Chapter 14: Bone Disease and Calcium Abnormalities in Elderly Patients With CKD

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An 81-yr-old African-American woman with end-stage kidney disease (ESKD) who has been on hemodialysis for 10 yr seeks a consultation with you. Her primary physician obtained a dual-energy x-ray absorptiometry (DEXA) scan and asked her to discuss the results with her nephrologist for further management. She is diagnosed with osteoporosis based on her T-scores of −5.1 (AP spine), −4.1 (left femoral neck), and −5.4 (left total hip). Her last dialysis laboratory results show serum calcium is 10.7 mg/dl, intact parathyroid hormone (PTH) is 207 pg/ml, phosphorus is 5.7 mg/dl, and alkaline phosphatase (ALP) is 122 IU/L. She receives paricalcitol 5 mg intravenously on hemodialysis three times per week.

Chronic kidney disease (CKD)-related bone disease is known as renal or uremic osteodystrophy. It is associated with derangements in bone and mineral metabolism that leads to abnormal regulation of calcium, phosphorous, vitamin D, and PTH. It encompasses a spectrum of conditions that are classified based on bone biopsy findings including osteitis fibrosa (high turnover disease), mixed uremic osteodystrophy, osteomalacia (low turnover disease), and adynamic bone disease. KDIGO (kidney disease: improving global outcomes) has proposed to define CKD-related bone and mineral metabolic abnormalities in the context of a systemic disorder called CKD–mineral and bone disorder (CKD-MBD).[1]

Osteoporosis is a condition characterized by low bone mass leading to reduced bone strength and an increased risk of fractures. Hip, spine, and wrist are most commonly affected. The WHO definition of osteoporosis is based on bone mineral density (BMD) measurements. The NIH consensus statement refers to osteoporosis as a skeletal disorder characterized by compromised bone strength predisposing to increased risk of fracture.

Osteoporosis and renal osteodystrophy may coexist in elderly patients with CKD, which makes the issue problematic to define. Osteoporosis in CKD is only a part of the constellation of metabolic bone problems. Therefore, its diagnosis and management may differ from general population. Bones are more severely affected in CKD than that from normal aging. In a patient with renal osteodystrophy, there is the potential for low BMD to coexist with an enormous range of functional abnormalities. These range from high turnover bone lesions in patients with uncontrolled hyperparathyroidism to severely reduced bone remodeling activity in patients with adynamic bone disease. This is in contrast to the non-CKD patient with osteoporosis where bone remodeling is not severely affected.

IMPACT ON QUALITY OF LIFE

Patients with CKD-MBD and osteoporosis are associated with increased risk of fractures and are at a high risk of cardiovascular disease.[2] The overall incidence of hip fractures among dialysis patients is about four-fold higher than that expected for general population. The risk is increased in both men and women.[3] Fractures may limit ambulation, leading to loss of independence and chronic pain, thereby decreasing quality of life. Mortality risk in dialysis patients with hip fracture is twice that of patients without hip fracture.[4] Women who are 65 yr of age and older and have moderate renal dysfunction (eGFR $<$ 60 ml/min per 1.73 m^2) are also at an increased risk of hip fractures.[5] In addition to the traditional risk factors, several risk factors for low BMD have been identified in the CKD population such as renal osteodystrophy, ethnicity, transplant status, and duration of dialysis.[6]

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EVALUATION

Assessment of bone strength in an elderly patient with CKD is complex. The initial evaluation of CKD-related bone and mineral disorders should include serum biomarkers and noninvasive imaging. Bone histomorphometric analysis might be needed in some cases. Bone strength is represented by two main features: bone density and bone quality. Bone density can be measured using several different radiologic techniques, but bone quality is difficult to assess because it depends on architecture, turnover, and mineralization. Correlation of BMD with bone histology is poor.

Serum Biomarkers

Surrogate markers of bone metabolism such as serum intact PTH, calcium (preferably ionized), phosphorus, alkaline phosphatases, and bicarbonate levels should be obtained initially. High intact PTH levels may correlate with high turnover bone disease. The optimal target level for intact PTH in CKD is not known.

Noninvasive Imaging

Several imaging tools are available to assess bone health including DEXA scan, quantitative computed tomography (qCT), and heel ultrasound. The value of BMD in evaluation of CKD-related bone disease is not well established.

DEXA scan is most commonly used to assess bone mass. It can only detect overall density but not quality of the bone. According to WHO definition, a T-score of −2.5 is defined as osteoporosis. The extension of this definition to groups other than postmenopausal Caucasian women is controversial. Because of vascular and extraskeletal calcifications in CKD, the interpretation may be affected by artifacts. However, it is commonly used because of low cost, accuracy, and wide availability. The distal radius may be the preferred site in CKD patients.[7] KDOQI recommends use of DEXA to measure BMD in patients with fractures and in those with known risk factors for osteoporosis.

