17 Management of Bone Disorders in Kidney Disease

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Introduction

In healthy individuals, normal serum concentrations of phosphorus and calcium are maintained through the interaction of three hormones: parathyroid hormone (PTH), calcitriol ($1,25(OH)_2D_3$), and fibroblast growth factor 23 (FGF-23). These hormones act on four primary target organs: bone, kidney, intestine, and parathyroid glands. The kidneys play a critical role in the regulation of serum calcium and phosphorus concentrations as well as these three hormones. In patients with chronic kidney disease (CKD), increased PTH concentrations are generally the first clinically measured abnormality observed in patients with evolving CKD; however, FGF-23 increases prior to PTH [1, 2]. Shortly following the increases in FGF-23 and PTH, calcitriol concentrations will fall [1]. Changes in these hormones in the early stages of the CKD are an adaptive mechanism to help maintain the serum phosphorus and calcium concentrations in the normal range. It is not until the development of CKD stages 4–5 (glomerular filtration rate less than 30 mL/min/1.73m^2) that measurable abnormalities of calcium and phosphorus become apparent [1].

With progression of CKD, these compensatory responses become unable to maintain normal mineral homeostasis, resulting in [1] altered concentrations of calcium, phosphorus, PTH, calcitriol, and FGF-23, [2] disturbances in bone remodeling and mineralization (renal osteodystrophy) and/or impaired linear growth in children, and [3] extra-skeletal calcification in soft tissues and arteries. In 2006, the term chronic kidney disease-mineral and bone disorder (CKD-MBD) was developed by the Kidney Disease Improving Global Outcomes (KDIGO) work group to describe this triad of abnormalities in biochemical measures, skeletal abnormalities, and extra-skeletal calcification [3]. Of note, osteoporosis was not defined as an independent skeletal disorder and should not be treated without considering the other metabolic disorders associated with CKD-MBD [3, 4]. The updated 2017 guidelines do recommend obtaining bone mineral densitometry in patients with CKD stages 3–5 if they have other risk factors for osteoporotic fractures; however, the results do not predict the specific bone lesion but may be useful for deciding to proceed with a bone biopsy [5]. The abnormalities that constitute CKD-MBD are interrelated in both the pathophysiology of the disease and the response to treatment. All three components of CKD-MBD are associated with increased risk of fractures, cardiovascular disease, and mortality in

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patients with advanced CKD. Treatment of CKD-MBD focuses on the prevention and correction of these hormonal abnormalities.

Pathophysiology of Chronic Kidney Disease-Mineral Bone Disorder

Parathyroid hormone, calcitriol, and FGF-23 work together to maintain normal phosphate and calcium homeostasis to achieve appropriate balance in the blood and urine so as to avoid extra-skeletal calcification and ensure adequate availability of these ions for bone remodeling. This response is a very complex system of multiple integrated feedback loops and is easier to understand if broken into loops that regulate phosphate, calcium, and calcitriol. Both PTH and FGF-23 have similar effects in stimulating renal phosphate excretion [6]. However, these hormones differ in their effects on vitamin D metabolism. Parathyroid hormone stimulates CYP27B1 activity, thus increasing the production of calcitriol, which in turn negatively feeds back on the parathyroid gland to decrease PTH secretion. In contrast, FGF-23 inhibits CYP27B1 and stimulates CYP24, thereby decreasing the production and increasing the deactivation of calcitriol and which results in limiting further secretion of FGF-23, as calcitriol normally stimulates FGF-23 production [7].

As CKD progresses, there is decreased renal phosphate excretion resulting in an increased phosphate load causing increases in both PTH and FGF-23 [1, 2]. Both the elevated PTH and FGF-23 increase urinary phosphate excretion through downregulation of the sodium-phosphate (NaPi) transporters [6]. Parathyroid hormone also increases renal calcium reabsorption preventing the worsening of hypocalcemia as well as minimizing the possibility of high urinary calcium and phosphate concentrations. Parathyroid hormone also stimulates the secretion of FGF-23 from osteocytes, and the increased FGF-23 inhibits PTH gene expression and secretion [7–9].

