Management of Osteoporosis in CKD

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Abstract

CKD mineral and bone disease is a common complication of kidney disease, and it affects the majority of patients with moderate to severe CKD. Recently, prospective studies have shown that measurement of bone mineral density by dual energy x-ray absorptiometry predicts incident fracture, providing nephrologists the ability to risk classify patients for skeletal fragility and targeted antifracture strategies for the first time. Furthermore, an expanding body of literature and anecdotal evidence suggest that pharmacologic agents used to treat osteoporosis in the general population can be safely used in patients with CKD. This review highlights the effects of the Kidney Disease Improving Global Outcomes updates on the management of CKD-associated osteoporosis, discusses recent investigations on the effects of antiosteoporotic agents in patients with CKD, and provides an overview of novel antiosteoporosis agents and the potential challenges related to their use in CKD.

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Introduction

CKD mineral and bone disease (CKD-MBD) is a common complication of CKD that arises early in the course of the disease, and it is associated with high morbidity and mortality. The term CKD-MBD is used broadly to describe abnormalities in mineral metabolism, skeletal health, and soft tissue calcifications. The skeletal derangements associated with CKD-MBD are associated with bone loss and fractures. Compared with the general population, fracture incidence rates are more than fourfold higher (1), and they are associated with greater morbidity and mortality (2). Although the pathogenesis of CKD-associated osteoporosis and propensity to fracture is complex and remains to be fully elucidated, clinicians still need to prevent fractures, but they are faced with an armamentarium of antifracture pharmacologic agents that have not been developed for or adequately studied in patients with CKD-MBD and have not been shown to have antifracture efficacy in patients with CKD-MBD. This review will discuss current management strategies as well as the pharmacologic advances in the treatment of CKD-associated osteoporosis.

Definitions and Diagnosis of CKD-Associated Osteoporosis

The World Health Organization defines osteoporosis as a *T* score ≤ -2.5 (Table 1). Osteoporosis can also be defined clinically as the presence of a low trauma fracture with or without bone mineral density (BMD) in the osteoporotic range. A mechanistic definition of osteoporosis was determined by the National Institutes of Health Consensus Development Panel on Osteoporosis: a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength is the integration of bone density and quality. Clinically, bone density is measured by assessment of BMD by dual energy x-ray absorptiometry (DXA). Bone quality reflects bone material properties and includes bone microarchitecture, turnover, microdamage, mineralization, and collagen structure. Disorders in bone quality help explain the finding that one half of all osteoporotic fractures occur in patients with *T* scores > -2.5. Cortical and trabecular microarchitecture can be measured noninvasively using high-resolution bone imaging methods; however, other components of bone quality are assessed by bone biopsy. Renal osteodystrophy, a complex heterogeneous disorder of bone quality and density, is a form of osteoporosis.

Diagnosis of CKD-associated osteoporosis can be on the basis of the 2017 Kidney Disease Improving Global Outcome (KDIGO) guidelines, which recommend measurement of BMD to assess fracture risk in patients with CKD-MBD and/or clinical risk factors for osteoporosis (3). The update applies to the majority of patients with CKD, because almost all patients with moderate to severe CKD have CKD-MBD; many of them are also older, frail, and/or managed with medications that are toxic to the skeleton. Fracture risk classification can be on the basis of the World Health Organization *T* score, because the four longitudinal studies that influenced the update reported that *T* scores performed similarly in patients with and without CKD (4–7).

