Treatment of osteoporosis in patients with chronic kidney disease

Bone disease and fractures are common in patients with chronic kidney disease (CKD). The etiology of bone disease in CKD is complex due to a combination of osteoporosis and/or CKD-mineral and bone disorder (CKD-MBD). Identifying the type of bone disease is important as treatments for osteoporosis may differ from CKD-MBD. In predialysis CKD, bone mineral density by dual energy x-ray absorptiometry may be useful in identifying those at high risk of fracture. The ability of noninvasive imaging to diagnose/predict fracture risk in later stages of CKD is unclear. Pharmacologic treatments approved for postmenopausal osteoporosis may be appropriate, in the absence of abnormal mineral metabolism, for use for a limited time in stages 1–3 CKD; however, use in stages 4–5D CKD would be off label. Further studies are needed.

KEYWORDS: bisphosphonates ■ bone mineral density ■ chronic kidney disease ■ fractures ■ osteoporosis ■ treatment

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Bone disease is common in men and women with chronic kidney disease (CKD) and is associated with an increased risk of fracture and poor outcomes following fracture, including excess morbidity and mortality [1]. The etiology of bone disease in CKD is complex and often multifactorial and includes osteoporosis and/or altered mineral metabolism, referred to as CKD–mineral and bone disorder (CKD-MBD). CKD-MBD describes the mineral and bone abnormalities that develop as a result of CKD [2], and includes high-turnover (hyperparathyroid) bone disease, low-turnover (adynamic) bone disease and impaired mineralization (osteomalacia).

Recent research has focused on identifying noninvasive methods that can discriminate fracture status in CKD; however, no study has identified a single, noninvasive measure that is able to accurately diagnose the type of bone disease in CKD (e.g., osteoporosis vs hyperparathyroid bone disease vs adynamic bone disease [AD]), and this limits treatment. Presumably (yet not demonstrated by data) treatment decisions may differ by bone disease type. This review will focus on the treatment of osteoporosis in men and women with CKD; however, it should be noted that treatment decisions may differ if a CKD patient is diagnosed with CKD-MBD rather than osteoporosis.

The burden of disease due to osteoporosis

Osteoporosis, as defined by the NIH Consensus Conference, is a systemic skeletal disease characterized by an impairment in bone strength (a reflection of bone density and bone quality – architecture, turnover and microfractures) that leads to an increased risk of fracture [3]. Clinically, osteoporosis is defined by the occurrence of a fragility fracture, and/or by WHO criteria that utilizes dual energy x-ray absorptiometry (DXA): T-score of -2.5 standard deviation or below. Worldwide, one in three women and one in five men will have an osteoporotic fracture, which is associated with increased morbidity, mortality and healthcare costs. For example, the 1-year mortality rate following a hip fracture is up to 20%; of those who survive, the average length of stay in an acute-care hospital after a hip fracture is 3 weeks; one in four patients must remain in long-term care institutions for at least 1 year and one in three who return home must depend on other people or devices for mobility [4].

Etiology & impact of fractures in CKD

There are two main reasons why osteoporosis and osteoporotic fractures are particularly common in men and women with CKD. First, aging is associated with both decreases in renal function and increases in the incidence of osteoporosis. Data from the National Health and Nutrition Examination Survey reported that the incidence of osteoporosis together with moderate-to-severe impairments in renal function (defined as an estimated creatinine clearance [CrCl] calculated by Cockcroft–Gault

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[CG] equation of <35 ml/min) is 0% among women aged 50–59 years old, 7.3% among those 60–69 years old, 21.3% among those aged 70–79 years old and 53.9% among those aged 80 years and older [5].

Second, men and women with CKD often have associated medical conditions and/or are taking medications that put them at risk for osteoporosis. These risk factors include, but are not limited to: the use of glucocorticoids and/or heparin, concomitant hypogonadism, hyperprolactinemia, suboptimal nutrition, vitamin D deficiency, hyperparathyroidism, metabolic acidosis, impaired neuromuscular function and physical inactivity. The reader should note that these risk factors may contribute to fractures independent of bone mineral density (BMD) by DXA; this is particularly the case in men and women with Type 2 diabetes mellitus who, despite BMD values higher than normal, are at an increased risk of fracture. The reason for this is not known, but explanations include alterations in bone quality (perhaps due to increases in advanced glycosylation end products) or an increased risk of falls (perhaps due to peripheral neuropathy) [6–8].