Quantitative CT

Information regarding use of qCT in assessing BMD in patients with CKD is limited. It has the advantage of distinguishing outer dense cortical bone from inner spongy trabecular bone. Hyperparathyroidism leads to sclerotic thickening of trabecular bone with increased BMD but stimulates resorption in cortical bone with significant reductions in BMD. Thinning of the cortical bone results in increased risk of fractures. A small study has reported association of radius cortical parameters with fractures in hemodialysis patients. qCT is more expensive than DEXA and results in greater exposure to radiation.[8]

Bone Biopsy

It remains the gold standard for diagnosis of renal osteodystrophy and assessment of bone architecture. The most accurate diagnostic test for determining the type of bone disease associated with CKD is iliac crest bone biopsy with double tetracycline labeling and bone histomorphometric analysis. Bone histology shows information about turnover, mineralization, and volume and may be helpful in guiding therapy. Bone biopsy is not performed routinely in clinical practice because it is invasive, available in limited centers, and requires special expertise and an experienced pathologist for interpretation. However, it should be considered in patients with Stage 5 CKD who have (1) fractures with minimal or no trauma (pathologic fractures); (2) intact plasma PTH levels between 100 and 500 pg/ml (11.0 to 55.0 pmol/L; in CKD Stage 5) with coexisting conditions such as unexplained hypercalcemia, severe bone pain, or unexplained increases in bone alkaline phosphatase activity; and (3) suspected aluminum bone disease, based on clinical symptoms or history of aluminum exposure.[2] Bone biopsy should be strongly considered before starting bisphosphonate therapy in patients with Stage 5 CKD.

TREATMENT

Whether the standard agents used for osteoporosis in general population can be applied to patients with CKD is unclear. The management of osteoporosis includes addressing modifiable risk factors and using pharmacologic agents.

(1) Smoking cessation is strongly recommended. Excess alcohol consumption should be avoided.

(2) Exercise: Moderate weight-bearing physical activity has been associated with improvement in bone density and reduction in risk of hip fractures. However, in older women, the benefit is modest.

(3) Calcium and vitamin D requirements: Vitamin D deficiency is common in older adults especially during winter. It may be related to reduced synthesis, inadequate intake, dietary restrictions, and inactive lifestyle in dialysis patients. 25(OH-)Vitamin D deficiency is associated with increased iPTH levels, reduced BMD, and increased rate of hip fractures. The extrarenal effects of vitamin D are also receiving increasing attention. Low 25(OH)vitamin D levels may be associated with increased risk of cardiovascular events in patients with peritoneal dialysis (PD)[9] and higher risk of myocardial infarction in men.[10] The optimal serum 25(OH)vitamin D concentration needed to maintain bone health has not been established. Calcium and vitamin D supplementation has been reported to result in small improvement in hip bone density. It did not significantly reduce hip fractures but increased the risk of kidney stones.[11] In CKD Stages 3 and 4, KDOQI recommends maintaining 25(OH)vitamin D levels above 30 ng/ml by supplementation with ergocalciferol. In CKD Stages 3 to 5, total elemental calcium intake including dietary and calcium based binders should not exceed 2000 mg/d. The National Osteoporosis Foundation recommends a daily calcium intake of 1200 mg and vitamin D intake of 800 to 1000 IU/d for adults 50 and older.

(4) Role of bisphosphonates: Bisphosphonates are effective in treating osteoporosis, but their use in CKD Stages 4 and 5 is controversial. No data are available that proves that bisphosphonates reduce risk of fractures in dialysis patients with osteoporosis. Use of bisphosphonates in CKD has been linked to nephrotic syndrome, acute renal failure, and progressive renal disease. It is imperative to make a correct diagnosis before treatment is initiated because bisphosphonates are not indicated in adynamic or osteomalacic bone disease. Bone biopsy is recommended before using bisphosphonates. Alterations in calcium, phosphorous, vitamin D deficiency, and hyperparathyroidism should be addressed before starting bisphosphonates. Bisphosphonates have been used in the setting of renal transplant to prevent bone loss in the posttransplant period. In small studies, alendronate, risedronate, clodronate, and ibandronate have been shown to be safe to use in CKD. Some authors recommend using bisphosphonates for short periods of time (2 to 3 yr) in the CKD population, although there is no evidence that it will result in reduction of fractures.[12]

(5) Calcitonin: Calcitonin binds to osteoclasts and inhibits bone resorption. It has a low side effect profile and can be given intranasally. It could help protect bone mass when used along with calcium and vitamin D supplementation, especially in the posttransplant population.[13]

(6) Estrogen/progestin therapy has fallen out of favor because of increased risk of breast cancer, stroke, and thromboembolism. It may be an option in women who are not able to tolerate other forms of treatment.