Epidemiology and Costs of CKD-Associated Osteoporosis and Fractures in CKD

Data from the National Health and Nutrition Examination Survey (NHANES) suggest that CKD and osteoporosis are highly coprevalent (8,9). Among NHANES III participants, osteoporosis was twice as common in those with an eGFR$<$60 ml/min compared with those with an eGFR$>$60 ml/min (9). Among women and

Table 1. Glossary of terms

Term	Definition
Primary osteoporosis	Chronic, progressive disease characterized by low bone mass, microarchitecture deterioration of bone tissue, bone fragility, and a consequent increase in fracture risk (51)
Postmenopausal	Caused by estrogen deficiency in postmenopausal women
Age related	Associated with aging in both men and women
Secondary osteoporosis	Osteoporosis secondary to medical conditions, nutritional deficiencies, and medication side effects (52)
CKD-MBD	A systemic disorder of mineral and bone metabolism due to CKD manifested by abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities of bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft tissue calcification
Renal osteodystrophy	A disorder of bone quality and strength secondary to CKD; the bone component of CKD-MBD
Adynamic bone disease	Low or absent bone formation and turnover (53)

CKD-MBD, CKD mineral and bone disease; PTH, parathyroid hormone.

men with osteoporosis, >80% and 50%, respectively, had a Cockcroft–Gault creatinine clearance <35 ml/min (8). In patients with predialysis CKD, a history of osteoporosis was reported to be associated with a greater than twofold odds of hip fracture compared with the general population (9). In general, fractures were reported to be greater than two- to 100-fold more common than in age-matched individuals without CKD (1,9), and mortality rates after fracture were greater than threefold greater (2) for patients with than without CKD. In 2010, health care–associated costs after fracture for patients with CKD exceeded $600 million (2). Thus, there is urgency for nephrologists to treat CKD-associated osteoporosis.

The Changing Paradigm of Managing CKD-Associated Osteoporosis

The paradigm to managing CKD-associated osteoporosis is evolving. The 2005 KDIGO committee shifted the historical nomenclature of renal osteodystrophy type to a unified classification system on the basis of bone turnover, mineralization, and volume, and turnover is now classified as low, normal, or high turnover renal osteodystrophy. The current treatment paradigm for renal osteodystrophy has focused on suppressing high turnover with active vitamin D and/or calcimimetics, while simultaneously avoiding the development of adynamic bone disease through excessive use of these same agents. There are no data to suggest that this approach has been successful in decreasing all-type fracture rates; in contrast, epidemiologic data suggest the opposite (10–13). We expect that the treatment paradigm for CKD-associated osteoporosis will evolve due to the update and that it will reflect the use of DXA to screen patients for risk of fracture and target them for antifracture strategies. Because of growing evidence suggesting that antiresorptive therapies have efficacy at preventing fractures in patients with creatinine clearance of 15–59 ml/min per 1.73 m^2 and because of the lack of evidence that these medications induce adynamic bone disease (Table 2), the update no longer mandates that a bone biopsy be obtained before starting osteoporosis treatment. Although bone biopsy is the gold standard for the diagnosis of renal osteodystrophy type and can inform treatment decisions, it is subject to important limitations, including cost, availability at only a few centers worldwide, time-consuming measurements, its ability to determine bone disease type at only a single time point, its degree of invasiveness and discomfort to the patient, and the fact that it has never been shown to predict fracture risk. The update acknowledges these limitations and suggests that circulating levels of parathyroid hormone (PTH) and bone-specific alkaline phosphatase can be used in the clinic to evaluate patients for bone disease, because markedly high or

Table 2. Overview of available therapies for kidney-associated osteoporosis

Drugs	Dosage	FDA-Approved eGFR Cutoffs	Effect on Mineral Metabolism
Alendronate	70 mg PO once weekly	eGFR≥35 ml/min	Hypocalcemia, hypophosphatemia
Ibandronate	150 mg PO once monthly or 3 mg iv every 3 mo	eGFR>30 ml/min	—
Risendronate	5 mg PO daily or 35 mg PO weekly	eGFR>30 ml/min	Hypocalcemia, hypophosphatemia, increased PTH levels
Abaloparatide	80 μg Subcutaneously once daily	Any eGFR, not studied in ESKD	Hypercalcemia, hypercalciuria
Teriparatide	20–40 μg Subcutaneous daily	eGFR>30 ml/min	Hypercalcemia, hypocalcemia, hypercalciuria
Denosumab	60 mg Subcutaneous every 6 mo	Any eGFR	Hypocalcemia, hypophosphatemia
Romosozumab	210 mg Subcutaneous monthly	Not studied in CKD	—

FDA, Food and Drug Administration; PO, per oral; iv, intravenous; —, unknown PTH, parathyroid hormone.

