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Treat or Not Osteoporosis in the Advanced Chronic Kidney Disease

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Chronic kidney disease (CKD) and osteoporosis (OP) both increase the risk of fracture and subsequent morbidity and mortality. Recent evidences point toward the necessity of evaluating the risk of fracture in the patients with CKD, and therefore, KDIGO CKD mineral and bone disease (CKD-MBD) guideline was updated in 2017 to assess bone mass density (BMD) by dual-energy X-ray absorptiometry (DXA) in the patients with CKD-MBD. Many classes of novel drugs have been introduced to treat OP in general population, which will affect the treatment guideline of OP in CKD as well. However, whether treatment of OP will improve long-term outcome in CKD is not clear at this point. Therefore, this review aims 1) to introduce diagnostic method to evaluate CKD-associated OP, 2) to discuss current management strategies in the treatment of CKD-associated OP, 3) and to overview novel pharmacological agents and the potential challenges related to their use in advanced CKD.

1. Diagnosis of CKD-associated OP

The term CKD-MBD is used broadly to describe abnormalities in mineral metabolism, bone health, and soft tissue calcifications. Traditionally called renal osteodystrophy, it is a complex heterogeneous disorder of bone quality and density, which is a form of osteoporosis. OP is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture and clinically defined as a T score ≤ -2.5 or the presence of a low trauma fracture. Current guideline recommends measurement of BMD to assess fracture risk by DXA as well as regular monitoring of serum calcium, phosphorus, and parathyroid hormone (PTH) level.

The gold standard for the diagnosis and classification of bone health in CKD is bone biopsy. However, its use in the clinic is limited due to high cost and invasiveness. Therefore, non-invasive method to measure bone quantity and quality have been introduced. DXA has been the most useful method to assess bone quantity and fracture risk, and recently, peripheral quantitative computed tomography (pQCT) and high-resolution pQCT (HRpQCT) have been used as well. The interval to assess DXA in CKD patients is not known, but based on the general population guidelines, every 2 years may be acceptable. Measurement of bone quality is more difficult than that of bone quantity since bone quality is determined by several components including bone turnover, bone mineralization and volume. In the place of bone biopsy, measurement of bone turnover markers became popular because it is non-invasive and easy to monitor outcome. The most useful markers include PTH and bone-specific alkaline phosphatase (bALP).

2. Management Strategy of CKD-associated OP

Once fracture risk and/or a diagnosis of CKD-associated OP has been established, lifestyle modification including proper nutrition, weight bearing exercise, smoking cessation, and limiting alcohol consumption should be recommended to all CKD patients before using pharmacological agents to treat CKD-associated OP.

First-line therapy for the management of CKD-associated OP is correction of the mineral and metabolic abnormalities associated with CKD-MBD. Management of hyperparathyroidism, hyperphosphatemia, and vitamin D deficiency needs to be done before starting OP specific treatment. PTH levels of 2 to 9 times the upper normal limit of the assay is recommended by the current guideline. Phosphate binders, vitamin D receptor activators (VDRA), and calcimimetics can be used to lower the level of PTH.

When deciding which agent should be used to treat CKD-associated OP, it is important to assess

bone turnover rate. Medications that inhibit osteoclast-mediated bone resorption may be helpful in preventing bone loss and fracture in patients with normal- to high-turnover bone disease, whereas anabolic agents will increase bone turnover and BMD.

3. Novel anti-osteoporotic agents

Antiresorptive agents include bisphosphonate and denosumab. Previously, bisphosphonate was contraindicated for the use in CKD patients under GFR 30 mL/min/1.73m2 since it has a high affinity with bone mineral and theoretically can cause adynamic bone disease. However, based on post-hoc analysis of the pivotal fracture trials and anecdotal experience, these agents are considered safe in CKD patients as well as general population. Denosumab is considered more favorable since it is not excreted through urine and it effectively increase bone density without affecting bone turnover rate. However, the risk of severe hypocalcemia is of concern when using antiresorptive agents, and therefore, supplements with calcium and vitamin D should be preceded OP treatment.

Anabolic agents include Teriparatide and Abaloparatide. They are forms of recombinant PTH or PTH-related peptide and therefore should not be used to treat high-turnover bone disease due to hyperparathyroidism. However, they may be beneficial in low-turnover or adynamic bone disease. Other novel anabolic agents include romosozumab, a humanized monoclonal antibody targeting sclerostin, and DKK1 antibody. They are of great interest to treat patients with OP with advanced CKD because they increase BMD without aggravating hyperparathyroidism. These novel agents should be evaluated further for their efficacy and safety.