Hypocalcemia is a potent stimulator of PTH and blunts FGF-23 release [10]. Thus, the decrease in FGF-23 release would result in less FGF-23 inhibition of both PTH and calcitriol synthesis thus offsetting the development of hypocalcemia. This process would maximize both the PTH effects to increase renal calcium reabsorption, increase bone resorption, and enhance calcitriol stimulation of intestinal calcium absorption with the goal of normalizing serum calcium concentrations. Hypercalcemia would stimulate FGF-23 (which reduces PTH and calcitriol synthesis) as well as directly inhibit calcitriol synthesis and PTH secretion [7]. The result is decreased intestinal calcium absorption, renal calcium reabsorption, and bone resorption.

Diagnosis of Chronic Kidney Disease-Mineral Bone Disorder

Parathyroid Hormone

Parathyroid hormone concentration in plasma or serum serves not only as an indicator of abnormal mineral metabolism in CKD-MBD but also as a noninvasive biochemical sign for the initial diagnosis of renal osteodystrophy, the bone component of CKD-MBD. Parathyroid hormone measurements also can be a useful index for monitoring the evolution of renal osteodystrophy and can serve as a surrogate measure of bone turnover in patients with CKD. Although the sensitivity and specificity of PTH as a marker of bone remodeling are not ideal, it appears to be the best biomarker currently available [11]. Unfortunately, it is not clear what the optimal PTH concentration should be at each stage of CKD. Thus, guidelines recommend using the same PTH assay for all measurements and evaluating trends rather than targeting precise levels [4, 5].

Vitamin D

Calcidiol concentrations are generally measured by immunoassays, although the gold standard for calcidiol measurement is high-performance liquid chromatography (HPLC), which is not widely available clinically. Similar to PTH, the optimal concentration of calcidiol in CKD-MBD is not

well defined. Vitamin D deficiency is associated with hyperparathyroidism in patients with normal kidney function and plays a role in CKD. Higher concentrations of calcidiol are required to maximally inhibit PTH with worsening CKD [12]. Calcitriol concentrations are universally low [1] and are generally not measured, except in the setting of hypercalcemia.

FGF-23

FGF-23 is currently measured primarily with two different assays: one which measures the intact hormone as well as C-terminal fragments and a second assay that detects the intact hormone. Although these two assays appear comparable in the association with clinical events at this time, they have poor agreement because of differences in FGF-23 fragment detection, antibody specificity, and calibration. From a clinical perspective, more data are required prior to the use of FGF-23 measurements for routine clinical management.

Bone-Specific Alkaline Phosphatase

Bone-specific alkaline phosphatase (BALP) is not renally cleared. BALP concentrations have relatively good correlation with bone formation in CKD and may be additive to the interpretation of parathyroid hormone measurements [4]. However, its concentration has limited ability as an independent measurement [11].

Bone Biopsy Assessment in Chronic Kidney Disease-Mineral Bone Disorder

The definitive method for establishing the specific type of renal osteodystrophy in individual patients requires bone biopsy [3–5, 11], an invasive diagnostic procedure, and access to specialized laboratory personnel and equipment capable of providing assessments of bone histology. Abnormalities of bone quality and quantity are common in CKD-MBD, leading to fractures and impaired growth in children. Clinically, bone biopsies are most useful for differentiating bone turnover as well as bone volume and mineralization. KDIGO recommends that the definition of renal osteodystrophy be limited to describing the alterations of bone morphology in patients with CKD and is one measure of the skeletal component of the systemic disorder of CKD-MBD that can be quantifiable by histomorphometry [3–5]. Three key histologic descriptors—bone turnover, mineralization, and volume (TMV system)—with any combination of each of the descriptors possible in a given specimen were developed to classify bone biopsies and help guide therapy [3].

Turnover reflects the rate of skeletal remodeling, which is normally the coupled process of bone resorption and bone formation. Bone turnover is affected mainly by hormones, cytokines, mechanical stimuli, and growth factors that influence the recruitment, differentiation, and activity of osteoclasts and osteoblasts. Mineralization reflects how well bone collagen becomes calcified during the formation phase of skeletal remodeling. Causes of impaired mineralization include inadequate vitamin D, mineral (calcium or phosphate) deficiency, acidosis, and bone aluminum toxicity. Volume indicates the amount of bone per unit volume of tissue, and an imbalance in bone resorption and formation can affect bone volume. For example, if resorption exceeds formation, negative bone balance and decreased bone volume result. Determinants of bone volume include age, sex, race, genetic factors, nutrition, endocrine disorders, mechanical stimuli, toxicities, neurologic function, vascular supply, growth factors, and cytokines. Osteoporosis would indicate low bone volume and could be diagnosed via a biopsy. Two large-scale analyses utilizing the TMV system revealed that this classification system provides clinically relevant information [11, 13].