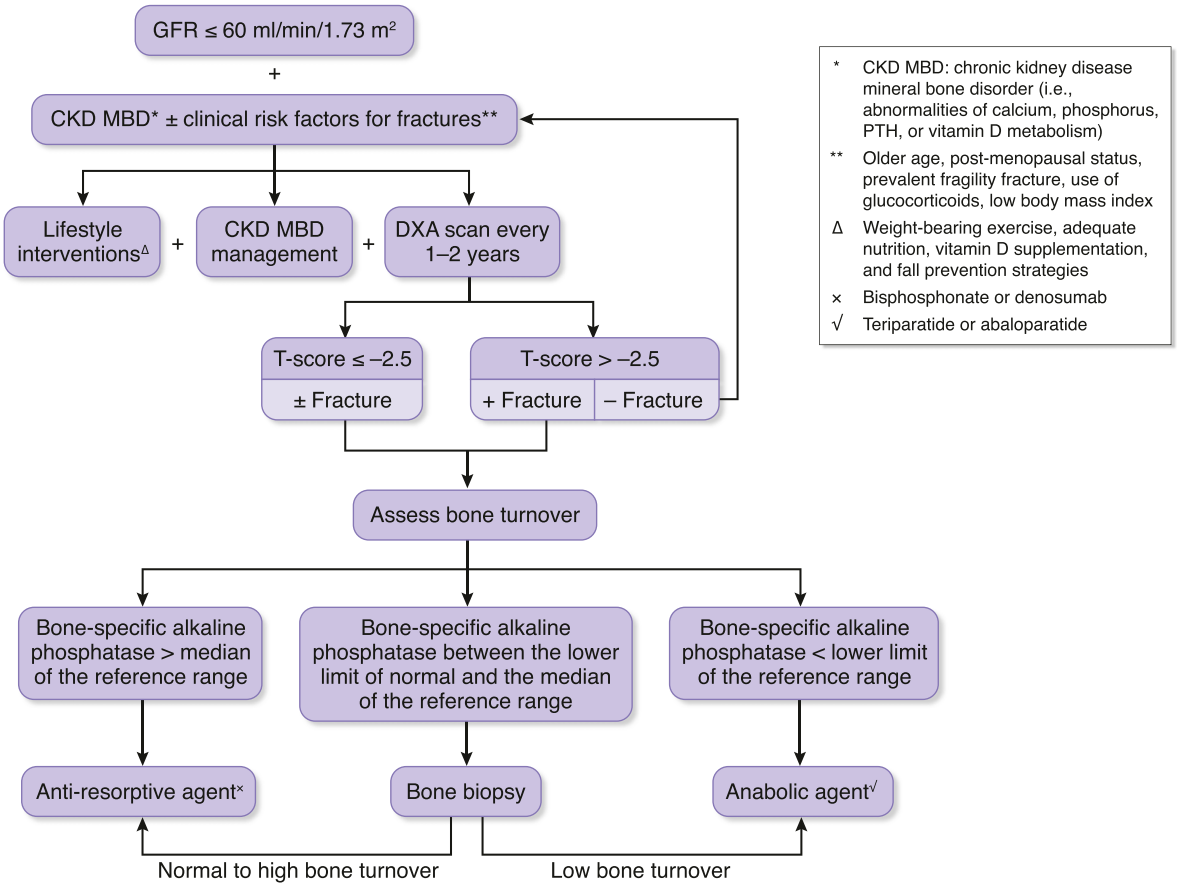

Figure 1. | **An algorithm for fracture risk screening and initiation of anti-fracture strategies in patients with CKD.** CKD-MBD, CKD mineral and bone disease; DXA, dual energy x-ray absorptiometry; PTH, parathyroid hormone.