(7) Selective estrogen receptor modulators (SERM): In a subgroup analysis, raloxifene was associated with a greater increase in spine BMD, a reduction in vertebral fractures, and no effect on nonvertebral fractures compared with placebo. It was safe to use in women with osteoporosis and mild to moderate CKD over the 2- to 3-yr observation period.[14] Some SERMs may increase the risk of deep venous thrombosis (DVT) and pulmonary embolism. Therefore, these agents should be avoided in women with active or history of DVT. They may also increase the risk of death caused by stroke in postmenopausal women with coronary heart disease. More information is needed on long-term safety and efficacy of these agents in CKD.

(8) Cinacalcet: It is a calcimimetic that increases the sensitivity of calcium-sensing receptors in the parathyroid gland to calcium, thereby playing a role in regulation of PTH levels. It helps in improving bone histology, reducing bone turnover, and reducing fibrosis in patients with secondary hyperparathyroidism. Some studies indicated that it may lower the risk of parathyroidectomy, fracture, and cardiovascular hospitalization.[15] Side effects include gastrointestinal intolerance and hypocalcemia, which may lead to seizures.

(9) Anabolic agents: A new class of anti-osteoporosis drugs are now available that stimulate bone formation. A subgroup analysis of patients with mild to moderate CKD included in the fracture prevention trial showed that teriparatide significantly increased lumbar spine and femoral neck BMD. Adverse effects included hypercalcemia and increased uric acid levels.[16] Safety data in dialysis patients or severe renal insufficiency are not available.

The above case shows difficult real-life situations faced by clinicians where no guidelines are available to recommend definitive treatment strategies. If this patient develops bone pain and pathologic fractures, bone biopsy could be considered. Some authors have suggested careful use of low-dose bisphosphonates in this situation, although data are extremely limited. A bone biopsy should be obtained to rule out adynamic disease before considering treatment with bisphosphonates. Conservative measures including mild weight-bearing exercise, smoking cessation, and avoiding alcohol should be encouraged. Fall prevention risk assessment and counseling should be provided.

CONCLUSION

Age-related bone loss is an important part of assessment in the growing aging dialysis and CKD population. Osteoporosis and renal osteodystrophy may coexist in the elderly CKD population, making diagnosis and management complicated. The DEXA scan is most commonly used to diagnose osteoporosis. Management of osteoporosis includes addressing modifiable risk factors and pharmacologic approaches. Patients with CKD are at greater risk for osteoporosis than general population. Osteoporotic fractures have significant morbidity and negative impact on quality of life. More data are needed to address the optimal management of mineral and bone disorders in the elderly.

TAKE HOME POINTS

- Bone disease in elderly persons with CKD is complicated by co-existence of renal osteodystrophy and osteoporosis
- Patients with CKD-MBD and osteoporosis are at increased risk of fractures and higher risk of cardiovascular disease
- Hip fractures in dialysis patients is associated with doubling of mortality
- Bone biopsy is the gold standard for diagnosis of renal osteodystrophy and assessment of bone architecture
- Although bisphosphonates are increasingly being used in the post renal transplant setting for prevention of bone loss, there is no evidence that it results in reduction of incidence of fractures

DISCLOSURES

None.

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REVIEW QUESTIONS: BONE DISEASE AND CALCIUM ABNORMALITIES IN ELDERLY PATIENTS WITH CKD

1. Incidence of hip fractures among dialysis patients compared with general population is about
   a. Two-fold
   b. Four-fold
   c. Six-fold
   d. Eight-fold

2. Risk of mortality in dialysis patients from hip fracture compared with those without hip fracture is
   a. Not affected
   b. Doubled
   c. Tripled
   d. Quadroupled

3. Bone strength is a function of bone density and quality; the best test for the assessment of bone quality is
   a. DEXA scan
   b. Quantitative CT
   c. Bone biopsy
   d. Serum intact PTH

4. Which of the following statements is false
   a. Calcitonin has been shown to protect bone mass in post transplant patients when used along with bisphosphonates, calcium and vitamin D
   b. SERMs increase the risk of DVT and thrombosis therefore should not be used in patients with active or history of DVT
   c. Some studies indicate that Cinacalcet may lower the risk of parathyroidectomy, fracture and cardiovascular hospitalization
   d. A subgroup analysis of the patients with mild to moderate CKD included in fracture prevention trial showed that treipartide significantly increased lumbar spine density and femoral neck BMD

5. Bisphophonates are increasingly being used in the posttransplant setting. Bisphosphonates
   a. Reduce incidence of fractures in the posttransplant period
   b. Reduce posttransplant bone loss
   c. Can be safely used in failed transplant patients who return to dialysis
   d. Can potentally benefit patients with adynamic bone disease