Dual-Energy X-Ray Absorptiometry

Dual-energy X-ray absorptiometry (DXA) measures areal bone mineral density (aBMD) in g/cm^2 using minimal radiation and rapid

scan times. Bone mineral density assessment by DXA has good reproducibility (<1–2% coefficient variation) and reliable reference ranges for age, sex, and race. In the general population, aBMD measured by DXA can be used clinically to define osteoporosis and is an accepted surrogate end point after prospective studies demonstrated an age-dependent predictive value of DXA for fractures [14]. However, DXA has not been found to be as sensitive and specific to assess fracture risk across the spectrum of CKD, in part as it cannot assess bone quality [15, 16]. The KDIGO guidelines recommend DXA to assess fracture risk in patients with CKD stage 1 through stage 3a, as long as biochemical testing does not suggest CKD-MBD [3, 5]. However, for patients with CKD stages 3b through 5, the current guidelines recommend DXA testing to assess fracture risk if results will impact treatment decisions [5]. Although previous studies and a meta-analysis demonstrated that DXA testing may have been lower in patients with CKD and a history of fracture, there is considerable overlap in aBMD results such that aBMD provides poor fracture discrimination in individuals [17]. Subsequent studies have demonstrated that aBMD was able to predict fractures in patients with CKD G3 to G5 [18, 19]. However, DXA cannot make a specific diagnosis as to why there is low bone density. Unlike patients with normal kidney function and a low DXA being classified as having osteoporosis, patients with CKD and low bone density should not be routinely treated with anti-osteoporosis therapies [3–5, 15].

Management of Chronic Kidney Disease-Mineral Bone Disorder

The primary objective of therapy is to correct the underlying pathophysiologic disturbances in mineral metabolism with the goal to prevent the development of severe hyperparathyroidism, fractures, and extra-skeletal mineralization. The KDIGO working group has published guidelines for managing CKD-MBD [4, 5].

Hyperparathyroidism

Most recently the KDIGO guidelines recommend measuring the serum calcium, phosphorus, alkaline phosphatase, and PTH at least once in persons with a glomerular filtration rate (GFR) <45 ml/min/1.73m^2. In people with GFR <45 ml/min/1.73 m^2 (GFR categories 3B–5/5D), the optimal PTH level is not known. In non-dialysis-dependent patients, it is suggested that levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. If any of these metabolic disorders are present, then initial therapy would be directed at correcting them [5]. In patients with CKD stage 5 undergoing dialysis, it is suggested to maintain PTH concentrations in the range of approximately two to nine times the upper normal limit for the specific assay. If there are marked changes in PTH levels in either direction within this range, therapy should either be initiated or altered to prevent progression to levels outside of this range [5]. An important element of the recent KDIGO guidelines is the recommendation to make clinical decisions on managing the PTH level on the change in PTH "trend over time" rather than a single measurement. This suggestion is in part due to the variability in PTH levels from day to day or from time of day and in part due to the variability among laboratories in the PTH immunoassay [20]. Thus, the clinical decisions in the management of a chronic disease such as secondary hyperparathyroidism should be made over time as well. Options for the treatment of hyperparathyroidism in CKD include controlling the serum phosphorus and/or serum calcium concentration, pharmacological use of agents that reduce PTH secretion by altering the calcium-sensing receptor which includes specific active vitamin D analogs or the calcimimetics, or surgical parathyroidectomy. Thus, the updated clinical guidelines recommend that PTH-lowering therapy should include the use of calcimimetics, calcitriol, or other active vitamin D analogs or a combination of calcimimetics with calcitriol

or active vitamin D analogs, without prioritizing therapy other than parathyroidectomy being considered when medical therapy fails [5].