low values reflect underlying bone turnover; bone biopsy may be used when diagnosis of turnover is not clear (3) (Figure 1). Regarding monitoring the efficacy of antifracture strategies in patients with CKD, there are no data to either inform the frequency of interval BMD measurement or suggest whether increases in BMD will translate into a reduction in overall fracture risk. In the general population, interval BMD testing for patients undergoing antifracture treatment ranges from 1 to 2 years, and similar intervals can be used in patients with CKD. However, these topics need to be the focus of future research.

Managing CKD-MBD

Before initiating an antiresorptive or anabolic agent to treat CKD-associated osteoporosis, we stress the importance of managing CKD-MBD through control of vitamin D deficiency, hyperphosphatemia, and hyperparathyroidism (3) (Figure 1). Secondary hyperparathyroidism is a major feature of CKD-MBD. It begins early in the course of CKD, and its prevalence increases as kidney function declines. Despite the seemingly beneficial adaptive increase in PTH secretion to increase calcium levels, decrease phosphate levels, and increase vitamin D levels, hyperparathyroidism becomes maladaptive over the long term. Correction of 25-hydroxyvitamin D deficiency can partially correct elevated PTH levels in patients with mild to severe CKD (14). Furthermore, data in patients with ESKD suggest that levels of 25-hydroxyvitamin D >30 ng/ml optimize bone mineralization (15). Lowering the plasma phosphate concentration with oral phosphate binders can partially reverse hypocalcemia and hyperparathyroidism. A meta-analysis of trials of phosphate binders found no significant decrease in mortality, hospitalization, or end of treatment calcium-phosphorus product levels with sevelamer compared with calcium-based binders (16). Other studies found a higher mortality with calcium-based binders compared with noncalcium-based binders (17). Calcium-based binders are thought to increase vascular calcification and cardiovascular mortality. When PTH levels remain elevated despite treatment of hyperphosphatemia, addition of a vitamin D analog is appropriate. Paricalcitol is a synthetic metabolically active vitamin D analog. It was well tolerated, and it effectively decreased PTH levels with minimal or no effect on calcium levels, phosphorus balance, and kidney function in patients with stages 3 and 4 CKD (18). Recent studies have also suggested that, in addition to vitamin D analogs, the use of the calcimimetic cinacalcet can reduce risk of fractures in patients with CKD and secondary hyperparathyroidism (19). One year of treatment with cinacalcet increased BMD of the femoral neck by 7.3% compared with 6.2% in subjects treated with and without cinacalcet,

respectively (20). In the Bone Biopsy Study for Dialysis Patients with Secondary Hyperparathyroidism of End Stage Renal Disease (BONAFIDE) Study, which investigated bone-tissue–level effects of cinacalcet in patients with ESKD and PTH≥300 pg/ml, cinacalcet induced a 48.3% median decrease in PTH levels ($P<0.001$) and a significant reduction ($P<0.001$) in the bone formation rate. Although none of the subjects had normal bone histology at the initiation of the study, 20 subjects had normalization of bone histology by study completion (21). Finally, nonpharmacologic strategies with proven antifracture efficacy should be used in all patients. For example, 60% of the observed reduction in fracture incidence in the general population has been attributed to lifestyle interventions, including calcium and vitamin D supplementation, smoking cessation, weight-bearing exercise, fall prevention (22), improved nutrition (23), and moderating alcohol intake (24) (Figure 1).