Generally speaking, isolated decreases in bone mass or osteoporosis develop early in the course of CKD – typically in stages 1–3 (stage 1 CKD: glomerular filtration rate [GFR] ≥90 ml/min/1.73m^2; stage 2 CKD: GFR 60–89 ml/min/1.73m^2; stage 3 CKD: GFR 30–59 ml/min/1.73m^2; stage 4 CKD: GFR 15–29 ml/min/1.73m^2; stage 5 CKD: GFR <15 ml/min/1.73m^2) [9] – before disturbances in mineral metabolism (i.e., CKD-MBD) are observed. The reader should note, however, that disturbances in mineral metabolism can occur as early as stage 3 CKD. Recall that hyperphosphatemia, vitamin D deficiency and hyperparathyroidism are common in patients with CKD, but in the early stages of the disease, alterations in mineral metabolism are typically mild and easily managed, and do not result in CKD-MBD.

Not surprisingly, the reduced bone mass, independent of overt disturbances in mineral metabolism in patients with early stages of CKD, results in fractures. Analyses using data from the SOF – a prospective cohort study designed to assess risk factors for osteoporosis and fractures in community-dwelling ambulatory women aged 65 years and older – demonstrated that compared to women with a CrCl ≥60 ml/min, the risk of hip fracture increased by 1.5-fold among those with a CrCl between 45 and 50 ml/min, and was doubled among women with a CrCl of <45 ml/min [10]. Consistent with findings from the SOF, data from the Third National Health and Nutrition Examination Survey reported an approximate twofold increased risk of hip fracture among those with an estimated GFR (calculated by the modification of diet in renal disease equation) of <60 ml/min/1.73 m^2, compared with those with an estimated GFR ≥60 ml/min/1.73m^2 [11].

Patients with more advanced stages of CKD often have sustained and persistent abnormalities of mineral metabolism. Over time this can result in osteomalacia, hyperparathyroid bone disease (osteitis fibrosa cystica), low bone turnover (AD) or mixed uremic osteodystrophy (a combination of histological features). Globally these conditions are captured within the term CKD-MBD. CKD-MBD is associated with an increase in fracture risk, and identifying the specific type of bone disease requires a bone biopsy. Analyses of data from the US renal data system reported that the relative risk (RR) of hip fracture was increased in both men (RR: 4.44) and women (RR: 4.40) with stage 5 CKD on dialysis (stage 5D) compared with the general population [12].

In addition to osteoporosis and renal osteodystrophy, men and women with CKD may have fractures due to falls from myopathy, neuropathy and postural hypotension, and if they do fall, the fall is more likely to lead to injury due to alterations in postural reflexes and/or a decrease in soft tissue padding from suboptimal nutrition. Finally, it is important to note that men and women with CKD can have more than one risk factor for fracture (i.e., both osteoporosis and a form of renal osteodystrophy) and that the risk factor(s) for fracture may change over time.

It is clear from the discussion above that, among men and women with later stages of CKD who fracture, the clinician must consider not only osteoporosis but also assess for the presence of CKD-MBD and type of renal osteodystrophy. The reader should note that identifying the cause of fracture in men and women with CKD is not simply an academic exercise, but may influence therapeutic decisions. For example, the appropriate treatment for osteitis fibrosa would be treatment of the hyperparathyroidism, treatment for osteomalacia would include vitamin D replacement, while antiresorptive therapy, which suppresses bone turnover, might not be appropriate in patients with AD.

How then does the clinician evaluate fracture risk in men and women with CKD? Tests that

may be useful include BMD testing by DXA to assess for osteoporosis, peripheral quantitative computed tomography (pQCT), which provides information on, among other things, cortical and trabecular bone components and microarchitecture, tests of neuromuscular function to assess fall risk and bone biopsy to determine the type and presence of renal osteodystrophy.