Phosphate Management

Practice guidelines suggest maintaining serum calcium and phosphorous with the normal range via dietary restriction and/or administration of phosphate binders [4, 5]. The use of vegetarian products as well as protein restriction is commonly suggested to limit phosphate intake [4]. However, diet is often insufficient to reach a desirable control of serum phosphate levels, and a wide range of phosphate binders are now available (Table 17.1). Aluminum-based binders are very effective; however, due to their potential toxicity, they have been replaced by other mineral-based and polymer-based phosphate

Table 17.1 Phosphate binders

Phosphate binder	Clinical considerations	Relative phosphate binding[a] (per gram binder)
Aluminum hydroxide	Very effective Well tolerated Liquid Low cost Risk of aluminum intoxication	1.9
Calcium carbonate	Effective High pill burden Risk of hypercalcemia Not recommended for patients with low PTH or vascular calcifications	1.0
Calcium acetate	Similar to calcium carbonate Slightly lower calcium load than calcium carbonate	1.0
Magnesium carbonate	Effective Anti-constipating Diarrhea Hypermagnesemia	1.7
Sevelamer hydrochloride	Effective Calcium-free resin High pill burden Lipid and uric acid lowering May bind bile acids and fat-soluble substances May worsen metabolic acidosis	0.75
Sevelamer carbonate	Effective Calcium-free resin High pill burden Lipid and uric acid lowering May bind bile acids and fat-soluble substances	0.75
Lanthanum carbonate	Effective Low pill burden Must be chewed GI side effects	2.0
Sucroferric oxyhydroxide	Effective Low pill burden Must be chewed Diarrhea	3.0
Ferric citrate	Effective High pill burden Iron absorption, may require less IV iron Diarrhea	0.9

[a]Relative phosphate binding capacity relative to calcium carbonate

binders [21]. Thus, guidelines suggest limiting the use of aluminum-based phosphate binders for cases of severe hyperphosphatemia and for a short period of time [4]. When compared to placebo, all available phosphate binders have been shown to lower serum phosphate to a similar extent [22–26]. However, differences among the drugs exist, which includes changes in serum calcium, effect on PTH control, and pill burden [22, 24–26]. Preliminary data also suggest that phosphate restriction and calcium-free phosphate binders may reduce FGF-23 [21, 27]. Although the clinical relevance of different biochemical profiles still needs to be elucidated, some lines of evidence suggest that calcium-based phosphate binders may accelerate vascular calcification deposition and progression when compared to calcium-free phosphate binders [28]. There is some evidence that calcium-free phosphate binders are associated with better survival when compared to calcium-based phosphate binders [29], and current guidelines advise restricting the use of calcium-containing binders [5].

Vitamin D

Nutritional vitamin D, calcifediol, calcitriol, and other vitamin D analogs are used in patients with CKD to prevent and treat secondary hyperparathyroidism (Table 17.2). Despite theoretical benefits of raising 25-hydroxyvitamin D levels with nutritional vitamin D (e.g., ergocalciferol and cholecalciferol) in CKD stage 3–4 patients, there has been limited effectiveness in correcting hyperparathyroidism [30, 31]. However extended release calcifediol has been shown to effectively increase vitamin D levels and correct hyperparathyroidism in these pre-dialysis patients [32]. Unfortunately, there are no trials in dialysis patients nor large long-term randomized controlled trials in patients with earlier stages of CKD supporting an improvement in PTH [33, 34]. Calcitriol and other active analogs, alphacalcidol, doxercalciferol, and paricalcitol, have all been demonstrated to effectively treat hyperparathyroidism in CKD stages 3–4 [35–38]. It was claimed that these analogs provided effective control of PTH without causing hypercalcemia or hyperphosphatemia compared to calcitriol [35, 36]. However, in the only prospective study comparing one of these analogs (paricalcitol) with calcitriol, there was equivalent control of PTH with no difference in the development of hypercalcemia or hyperphosphatemia [39]. Thus, guidelines do not differentiate the use of any of these compounds in CKD stages 3–4 [5].