Antiresorptive Agents

Pharmacologic strategies that inhibit osteoclast-mediated bone resorption may be helpful in preventing bone loss and fracture in patients with normal- to high-turnover bone disease. These agents can be used in patients similar to those included in the *post hoc* analyses of the pivotal fracture trials, and on the basis of anecdotal experience, these agents are considered safe in patients without low-turnover or adynamic bone disease. However, there are no primary data on any of these agents on skeletal and extraskeletal safety and antifracture efficacy in patients with CKD-MBD; therefore, clinical trials in patients with CKD-MBD are needed to determine skeletal and extraskeletal safety and antifracture efficacy (25).

Bisphosphonates

Bisphosphonates are taken up by osteoclasts and inhibit farnesyl pyrophosphate synthase, a crucial enzyme in the synthesis of isoprenoid compounds that are essential for osteoclast function; except for the nitrogen-containing bisphosphonates, they induce osteoclast apoptosis. They have a high affinity for bone mineral, and therefore, they are typically retained in the skeleton for several years. Bisphosphonates are not taken up by other organs, and residual drug that is not absorbed by osteoclasts is cleared by the kidney. Therefore, these agents have not been recommended in patients with an eGFR<30 ml/min due to concern of excessive accumulation of bisphosphonate in the skeleton, thus resulting in oversuppression of bone remodeling. However, over the past decade, data suggest that these agents are safe in patients with an eGFR of 15–59 ml/min per 1.73 m^2 due to age-related declines in kidney function and without CKD-MBD (26,27). In a *post hoc* analysis of nine double-blinded, controlled trials investigating the effect of risendronate on postmenopausal osteoporosis, 8996 women were identified as having kidney impairment on the basis of creatinine clearance at the time of receiving risedronate (26). Women with lower creatinine clearance treated with risedronate had a significant increase in BMD and reduction in vertebral fractures compared with women treated with placebo. Risedronate did not have adverse effects on kidney function. Transiliac crest bone biopsies in 43 and 14 subjects with creatinine clearance between 50 and 80 ml/min and between 30 and 49 ml/min, respectively, did not reveal adynamic bone disease or mineralization defects. In a secondary analysis of the Fracture Intervention Trial, 9.9% of the subjects were found to have an eGFR<45 ml/min (27). More recently, Shigematsu *et al.* (28) performed a *post hoc* analysis of pooled data from three Japanese clinical trials on 852 subjects with osteoporosis who were administered risendronate. The eGFRs of the subjects ranged from 30 to ≥90 ml/min per 1.73 m^2. Over the 48 weeks of follow-up, risendronate administration did not result in a significant change in eGFR (P value $=0.60$). A significant improvement in lumbar spine BMD ($P<0.001$) and a significant suppression in the bone turnover markers urine N-terminal telopeptide of type 1 collagen, urine C-terminal telopeptide of type 1 collagen, and bone alkaline phosphatase ($P<0.001$) were observed. The increase in lumbar spine BMD did not differ between subjects with eGFR≥30 to <60, ≥60 to <90, and ≥90 ml/min per 1.73 m^2 (28). Treatment with alendronate similarly increased BMD at the spine and hip and reduced the risk of clinical and spine fractures in subjects with and without an eGFR<45 ml/min. There were no adverse effects on kidney function. Few studies have investigated bisphosphonate safety and efficacy specifically in patients with CKD-MBD (29,30). Toussaint *et al.* (29) reported that 18 months of alendronate versus placebo resulted in an increase in lumbar spine T score by 0.3 ($P=0.03$) in patients with CKD stages 3 and 4. Bergner *et al.* (30) administered ibandronate to 16 patients on dialysis who had a lumber spine T score <-1.0 by DXA and PTH levels greater than twofold the upper limit of normal. After 48 weeks, mean T scores increased from -3.08 ± -1.11 to -2.78 ± -1.27 ($P<0.01$), and PTH levels did not change. Neither of these studies obtained bone biopsies to assess tissue-level safety. Ota *et al.* (31) investigated bone-tissue–level safety of alendronate in 5/6-nephrectomized rats with CKD stage 4. Alendronate improved femoral trabecular bone volume fraction, the mineral-to-matrix ratio of the endosteal and periosteal regions of cortical bone, and the carbonate-to-phosphate ratio of both trabecular and cortical bone; kidney function was not affected (31).