Diagnosis of bone disease in predialysis CKD

The mild disturbances in mineral metabolism found in stages 1–3 CKD include intermittent hyperphosphatemia and mild increases in parathyroid hormone (PTH); derangements that have not been associated with renal osteodystrophy; or increased rates of fracture [13]. These observations are consistent with the fact that the predominant cause of fractures in patients with stages 1–3 CKD, in the absence of persistent metabolic derangements, is osteoporosis. As such, BMD testing by DXA can be used to evaluate fracture risk in these patients. The reader should note that this concept is supported by The Kidney Disease: Improving Global Outcomes working group conclusions [2].

DXA is a radiological technique that uses two x-ray beams to measure a 3D structure (i.e., bone). DXA measures the quantity of bone via 2D projection images. DXA is strongly predictive of future fracture risk in postmenopausal women; however, it is important to note that the 2D projection of DXA is limited since the images do not capture the 3D components of cortical or trabecular bone microarchitecture [14,15] – both of which may be important to assess in CKD, especially in later stages when CKD-MBD is prevalent.

Despite the potential limitations of measuring BMD by DXA in identifying those at high fracture risk with later stages of CKD who may have CKD-MBD, there are two sets of data that support the concept that in the early stages of CKD the predominant cause of fracture is osteoporosis and that measuring BMD by DXA has clinical utility. First, there are the registration trials of pharmacologic agents approved for osteoporosis, including teriparatide, risedronate, raloxifene and denosumab. These trials included many postmenopausal women who had calculated CrCls consistent with stages 1–3 CKD despite a serum creatinine in the normal range, and in these postmenopausal women BMD did predict fracture risk, and increases in BMD in response to treatment were associated with decreases in fracture risk [16–19]. While we recognize that some of these patients might simply have had age-related declines in renal function, it is likely that some had overt kidney disease. Second, there are cross-sectional studies that support the ability of BMD by DXA to discriminate fracture status in men and women with predialysis CKD [20–22]. These studies found that in men and women with predialysis CKD (stage 3–5 CKD), BMD measured by DXA at the lumbar spine, total hip and ultradistal radius were associated with fractures [20–22] with areas under the receiver operating characteristic curve (AUROC) ranging from 0.70 to 0.80 [22]. In a recent study, BMD at the ultradistal radius was the strongest discriminator of fracture status (AUROC: 0.80; 95% CI: 0.74–0.87) among men and women with stage 3–5 CKD, and as such, may be the preferred site of BMD measurement in these patients [22]. The reader should note that those with stage 3–5 CKD in our study had only slight metabolic disturbances, consistent with the concept that for the most part the patients did not have CKD-MBD. However, this latter point was not confirmed by bone biopsy.

Considered together, the data suggest that BMD measured by DXA can be used to assess fracture risk in patients with predialysis CKD as osteoporosis is the most probable cause of bone disease (in the absence of persistent metabolic derangements that would suggest CKD-MBD). However, these findings should be interpreted with caution: there are no biopsy data that confirm the diagnosis of osteoporosis in this setting and classification of CKD in these studies is based solely on estimated creatinine clearance and does not take into account other measures such as proteinuria. Furthermore, secondary data analyses suggest that pharmacologic treatments for these patients are the same treatments that are currently approved for use in postmenopausal osteoporosis. The reader should note that these agents, when administered in stages 1–3 CKD, do not require dose adjustments. However, as CKD may progress, ongoing monitoring of renal function would be appropriate.

Diagnosis of bone disease in stage 5D CKD

Men and women with more advanced stages of CKD may be at high fracture risk due to CKD-MBD and so-called renal osteodystrophy. Renal osteodystrophy is classified into four types based on the rates of bone turnover, degree of mineralization and volume [2]. The four types of renal osteodystrophy are: AD (low or absent turnover); osteomalacia (unmineralized bone);

osteitis fibrosa cystica (high-turnover disease usually due to hyperparathyroidism); and mixed uremic osteodystrophy (more than one histological picture). A recent review reported on the prevalence of bone disease by stage of CKD and type of dialysis (hemodialysis vs peritoneal) [2]. They found that osteitis fibrosa cystica was the most prevalent abnormality in patients with stages 3–5 CKD, as well as among patients on hemodialysis, occurring approximately a third of the time. By contrast, among those on peritoneal dialysis, 50% of patients had AD bone disease. The reader should note that the prevalence of bone disease is different in patients with diabetes. Specifically, histomorphometric data from patients on dialysis demonstrate that those with Type 2 diabetes have a higher prevalence of AD compared with those without diabetes [23,24].

