

## 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  $\leq -2.5$  (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

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**Table 1. Glossary of terms**

Term	Definition
<b>Primary osteoporosis</b>	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
<b>Secondary osteoporosis</b>	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

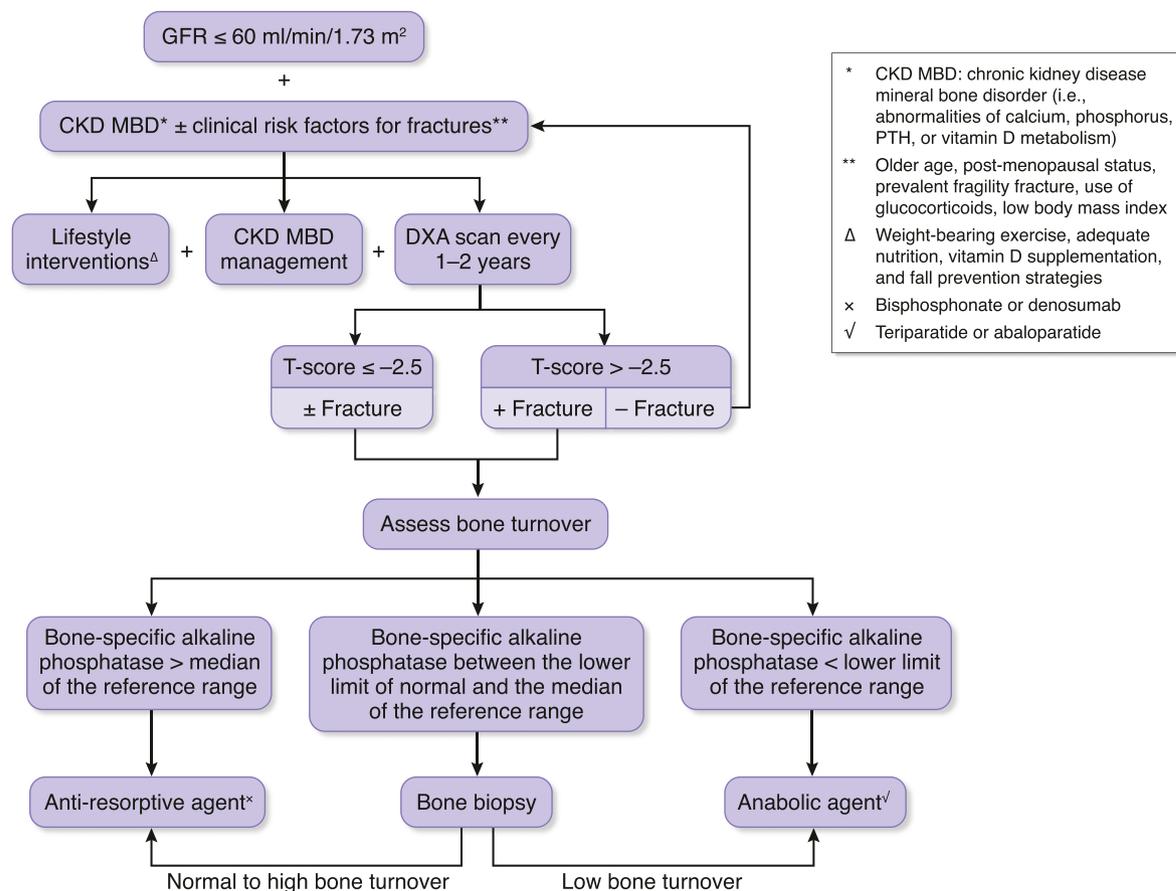
The paradigm to managing CKD-associated osteoporosis is evolving. The 2005 KDIGO committee shifted the historical nomenclature of renal osteodystrophy type to a unified classification system on the basis of bone turnover, mineralization, and volume, and turnover is now classified as low, normal, or high 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<sup>2</sup> 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  $\text{PTH} \geq 300$  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  $\text{eGFR} < 30$  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  $\text{eGFR}$  of 15–59 ml/min per  $1.73 \text{ m}^2$  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 risendronate (26). Women with lower creatinine clearance treated with risendronate had a significant increase in BMD and reduction in vertebral fractures compared with women treated with placebo. Risendronate 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  $\text{eGFR} < 45$  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  $\text{eGFR}$ s of the subjects ranged from 30 to  $\geq 90$  ml/min per  $1.73 \text{ m}^2$ . Over the 48 weeks of follow-up, risendronate administration did not result in a significant change in  $\text{eGFR}$  ( $P$  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  $\text{eGFR} \geq 30$  to  $< 60$ ,  $\geq 60$  to  $< 90$ , and  $\geq 90$  ml/min per  $1.73 \text{ m}^2$  (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  $\text{eGFR} < 45$  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 lumbar 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  $-3.08 \pm -1.11$  to  $-2.78 \pm -1.27$  ( $P < 0.01$ ), 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- $\kappa$ B 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<sup>2</sup>. 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  $23.7\% \pm 4.0\%$  and  $17.1\% \pm 2.6\%$ , 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- $\kappa$ B 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  $\leq -2.5$  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 subject 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.