Denosumab

Denosumab is a potent antiresorptive agent. It is an mAb against the receptor activator of NF-κB ligand, and it inhibits osteoclast proliferation and development. In contrast to bisphosphonates, denosumab is not cleared by the kidney; therefore, there is no risk of oversuppressing bone turnover due to drug accumulation in CKD. The role of denosumab in managing osteoporosis in patients with age-related kidney disease was explored in a *post hoc* analysis of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) Trial (32). The registration trial included 7868 postmenopausal women and showed that treatment with denosumab for 36 months reduced vertebral, hip, and nonvertebral fracture risks by 68%, 40%, and 20%, respectively (33). Jamal *et al.* (32) showed that 73 and 2817 women in the FREEDOM Trial had creatinine clearance between 15 and 29 ml/min and between 30 and 59 ml/min, respectively. There was no

interaction between treatment effect and kidney function, and adverse events did not differ by creatinine clearance. Denosumab increased BMD at the spine and hip and resulted in a 68% lower odds of vertebral fracture in subjects with an eGFR of 30–59 ml/min per 1.73 m^2. Although the results of the FREEDOM Trial did not show relationships between hypocalcemia and kidney function, patient reports and clinical experience indicate that mild to severe hypocalcemia may occur in patients with CKD and hyperparathyroidism (34). Block *et al.* (34) gave single-dose denosumab to 55 patients with various degrees of kidney disease and monitored levels of serum calcium and the bone resorption marker C-telopeptide for 112 days post-administration. Although 15% of patients experienced mild to severe hypocalcemia, no subject taking adequate supplementation with calcium and vitamin D (up to 1000 mg daily and 800 IU daily, respectively) became hypocalcemic. In multiple linear regression, there was insufficient power to detect an association between severity of kidney disease and severity of decreases in serum calcium (P value $=0.08$). Chen *et al.* (35) administered a single dose of denosumab to 12 patients with ESKD on dialysis with PTH>1000 pg/ml, T score <-1.0, and bone pain who were poor candidates for parathyroidectomy; dialysate calcium, calcitriol, and phosphate binders were adjusted according to serum chemistries. At 6 months, mean increases in femoral neck and lumbar spine BMD were 23.7%±4.0% and 17.1%±2.6%, respectively. Although PTH levels initially increased, at 6 months, they were lower than baseline due to an increase in calcitriol dose. Hypocalcemia was the most common adverse event, but none of the patients managed with calcium supplementation, higher calcium dialysate, and calcitriol were symptomatic. Festucci *et al.* (36) aimed to evaluate the safety of denosumab in 12 subjects with ESKD and osteoporosis. Sixty milligrams of denosumab was administered every 6 months, and subjects were followed for 24 months. Bone alkaline phosphatase levels decreased gradually by 184% at 2 years ($P>0.05$). Serum calcium levels decreased starting at day 20 and nadired at 2 months before improving toward normal levels at 3 months. Hypocalcemia recurred but was less severe with subsequent doses, and it was alleviated by using high-calcium dialysate bath and supplementing with calcium and vitamin D (36). These and other clinical data suggest that denosumab can be safely administered to patients with CKD-associated osteoporosis as long as patients are supplemented with vitamin D, have adequate calcium intake, and are monitored for hypocalcemia. Regarding bone tissue safety data, there are no data on humans, but animal data suggest that receptor activator of NF-κB ligand inhibition should improve bone quality (37).