The gold standard to diagnose renal bone disease is bone biopsy, which has some limitations preventing its widespread use. These limitations include the fact that the procedure is invasive and requires specialized expertise to interpret the findings. In addition, bone biopsy represents findings from a single site at a single time point, and bone biopsy may vary by site sampled, as well as by duration and stage of CKD. The limitations of bone biopsy have fuelled an interest in identifying alternative methods by which to assess fracture risk and etiology of CKD-MBD. These noninvasive methods include BMD by DXA and pQCT.

Our group published a meta-analysis that reported on the association between BMD by DXA and fractures in men and women with stage 5D CKD [25]. It was found that BMD was lower in patients with stage 5D CKD who have fractures, particularly at cortical sites such as the radius [26,27]. Since that meta-analysis, three published studies have reported on the association between BMD measured by DXA and fracture in men and women with stage 5D CKD with divergent results [28–30]. One study reported no association between fractures and lumbar spine or femoral neck BMD by DXA [28], another reported that lower BMD by DXA at the femoral neck is associated with an increased prevalence of fractures [29], while the most recent study reported that those with fracture had reduced BMD at the distal radius site [30].

Overall, the ability of BMD measured by DXA to discriminate fracture status in stage 5D CKD is limited to cross-sectional data and is conflicting. pQCT and/or high-resolution (HR) pQCT have several advantages over BMD measured by DXA that are of particular relevance in patients with stage 5D CKD, with the predominant advantage being that pQCT/HRpQCT can accurately differentiate between cortical and trabecular bone components – this allows for the estimation of the differential effects of PTH on bone.

Two studies have reported on the association between pQCT or HRpQCT and fracture in stage 5D CKD [31,32]. Our group found that, among 52 men and women with stage 5D CKD on hemodialysis for at least 1 year, a decrease in cortical density, area and thickness were all associated with fractures (cortical density: odds ratio [OR]: 16.7; 95% CI: 2.9–83.3; cortical area: OR: 3.0; 95% CI: 1.3–7.3; cortical thickness: OR: 3.3; 95% CI: 1.4–7.9). It was also found that fractures were not associated with trabecular measures [31]. The second cross-sectional study measured HRpQCT at the radius and tibia in 74 stage 5D CKD patients on hemodialysis with and without fractures. Compared with those without fractures, those with fractures had impairments in cortical and trabecular microarchitecture and the strongest discriminator of fracture status was trabecular density at the tibia (AUROC: 0.90; 95% CI: 0.80–0.99) [32].

Data on the utility of pQCT and HRpQCT to discriminate fracture status in stage 5D CKD are limited to cross-sectional studies with conflicting results. Furthermore, neither DXA nor HRpQCT are able to assess dynamic qualities of bone, specifically bone turnover, and as such cannot be used to identify the presence of CKD-MBD or the type of renal osteodystrophy. The current limitations of noninvasive testing impair our ability to identify and treat men and women with CKD at high fracture risk.

Treatment

Treatments for patients with renal bone disease who fracture may vary based on the stage of CKD (Figure 1). As noted above, BMD measured by DXA is useful in assessing fracture risk in patients with predialysis CKD (stages 1–3) in the absence of persistent metabolic derangements that would suggest CKD-MBD. Among patients with osteoporosis (i.e., a BMD measured by DXA T-score ≤-2.5 and/or fragility fractures) one can prescribe treatments that have been approved for use in postmenopausal osteoporosis without dose adjustment.