### References

1. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C: Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 58: 396–399, 2000

2. Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM: Hip fracture in patients with non-dialysis-requiring chronic kidney disease. *J Bone Miner Res* 31: 1803–1809, 2016
3. Ketteler M, Block GA, Evenepoel P, Fukagawa M, Herzog CA, McCann L, Moe SM, Shroff R, Tonelli MA, Toussaint ND, Vervloet MG, Leonard MB: Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) guideline update: What's changed and why it matters. *Kidney Int* 92: 26–36, 2017
4. Yenckel RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, Harris TB, Newman AB, Cauley JA, Fried LF; Health, Aging, and Body Composition Study: Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 7: 1130–1136, 2012
5. Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, Kuwahara M, Sasaki S, Tsukamoto Y: Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. *Nephrol Dial Transplant* 27: 345–351, 2012
6. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, Fusaro M, Wald R, Weinstein J, Jamal SA: Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 30: 913–919, 2015
7. Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, Adachi JD, Morin S, Goltzman D, Lentle B, Jackson SA, Josse RG, Jamal SA: Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* 10: 646–653, 2015
8. Klawansky S, Komaroff E, Cavanaugh PF Jr, Mitchell DY, Gordon MJ, Connelly JE, Ross SD: Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int* 14: 570–576, 2003
9. Nickolas TL, McMahon DJ, Shane E: Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 17: 3223–3232, 2006
10. Arneson TJ, Li S, Liu J, Kilpatrick RD, Newsome BB, St Peter WL: Trends in hip fracture rates in US hemodialysis patients, 1993–2010. *Am J Kidney Dis* 62: 747–754, 2013
11. Nair SS, Mitani AA, Goldstein BA, Chertow GM, Lowenberg DW, Winkelmayr WC: Temporal trends in the incidence, treatment, and outcomes of hip fracture in older patients initiating dialysis in the United States. *Clin J Am Soc Nephrol* 8: 1336–1342, 2013
12. Wagner J, Jhaveri KD, Rosen L, Sunday S, Mathew AT, Fishbane S: Increased bone fractures among elderly United States hemodialysis patients. *Nephrol Dial Transplant* 29: 146–151, 2014
13. Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA: Temporal trends in fracture rates and post-discharge outcomes among hemodialysis patients. *J Am Soc Nephrol* 24: 1461–1469, 2013
14. Kandula P, Dobre M, Schold JD, Schreiber MJ Jr, Mehrotra R, Navaneethan SD: Vitamin D supplementation in chronic kidney disease: A systematic review and meta-analysis of observational studies and randomized controlled trials. *Clin J Am Soc Nephrol* 6: 50–62, 2011
15. Coen G, Mantella D, Manni M, Balducci A, Nofroni I, Sardella D, Ballanti P, Bonucci E: 25-Hydroxyvitamin D levels and bone histomorphometry in hemodialysis renal osteodystrophy. *Kidney Int* 68: 1840–1848, 2005
16. Navaneethan SD, Palmer SC, Craig JC, Elder GJ, Strippoli GF: Benefits and harms of phosphate binders in CKD: A systematic review of randomized controlled trials. *Am J Kidney Dis* 54: 619–637, 2009
17. Patel L, Bernard LM, Elder GJ: Sevelamer versus calcium-based binders for treatment of hyperphosphatemia in CKD: A meta-analysis of randomized controlled trials. *Clin J Am Soc Nephrol* 11: 232–244, 2016
18. Coyne DW, Goldberg S, Faber M, Ghossein C, Sprague SM: A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3–4 CKD. *Clin J Am Soc Nephrol* 9: 1620–1626, 2014
19. Moe SM, Abdalla S, Chertow GM, Parfrey PS, Block GA, Correa-Rotter R, Floege J, Herzog CA, London GM, Mahaffey KW, Wheeler DC, Dehmel B, Goodman WG, Drüeke TB; Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial Investigators: Effects of cinacalcet on fracture events in patients receiving hemodialysis: The EVOLVE trial. *J Am Soc Nephrol* 26: 1466–1475, 2015