In patients undergoing chronic dialysis, calcitriol and the other active analogs, alphacalcidol, doxercalciferol, and paricalcitol, have all been shown to lower PTH concentrations. Among patients undergoing chronic hemodialysis, the use of intravenous doses given thrice weekly during each dialysis session became a common practice, especially in the United States. This practice was supported by a meta-analysis which found that the parenteral forms of active vitamin D analogs were superior to the oral form in reducing PTH

Table 17.2 Comparison of vitamin D therapies

Class	Sterol	Comment	Effect on blood levels		
			25-D	Ca/Phos	PTH
Nutritional vitamin D	Cholecalciferol	D_3 animal source	Mild Inc	None	Mild Dec
	Ergocalciferol	D_2 plant source	Mild Inc	None	Mild Dec
Vitamin D	Calcifediol 25(OH)D_3	D_3 prohormone	Mod Inc	None	Mod Dec
Vitamin D receptor agonists (VDRA)	Calcitriol 1,25$(OH)_2D_3$	D_3 natural analog	Mild Dec	Mod Inc	Marked Dec
	Alphacalcidol 1(OH)D_3	D_3 synthetic prohormone	Mild Dec	Mod Inc	Marked Dec
	Doxercalciferol 1(OH)D_2	D_2 synthetic prohormone	Mild Dec	Mod Inc	Marked Dec
	Paricalcitol 19nor,1,25$(OH)_2D_2$	D_2 synthetic analog	Mild Dec	Mod Inc	Marked Dec

concentrations [40]. However, when one study that used very high doses of intravenous analogs was removed from the meta-analysis, there were no differences in the PTH concentrations. Thus, the evidence supporting the use of large intermittent intravenous doses of vitamin D analogs is limited. Thus, the recent therapeutic trend is to use oral forms of calcitriol and its analogs. As previously discussed, KDIGO guidelines recommend maintaining PTH concentrations between two and nine times the upper limit of normal in dialysis patients [4, 5]. Both the oral and intravenous formulations of the active vitamin D analogs increase the risk of hypercalcemia, especially as the PTH decreases and the updated guidelines recommend decreasing or stopping analogs as the calcium increases [5].

Calcimimetics

Calcimimetics are agents for the treatment of hyperparathyroidism that bind to and activate the calcium-sensing receptor (CaSR) resulting in a decrease in PTH production and release [41–44]. Currently available calcimimetics include cinacalcet hydrochloride which is a small organic molecule that is orally administered with a relatively short half-life [41, 42, 45], whereas etelcalcetide is a parenterally administered synthetic peptide with a longer half-life which can be administered thrice weekly at the end of hemodialysis [43, 44]. As opposed to the active vitamin D analogs, these agents are effective in lowering PTH concentrations while also decreasing serum and phosphate concentrations. In the pivotal phase 3 study, treatment of uncontrolled secondary hyperparathyroidism with cinacalcet or placebo for 26 weeks resulted in a greater proportion of patients in the cinacalcet arm achieving PTH concentrations ≤250 pg/mL with better control of serum calcium and phosphorous [41]. Subsequent studies further demonstrated efficacy of cinacalcet as monotherapy to suppress PTH when compared with active vitamin D analogs [46]. Furthermore, cinacalcet therapy was associated with a decrease in FGF-23 as opposed to an increase seen in those treated with the active vitamin D analogs [47]. Clinical studies with etelcalcetide demonstrated similar results as those with cinacalcet when compared to placebo [44] and were non-inferior to cinacalcet [43]. Notably, in all these studies, mild-to-moderate hypocalcemia, nausea, and vomiting were common, albeit easily managed, side effects. Unfortunately, the EVOLVE study, which was the largest placebo-controlled, double-blind clinical trial with cinacalcet conducted in dialysis patients with secondary hyperparathyroidism designed to evaluate hard outcomes, was not able to meet the primary endpoint (i.e., time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) [48]. However, serum concentrations of PTH, calcium, phosphate, and FGF-23 were better controlled among patients allocated to cinacalcet [48]. Current recommendations are that calcimimetics should only be used in dialysis patients as when administered to pre-dialysis CKD patients they will increase serum phosphorus and decrease serum calcium [5, 49, 50].