The treatment of bone disease in patients with stage 4–5D CKD at high fracture risk requires at least two considerations. First, one should consider the fact that in cases with severe

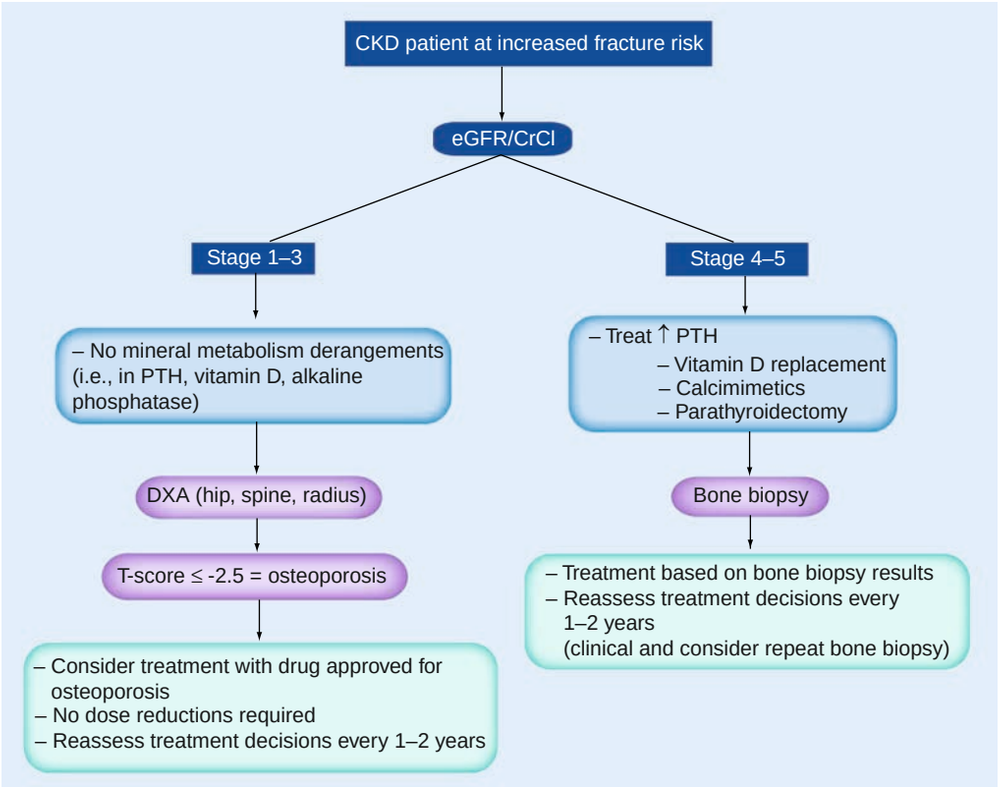

Figure 1. Suggested management algorithm.
CKD: Chronic kidney disease; CrCl: Creatinine clearance; DXA: Dual energy x-ray absorptiometry; eGFR: Estimated glomerular filtration rate; PTH: Parathyroid hormone.

secondary hyperparathyroidism commonly observed in stage 5 CKD there is an increased fracture risk [33,34]. While there are no randomized trial data, it would be appropriate to control serum PTH. Approaches include ensuring vitamin D replacement (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D), use of calcimimetics and parathyroidectomy. Guidelines on managing hyperparathyroidism in CKD have been recently published by Kidney Disease: Improving Global Outcomes [2]. Second, one should consider the use of a pharmacological agent discussed in detail below.

Nitrogen-containing oral bisphosphonates are excreted by the kidney, and as such the US FDA does not recommend the use of these agents in stages 4, 5 and 5D CKD [2,35]. In addition, the reader should note that with the use of intravenous bisphosphonates there were rare cases of kidney failure requiring dialysis and/or fatal outcomes that were reported in osteoporotic patients with pre-existing kidney dysfunction [101], further highlighting the concern regarding the use of bisphosphonates in those with reduced renal function. However, randomized controlled trials that reported on the efficacy of oral bisphosphonates in postmenopausal women often randomized women who had calculated CrCls ranging from stage 1 to 4 CKD, which resulted in several *post hoc* analyses that are described below.