20. Tsuruta Y, Okano K, Kikuchi K, Tsuruta Y, Akiba T, Nitta K: Effects of cinacalcet on bone mineral density and bone markers in hemodialysis patients with secondary hyperparathyroidism. *Clin Exp Nephrol* 17: 120–126, 2013
21. Behets GJ, Spasovski G, Sterling LR, Goodman WG, Spiegel DM, De Broe ME, D'Haese PC: Bone histomorphometry before and after long-term treatment with cinacalcet in dialysis patients with secondary hyperparathyroidism. *Kidney Int* 87: 846–856, 2015
22. West SL, Jamal SA, Lok CE: Tests of neuromuscular function are associated with fractures in patients with chronic kidney disease. *Nephrol Dial Transplant* 27: 2384–2388, 2012
23. Schürch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP: Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 128: 801–809, 1998
24. Brauer CA, Coca-Perrillon M, Cutler DM, Rosen AB: Incidence and mortality of hip fractures in the United States. *JAMA* 302: 1573–1579, 2009
25. Wilson LM, Rebolz CM, Jirru E, Liu MC, Zhang A, Gayleard J, Chu Y, Robinson KA: Benefits and harms of osteoporosis medications in patients with chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med* 166: 649–658, 2017
26. Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE: Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: A pooled analysis of nine clinical trials. *J Bone Miner Res* 20: 2105–2115, 2005
27. Jamal SA, Bauer DC, Ensrud KE, Cauley JA, Hochberg M, Ishani A, Cummings SR: Alendronate treatment in women with normal to severely impaired renal function: An analysis of the fracture intervention trial. *J Bone Miner Res* 22: 503–508, 2007
28. Shigematsu T, Muraoka R, Sugimoto T, Nishizawa Y: Risedronate therapy in patients with mild-to-moderate chronic kidney disease with osteoporosis: Post-hoc analysis of data from the risedronate phase III clinical trials. *BMC Nephrol* 18: 66, 2017
29. Toussaint ND, Lau KK, Strauss BJ, Polkinghorne KR, Kerr PG: Effect of alendronate on vascular calcification in CKD stages 3 and 4: A pilot randomized controlled trial. *Am J Kidney Dis* 56: 57–68, 2010
30. Bergner R, Henrich D, Hoffmann M, Schmidt-Gayk H, Lenz T, Uppenkamp M: Treatment of reduced bone density with ibandronate in dialysis patients. *J Nephrol* 21: 510–516, 2008
31. Ota M, Takahata M, Shimizu T, Kanehira Y, Kimura-Suda H, Kameda Y, Hamano H, Hiratsuka S, Sato D, Iwasaki N: Efficacy and safety of osteoporosis medications in a rat model of late-stage chronic kidney disease accompanied by secondary hyperparathyroidism and hyperphosphatemia. *Osteoporos Int* 28: 1481–1490, 2017
32. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, Ebeling PR, Franek E, Yang YC, Egbuna OI, Boonen S, Miller PD: Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res* 26: 1829–1835, 2011
33. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C; FREEDOM Trial: Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 361: 756–765, 2009
34. Block GA, Bone HG, Fang L, Lee E, Padhi D: A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res* 27: 1471–1479, 2012
35. Chen CL, Chen NC, Hsu CY, Chou KJ, Lee PT, Fang HC, Renn JH: An open-label, prospective pilot clinical study of denosumab for severe hyperparathyroidism in patients with low bone mass undergoing dialysis. *J Clin Endocrinol Metab* 99: 2426–2432, 2014
36. Festuccia F, Jafari MT, Moiola A, Fofi C, Barberi S, Amendola S, Sciacchitano S, Punzo G, Menè P: Safety and efficacy of denosumab in osteoporotic hemodialysed patients. *J Nephrol* 30: 271–279, 2017
37. Padagas J, Colloton M, Shalhoub V, Kostenuik P, Morony S, Munyakazi L, Guo M, Gianneschi D, Shatzen E, Geng Z, Tan HL, Dunstan C, Lacey D, Martin D: The receptor activator of nuclear factor-kappaB ligand inhibitor osteoprotegerin is a bone-protective agent in a rat model of chronic renal