Parathyroidectomy

In both CKD and dialysis patients with severe hyperparathyroidism who fail to respond to medical therapy, parathyroidectomy is recommended [5]. Successful parathyroidectomy can yield a dramatic reduction in PTH concentrations and clinical symptoms. Furthermore, some investigators have reported that parathyroidectomy may be more cost-effective than calcimimetics in treating patients with uncontrolled hyperparathyroidism [51]. However, an analysis of 4435 hemodialysis patients undergoing parathyroidectomy demonstrated a 2% perioperative mortality rate and a 39% increase in overall hospitalizations in the subsequent year [52]. Another retrospective review of dialysis patients with severe and unresponsive hyperparathyroidism indicated that parathyroidectomy did not improve cardiovascular outcomes compared with standard medical treatment [53]. Furthermore, in some instances hyperparathyroidism may persist after parathyroidectomy because of incomplete resection or because of ongoing PTH secretion

from autotransplanted parathyroid tissue. Thus, recommendations are that parathyroidectomy be reserved to when medical therapy fails [5].

Treatment of Osteoporosis in CKD

Clinical studies evaluating all the approved pharmacologic therapies for osteoporosis included subjects with CKD stages 1–3a (GFR >45 ml/min/1.73m^2). Thus, osteoporosis management should not differ in CKD stages 1–3a as it is in persons without CKD, as long as there are no biochemical markers suggestive of the presence of CKD-MBD [3, 5, 54]. There is a lack of data demonstrating fracture risk reduction in patients with CKD stages 3b–5, with the exception of a few post hoc analyses in a small number of patients from the registered cohorts for postmenopausal osteoporosis. Approved anti-osteoporosis agents include calcitonin, estrogens, selective estrogen receptor modulators, bisphosphonates, teriparatide, abaloparatide, and denosumab (Table 17.3).

Table 17.3 Use of osteoporosis therapeutic agents in chronic kidney disease-mineral bone disorder

Estrogen
Potential use in hypogonadism
Safety data lacking
Increased drug half-life
Increases BMD, no fracture data
Selective estrogen receptor modulators (SERMs)
Safety data lacking
Efficacy unknown
Post hoc analysis appears to be similar vertebral fracture protection in CKD 3
Calcitonin
Efficacy unknown
Probably safe
Bisphosphonates
Post hoc analysis efficacious for stabilizing/increasing BMD in CKD 3–4
Effect on fracture rate in advanced CKD subset is unknown
May be useful in treating calciphylaxis
Theoretically dangerous in low-turnover bone disease
Safety data not available
Prolonged T1/2
Removed by dialysis
Consider bone biopsy prior to use to further evaluate CKD-MBD
Teriparatide (1–34 parathyroid hormone analog)
Limited data
Improved BMD in patients with low bone turnover
Abaloparatide (1–34 parathyroid hormone-related protein analog)
No data in CKD
Likely the same as teriparatide
Denosumab (monoclonal antibody to RANK-L)
Women with CKD 3 had similar vertebral fracture reduction as normal
May have exaggerated increase in PTH
Safety data are not available
Romosozumab (monoclonal antibody to sclerostin)
No published data in CKD

Anti-resorptive Agents

Anti-resorptive agents have a common pathway resulting in the inhibition of bone resorption. Available anti-resorptive agents include calcitonin, estrogens, selective estrogen receptor modulators, bisphosphonates, and denosumab. Each anti-resorptive agent has its own unique mechanism of action. Since bisphosphonates and denosumab are the most widely used anti-resorptive agents for osteoporosis, these agents will be further discussed. Bisphosphonates are biological analogs of naturally occurring pyrophosphates (P-O-P), degradation products of adenosine triphosphate (ATP) metabolism. Pyrophosphates are rapidly metabolized by the ubiquitous presence of pyrophosphatases, while bisphosphonates (P-C-P) are not metabolized [55]. Bisphosphonates are rapidly taken up by the bone and inhibit bone resorption by two mechanisms: a physiochemical one by stabilizing the calcium-phosphorus surface and a cellular one by inhibiting osteoclast activity. Bisphosphonates are cleared by the kidney by both glomerular filtration and active proximal tubular secretion. Bisphosphonates are retained in the bone in the remodeling resorption cavity, and the amount of bisphosphonate retained is probably a function of the rate of bone turnover and the GFR. While oral bisphosphonates are poorly (<1%) absorbed, approximately 50% is renally excreted. Intravenous bisphosphonates have a