Osteoanabolic Agents

The use of osteoanabolic agents in patients with CKD is controversial, because these drugs are forms of recombinant PTH or PTH-related peptide. Studies indicate that, although teriparatide increased cortical thickness, cortical porosity increased, and density decreased, while bone strength was maintained. In CKD, high baseline levels of PTH drive cortical losses through increases in cortical porosity and thinning due to endocortical trabecularization. Hyperparathyroidism is also linked to adverse cardiovascular outcomes Therefore, osteoanabolic agents should not be used to treat high-turnover bone disease due to hyperparathyroidism. In patients with low-turnover or adynamic bone disease, these agents may increase bone turnover and result in increased BMD. Data on the antifracture efficacy of these agents exist for patients with age-related kidney function decline without CKD-MBD. Although trials are needed with fracture and cardiovascular end points in patients with moderate to severe CKD before osteoanabolic agents are widely adapted in patients with CKD-associated osteoporosis, the current body of literature suggests that teriparatide is safe in patients fitting the criteria of the Fracture Prevention Trial and patients with CKD and low-turnover bone disease (*e.g.*, after parathyroidectomy) with high risk for fracture on the basis of BMD and clinical history.

Teriparatide

Teriparatide is a recombinant peptide of the first 34 amino-terminal residues of PTH. It was the first Food and Drug Administration (FDA)–approved osteoanabolic agent to treat osteoporosis and prevent fractures in both age-related and glucocorticoid-induced osteoporosis. Miller *et al.* (38) conducted a *post hoc* analysis of the Fracture Prevention Trial to assess safety and efficacy in postmenopausal women with osteoporosis and age-related declines in kidney function determined by creatinine clearance. Mild, moderate, and severe CKD were defined as creatinine clearance between 50 and 79 ml/min, between 30 and 49 ml/min, and <30 ml/min, respectively. Teriparatide increased BMD at the spine and femoral neck in all kidney function groups and had similar efficacy in preventing vertebral and nonvertebral fracture in patients with creatinine clearance <80 ml/min compared with >80 ml/min. Adverse events included hypercalcemia and hyperuricemia, which were more common in patients with the lowest levels of creatinine clearance. Data on the use of teriparatide in patients with moderate to severe CKD-MBD are available from small observational studies. Cejka *et al.* (39) administered teriparatide for 6 months to seven patients with ESKD on dialysis with biopsy-proven adynamic bone disease. Teriparatide increased lumbar spine BMD, improved the monthly change in BMD at both the spine and the hip, and did not affect changes in coronary artery calcification scores. Sumida *et al.* (40) administered teriparatide once weekly to patients with ESKD on dialysis with hypoparathyroidism and osteoporosis defined by a T score ≤ -2.5 at the spine, hip, or forearm or a T score between -2.5 and -1.0 with a prevalent fragility fracture. Over the course of treatment, both bone formation and resorption markers increased, serum calcium levels decreased, BMD at the spine increased, and the formation marker bone-specific alkaline phosphatase was positively associated with the 48-week percentage change in lumbar spine BMD. The most common adverse event was transient hypotension, and no patient developed hypercalcemia.

Abaloparatide

Abaloparatide is a novel osteoanabolic agent recently approved by the FDA for treatment of osteoporosis and

prevention of fractures. Abaloparatide is an analog of PTH-related peptide, and it was designed to have relatively greater affinity for the transient state of PTH/PTH1 receptor, thus being more purely anabolic. In ovariectomized rats, abaloparatide increased bone formation and mass without increasing bone resorption (41). In human clinical trials, abaloparatide increased BMD at the spine and hip (42) and decreased risk of spine and nonspine fractures with approximately 50% lower risk of hypercalcemia than teriparatide (43). Bone histomorphometry in postmenopausal women treated with 12–18 months of abaloparatide showed no evidence of excessive osteoid, marrow fibrosis, or abnormalities in mineralization (44). Furthermore, patients treated with abaloparatide had lower eroded surface on histomorphometry versus the placebo group (43), but they had equivalent increases in cortical porosity compared with teriparatide (44). These observations are consistent with the clinical trial bone turnover marker data showing that the rise in C-telopeptide, a resorption marker, was significantly less pronounced with abaloparatide than with teriparatide (44). On the basis of the ability of abaloparatide to increase bone mass and formation with less risk of hypercalcemia, it may be an ideal agent to treat patients with CKD-MBD and low to normal bone turnover with high fracture risk. However, there are no data in patients with CKD-MBD.