Post hoc analysis of the alendronate fracture trial (FIT) assessed 581 women with a CrCl by CG of <45 ml/min, and 5877 women with a CrCl of ≥45 ml/min, and reported an increase in total hip BMD and a decrease in clinical and vertebral fractures in those that were treated with alendronate versus placebo regardless of renal function [36]. A pooled analysis of nine risedronate studies included 572 women with a CrCl by CG of <30 ml/min, 4071 women with a CrCl of between 30 and 50 ml/min and 4353 women with a CrCl between 50 and 80 ml/min; this study reported preserved BMD and reduced incident vertebral fractures in the treatment group regardless of renal function [18]. Similar findings were also reported for raloxifene (a selective estrogen receptor modulator, MORE trial, with 1480 women with a CrCl of <45 ml/min, 3493 with a CrCl of 45–59 ml/min and 2342 with a CrCl of >60 ml/min) [19].

There are limitations in applying these *post hoc* findings to all patients with stage 1–4 CKD, including the fact that most of the studies examined otherwise healthy postmenopausal women

with no significant aberrations in markers of mineral metabolism and were short term in duration (at most 3 years).

A secondary analysis of the FTP, a trial that evaluated teriparatide, an anabolic agent (PTH: 1–34), assessed 885 women with normal renal function (CrCl: ≥ 80 ml/ min), 648 women with mild renal impairment (CrCl: 50–79 ml/min) and 83 women with moderate renal impairment (CrCl: 30–49 ml/min). Compared with placebo, teriparatide use increased bone formation, lumbar spine and femoral neck BMD and reduced vertebral and nonvertebral fracture incidence regardless of renal function. Adverse events were similar by treatment assignment and by renal function [17]. The reader should note that because teriparatide is an anabolic agent it may be attractive for the treatment of AD. However, given the skeletal resistance to PTH in later stages of CKD the dose that would need to be administered to generate an anabolic effect is unknown [37].

Denosumab may be of particular relevance for use in men and women with CKD because it is not renally excreted or metabolized. Denosumab is a fully human monoclonal antibody against the RANKL, and RANKL is a cytokine essential in osteoclast formation, function and survival. When RANKL binds to the RANK receptor on osteoclasts, bone breakdown is initiated. Denosumab binds to RANKL and prevents the interaction of RANKL with its receptor RANK and, as a result, osteoclast-mediated bone resorption is inhibited [16,38].

Our group conducted a secondary analysis of the FREEDOM Trial [16]. Specifically, we examined incident fracture rates, changes in BMD, serum calcium, creatinine and the incidence of adverse events after 36 months of follow-up stratified by level of kidney function. We included 842 women with CG-calculated CrCl stage 1 CKD, 4069 women with stage 2 CKD, 2817 women with stage 3 CKD and 73 women with stage 4 CKD. Overall, compared with placebo, denosumab reduced the incidence of vertebral fractures (OR: 0.30; 95% CI: 0.23–0.39) and nonvertebral fractures (OR: 0.78; 95% CI: 0.66–0.93) over 36 months, and treatment efficacy did not differ by level of kidney function. In addition, compared with placebo, denosumab use was not associated with differences in adverse events or changes in CrCl from baseline to 36 months. Findings from this study suggest that denosumab may be safe and effective at reducing fracture risk regardless of renal function [16].

The FDA label for denosumab for the treatment of postmenopausal osteoporosis does not have any lower cutoff for renal function [38]. However, randomized controlled trials for the use of denosumab in men and women with CKD with alterations in mineral metabolism and those with more advanced CKD (stages 5 and 5D) are needed.

Treatment summary

Among men and women with stages 1–3 CKD with low-trauma fractures, and/or a BMD measured by DXA T-score of ≤ -2.5, and who do not have biochemical evidence that may suggest CKD-MBD, any registered pharmacological agent for use in osteoporosis can be used without dose adjustment (Figure 1). Treatment decisions are more difficult in men and women with stages 4–5 CKD who have fractures. A few *post hoc* analyses included a small number of subjects with CrCls down to approximately 15 ml/min (stage 4/5 CKD). In the absence of biochemical abnormalities, patients with stage 4 CKD who fracture can be treated with these agents for no more than 3 years [18,19,36].