- insufficiency and hyperparathyroidism. *Calcif Tissue Int* 78: 35–44, 2006
38. Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH: Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int* 18: 59–68, 2007
  39. Cejka D, Kodras K, Bader T, Haas M: Treatment of hemodialysis-associated adynamic bone disease with teriparatide (PTH1-34): A pilot study. *Kidney Blood Press Res* 33: 221–226, 2010
  40. Sumida K, Ubara Y, Hoshino J, Mise K, Hayami N, Suwabe T, Kawada M, Imafuku A, Hiramatsu R, Hasegawa E, Yamanouchi M, Sawa N, Takaichi K: Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: A prospective study. *Osteoporos Int* 27: 1441–1450, 2016
  41. Bahar H, Gallacher A, Downall J, Nelson CA, Shomali M, Hattersley G: Six weeks of daily Abaloparatide treatment increased vertebral and femoral bone mineral density, microarchitecture and strength in ovariectomized osteopenic rats. *Calcif Tissue Int* 99: 489–499, 2016
  42. Leder BZ, O’Dea LS, Zanchetta JR, Kumar P, Banks K, McKay K, Lyttle CR, Hattersley G: Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 100: 697–706, 2015
  43. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbin CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C; ACTIVE Study Investigators: Effect of Abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: A randomized clinical trial. *JAMA* 316: 722–733, 2016
  44. Moreira C, Fitzpatrick LA, Wang Y, Recker RR: Effects of Abaloparatide-SC (BA058) on bone histology and histomorphometry: The ACTIVE phase 3 trial. *Bone* 97: 314–319, 2016
  45. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, Langdahl BL, Reginster JY, Zanchetta JR, Wasserman SM, Katz L, Maddox J, Yang YC, Libanati C, Bone HG: Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* 370: 412–420, 2014
  46. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, Maddox J, Fan M, Meisner PD, Grauer A: Romosozumab or Alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* 377: 1417–1427, 2017
  47. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, Lau E, Lewiecki EM, Miyauchi A, Zerbin CA, Milmont CE, Chen L, Maddox J, Meisner PD, Libanati C, Grauer A: Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med* 375: 1532–1543, 2016
  48. Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, Engelke K, Finkelstein JS, Genant HK, Goemaere S, Hyldstrup L, Jodar-Gimeno E, Keaveny TM, Kendler D, Lakatos P, Maddox J, Malouf J, Massari FE, Molina JF, Ulla MR, Grauer A: Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: A randomised, open-label, phase 3 trial. *Lancet* 390: 1585–1594, 2017
  49. Didangelos A, Yin X, Mandal K, Baumert M, Jahangiri M, Mayr M: Proteomics characterization of extracellular space components in the human aorta. *Mol Cell Proteomics* 9: 2048–2062, 2010
  50. Brandenburg VM, Kramann R, Koos R, Krüger T, Schurgers L, Mühlenbruch G, Hübner S, Gladziwa U, Drechsler C, Ketteler M: Relationship between sclerostin and cardiovascular calcification in hemodialysis patients: A cross-sectional study. *BMC Nephrol* 14: 219, 2013
  51. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R; National Osteoporosis Foundation: Clinician’s guide to prevention and treatment of osteoporosis. *Osteoporos Int* 25: 2359–2381, 2014
  52. Fitzpatrick LA: Secondary causes of osteoporosis. *Mayo Clin Proc* 77: 453–468, 2002
  53. Address DL: Adynamic bone in patients with chronic kidney disease. *Kidney Int* 73: 1345–1354, 2008

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