New Agents

Several new antifracture agents have been studied in the general population. These agents were associated with large increases in bone mass and fracture risk reductions. They have not been studied in patients with CKD and should not be used until trial cardiovascular event data are completely understood.

Sclerostin

Sclerostin is a glycoprotein product of the SOST gene, and it is secreted almost exclusively by osteocytes. Sclerostin inhibits Wnt signaling, which is a key negative regulator of bone formation. Loss of function SOST mutations result in high-bone mass phenotypes through uncoupling formation and resorption in favor of formation. Therefore, since inhibition of sclerostin favors bone formation over resorption, it could provide great utility in treating CKD-associated osteoporosis as its use is not associated with the induction of low turnover bone disease - a theoretical risk of using antiresorptive agents. In clinical trials, romosozumab, a humanized mAb that targets sclerostin, resulted in an increase in BMD to a greater extent than alendronate and teriparatide and a decrease in risk of vertebral and nonvertebral fractures in postmenopausal women (45–47). Furthermore, of high interest to patients with CKD, which is associated with cortical losses from the actions of PTH, Langdahl *et al.* (48) reported that cortical BMD increased in greater proportion to trabecular BMD over 12 months in patients switched from a bisphosphonate to romosozumab. Moreover, in the comparator group, in which subjects were switched to teriparatide, subjects experienced a decrease in cortical BMD. It is interesting to note that the bone turnover marker data from these trials suggested an uncoupling of bone remodeling in favor of bone formation, which might be an advantageous pharmacologic property for patients with CKD. For example, bone formation markers increased within a week of administration of romosozumab and peaked at 14 days to 1 month before declining toward or below baseline levels, whereas bone resorption markers decreased from baseline within a week of administration and remained below baseline for at least 12 months (45–47). However, in a recent study by Saag *et al.* (46), patients given 12 months of romosozumab followed by 12 months of alendronate versus 24 continuous months of alendronate had an increase in serious cardiovascular adverse events (odds ratio [OR], 1.31; 95% confidence interval [95% CI], 0.85 to 2.00) that was driven by cardiac ischemic events (OR, 2.65; 95% CI, 1.03 to 6.77) and cerebrovascular events (OR, 2.27; 95% CI, 0.93 to 5. 22). It is important to note that cardiovascular events have not been reported in other studies (47,48). Whether these results indicate that romosozumab increases cardiac risk or that alendronate is cardioprotective is not known, and these results are the study of intense investigation. Although sclerostin is constitutively expressed in the aorta (49) and upregulated in foci of vascular calcification (50), its function in the vasculature is not known.

Cathepsin K Antagonists

Cathepsin K is a cysteine protease expressed highly in osteoclasts that degrades the bone collagenous matrix; therefore, cathepsin K inhibitors decrease bone resorption. Odanacatib was the only cathepsin K inhibitor studied in phase 3 clinical trials; however, it was withdrawn from FDA consideration after it was associated with increased risk of cerebrovascular events.

Conclusions

As nephrologists, we must take action to tackle the longstanding and complex disorder of bone disease in patients with CKD so that we can improve our patients' short- and long-term clinical outcomes. Although treatment strategies for patients who meet the inclusion criteria for the pivotal fracture trials can be easily chosen, the majority of patients seen by nephrologists will require a personalized approach to determine the underlying renal osteodystrophy type and appropriateness of administering one of the current antiosteoporosis agents that has FDA approval for use in the general population. The future of the field must be patient-centric. We need to show that the battery of agents used in the general population has skeletal and nonskeletal safety and antifracture efficacy in patients with CKD-MBD, and we must push for the development of agents that are specific to the treatment of CKD-associated osteoporosis.

Disclosures

None.

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