There are no published data on the safety and efficacy of any approved pharmacological agent for the treatment of osteoporosis among men and women with stage 5 or 5D CKD. A reasonable clinical approach would be to consider pharmacological therapy in those with fractures – not exclusively based on BMD results. Prior to the initiation of treatment, a transiliac crest biopsy is needed to determine the underlying bone disease resulting in fractures. If the transiliac bone biopsy demonstrates high-turnover osteoporosis and a decision is made to treat with bisphosphonates, they should be used in half of the usual dose prescribed for osteoporosis for no more than 3 years owing to concerns of long-term retention of these agents in those with substantial renal impairment. Dose adjustment is not required for denosumab. The dose of teriparatide that would give an anabolic response in patients with advanced CKD and low bone turnover is not known and requires further study. The reader should note that to date these recommendations have not been made based on evidence, but on clinical consensus.

Nonpharmacologic treatment options should also be considered to prevent fractures. Patients with stage 3–5D CKD experience decreases in neuromuscular function, and these neuromuscular impairments have been associated with fracture in both the stage 3–5 predialysis CKD population and those with stage 5D CKD [39,40]. This, in combination with the high risk of falling in patients with CKD, indicates that it would be reasonable to consider a home assessment to remove falling hazards, advise on the use of a

cane or walker where appropriate, and a prescription for hip protectors. While we recognize that data on interventions to reduce falls and fractures in patients with CKD are lacking, these interventions are simple, cost effective and probably do no harm – studies that assess the impact of an exercise intervention to treat the impairment in neuromuscular function are warranted.

Conclusion

Bone disease and fractures are a common and debilitating comorbidity in men and women with CKD. The etiology of bone disease in CKD is complex and in later stages may require bone biopsy. The difficulty in diagnosing bone disease in CKD makes treatment decisions challenging. In the absence of derangements in mineral metabolism one can prescribe approved pharmacologic treatments for postmenopausal osteoporosis without dose adjustment in stage 1–3 CKD; however, the use in more advanced stages of CKD, even in the absence of biochemical abnormalities that suggest CKD-MBD, would be off label. Further studies on the use of nonrenally excreted medications, including denosumab, as well as nonpharmacological approaches to treating increased fracture risk, are needed.

Future perspective

In 5–10 years, we anticipate advances in the noninvasive assessment of bone disease in CKD and prediction of fracture risk. Potential noninvasive tests include novel bone turnover markers and markers of mineral metabolism that may be of particular relevance in CKD, including osteocalcin, N-terminal propeptide of human procolagen type I and tartrate-resistant acid phosphatase-5b, which have been associated with fractures in predialysis CKD [21]. In addition, alternative imaging techniques, including hip structure analysis and finite element analysis, both of which can determine measures of bone geometry and bone strength [41] may be studied in CKD. We anticipate that novel nonpharmacological and pharmacologic therapies, such as sclerostin inhibitors, which have been demonstrated to increase cortical and trabecular bone in mice and ovariectomized rats [42,43], may be available and studied for use in CKD, and that there will be further longitudinal studies with denosumab in advanced CKD.

Financial & competing interests disclosure

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Executive summary

Background

- Bone disease in men and women with chronic kidney disease (CKD) is common and results in fractures.

Etiology & impact of fractures in CKD

- The etiology of bone disease in CKD is complex and includes osteoporosis and CKD-mineral and bone disorder.
- Identifying the type of bone disease may be important for treatment decisions.

Diagnosis of bone disease in predialysis CKD

- In predialysis CKD, bone mineral density as measured by dual energy x-ray absorptiometry may be useful in discriminating fracture status.

Diagnosis of bone disease in stage 5D CKD

- In stage 5D CKD, data on bone mineral density by dual energy x-ray absorptiometry and high-resolution peripheral quantitative computed tomography to discriminate fracture status are conflicting.
- There are no noninvasive tests able to discriminate fracture status or identify the type of bone disease present in stage 4, 5 and 5D CKD.

Treatment

- Current approved pharmacologic treatments for postmenopausal osteoporosis can be used without dose adjustment in stage 1–3 CKD in the absence of derangements in mineral metabolism.
- Among men and women with stage 4–5D CKD with no biochemical abnormalities to suggest CKD-mineral and bone disorder, some *post hoc* analyses support the use of agents currently available for the treatment of osteoporosis; however, this would be off label.

Conclusion

- Further studies on the use of denosumab and nonpharmacological treatment options in CKD are needed.

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