calcium and vitamin D supplementation, phosphate binders, and bisphosphonates. Treatment must be individualized based on the patient's underlying disease, comorbidities, and medication regimen.

The prognosis for MBD and osteoporosis in CKD patients can be improved with appropriate treatment and management. Regular monitoring and follow-up are essential for achieving optimal outcomes.

Overall, the management of MBD and osteoporosis in CKD patients requires a multidisciplinary approach involving nephrologists, endocrinologists, and bone specialists. By addressing these conditions in a timely and effective manner, CKD patients can improve their quality of life and reduce their risk of complications.

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