100% bioavailability, also with 50% being renally excreted [55, 56]. Thus, in patients with CKD stage 3 who have a low bone mineral density and/or fragility fractures, bisphosphonate therapy should be considered after addressing the biochemical abnormalities associated with CKD-MBD [5]. Whereas in patients with CKD stages 4–5, limited data suggests that bisphosphonates have no effect on bone density [57], however, there are no clinical studies in which CKD-MBD abnormalities are addressed; thus, a bone biopsy should be considered prior to initiating bisphosphonate therapy [4, 5].

Denosumab is a fully humanized monoclonal antibody that binds to an osteoblast (and osteocyte)-derived glycoprotein and receptor activator of nuclear factor kappa-B ligand (RANK-L), inhibiting RANK-L from binding to an osteoclast membrane receptor, RANK, and, thereby, inhibiting osteoclastogenesis [58]. In clinical studies, similar fracture reduction was noted in patients with CKD stages 3–4 as to those with normal kidney function; however, in order to be included in the studies, all subjects had normal PTH concentrations [59]. There was also the observation that in patients with advanced CKD, denosumab may produce marked increases in PTH as well as profound hypocalcemia [60, 61]. This hypocalcemic and hyperparathyroid effect may be mitigated by ensuring adequate vitamin D and calcium intake [60]. Furthermore, since denosumab decreases bone turnover, until further data are available, it should be avoided in subjects with advanced kidney disease who are at risk for low bone turnover.

Anabolic Agents

Currently available anabolic agents include teriparatide which is a recombinant human 1–34 PTH analog [62] and abaloparatide which is 1–34 analog of human parathyroid hormone-related protein (PTHrP) [63]. Abaloparatide effectively improves bone density and decreases fractures in postmenopausal women. However, it has not been studied in men or analyzed in patients with decreasing GFR [64, 65]. In both women and men with osteoporosis, treatment with teriparatide compared with placebo increased bone mineral density as well as decreased the risk of vertebral and nonvertebral fractures [62, 66, 67]. Furthermore, teriparatide has also been shown to be effective in steroid-induced osteoporosis [68, 69]. The teriparatide trials did not randomize subjects with known CKD stages 4–5. However, during subsequent analysis, it was noted that these studies had subsets of patients with eGFR down to 30 ml/min [70, 71]. In these subsets, there were similar increases in bone mineral density across tertiles of eGFR. Fracture numbers were too small to have power for statistical analysis across these three tertiles. There were no changes in renal function as assessed by changes in serum creatinine or serum calcium concentrations as a function of eGFR. There are no studies on the effect of teriparatide or patients with advanced CKD stages 4–5 or in subjects with bone biopsy-proven low-turnover bone disease, other than a few case reports which demonstrate a positive effect on both bone mineral density and fractures [57, 72, 73]. Thus, it is possible, though unproven, that teriparatide may have a beneficial role in patients with advanced CKD and low-turnover bone disease.

Summary

The management of patients with fragility fractures across the spectrum of CKD should not differ between persons without reductions in GFR or persons with CKD stages 1–3, at least as it pertains to patients with age-related reductions in GFR with normal mineral metabolism [5]. This suggestion is predicated on the absence of information that could suggest the presence of CKD-MBD. In patients with CKD stages 4–5 and who have fragility fractures, the first management step is making the correct diagnosis. Diagnosis of osteoporosis in CKD stages 4–5 is an exclusionary one. Exclusion is best made by bone biopsy, a clinical service that is not widely available. Biochemical markers of bone turnover, in particular serum PTH and bone-specific alkaline phosphatase, may help provide differentiation between biopsy-proven low-turnover and

high-turnover disease; however, as previously discussed, these measurements do not have high specificity [11]. The exclusion, in particular, of low-turnover bone disease is especially important as the use of anti-resorptive agents may not be beneficial and in fact could worsen the low bone turnover state. There is a great need to gain knowledge and evidence for the appropriate use of traditional anti-osteoporosis treatments in patients with CKD stages 4–5 who have low bone density or have sustained a low-trauma fracture.

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