Osteoporosis and fractures are common in persons with advanced chronic kidney disease (CKD) and on maintenance dialysis. Although the diagnosis of osteoporosis in this population can be difficult, imaging, especially with dual-energy x-ray absorptiometry (DXA), is helpful in identifying persons with CKD at the highest risk of fracture. Although blood biomarkers including parathyroid hormone and bone-specific alkaline phosphatase concentrations can aid in assessing bone turnover state, bone biopsy remains the gold standard in determining bone turnover in persons with advanced kidney disease and osteoporosis. With the increasing armamentarium of osteoporosis drugs, it now may be possible to prevent many fractures in advanced CKD. Unfortunately, data on these drugs are limited in persons with advanced CKD. Clinicians, aided by advances in imaging, biomarkers, and bone biopsy can now use these novel agents to target bone turnover abnormalities such as adynamic bone disease and high bone turnover disease. This review will discuss the most recent literature surrounding the diagnosis, management, and monitoring of osteoporosis and fractures in persons with advanced CKD or on maintenance dialysis.

Clinical Vignette
A 46-year-old man presents for a follow-up visit in the peritoneal dialysis (PD) clinic. He initiated dialysis treatments at age 27, and he underwent a living related kidney transplantation at age 30. After 13 years, his allograft failed, and he returned to PD approximately 3 years ago.

Three weeks ago, he tripped and fell and suffered bilateral tibia and fibula fractures, which were treated by open reduction and internal fixation. He remains unable to ambulate. His endocrinologist ordered a dual-energy x-ray absorptiometry (DXA), which showed a T score that was more than 2.5 SD below the mean for his sex at multiple anatomic sites, consistent with the diagnosis of osteoporosis.

Over the last year his serum phosphate level has ranged between 5.5 and 7.7 mg/dL, and his corrected serum calcium has ranged between 8.2 and 9.6 mg/dL. His 25-hydroxyvitamin D level has consistently tested over 30 ng/mL, and his parathyroid hormone concentration has ranged from 550 to 1,300 pg/mL. For phosphate control, he is prescribed 3 tablets of ferric citrate and 2 tablets of calcium acetate with each meal. He is also prescribed cinacalcet at 30 mg twice daily, but he frequently only takes his nighttime dose due to nausea. He had been taking calcitriol at 0.5 μg daily, but this was recently reduced to 0.25 μg daily due to hyperphosphatemia. He and his endocrinologist ask for options for repeat fracture prevention, including whether treatment with bisphosphonates would be safe and efficacious.

Introduction
Osteoporosis is a disease that is characterized by poor bone quality and low bone mineral density (BMD) and strength leading to risk of fractures. The World Health Organization defines osteoporosis based on a decreased BMD T score ≤ −2.5; or, put another way, in osteoporosis a person’s bone density is 2.5 SD below the average value for persons aged 20-29 years of the same sex. However, this definition does not capture all patients with poor bone quality and high fracture risk, and thus other definitions also account for persons with history of fragility fractures without evidence of severe abnormalities in BMD. More than half of fractures in the general population occur in persons without osteoporosis as defined by T score, supporting a broader definition of osteoporosis. Large systematic reviews document that persons with advanced chronic kidney disease are at 3- to 5-fold increased risk of osteoporosis and fractures compared with the general population.

The chronic kidney disease–mineral bone disorder (CKD-MBD) captures a broader systemic disorder, including both bone and vascular disease, within which osteoporosis resides as one of the bone components of the CKD-MBD. The diagnosis and management...
of osteoporosis in persons with advanced kidney disease is complex due to the highly variable pathophysiology of bone disease and due to limitations and unique side effects of the current therapeutic options. In recognition of this, the European Renal Association–European Dialysis and Transplant Association recently released a consensus statement calling for standardized diagnostic and treatment practices to prevent fragility fractures in persons with advanced CKD.

In this review, our goal is to discuss the contemporary diagnosis and management of osteoporosis in persons with advanced CKD or on maintenance dialysis. This population has been systematically excluded from large-scale phase 3 trials of medications developed for the treatment of osteoporosis, so many of our recommendations are based on opinion and experience.

Epidemiology of Osteoporosis and Fractures in Advanced CKD

According to the Third National Health and Nutrition Examination Survey (NHANES III), 24% of women and 11% of men with osteoporosis have advanced CKD (defined here as an estimated glomerular filtration rate [eGFR] < 35 mL/min/1.73 m²). Compared with persons who do not have CKD, those with CKD have a more than 2.5-fold higher risk of fractures, and those who are on dialysis have more than 4-fold risk. Recent studies have suggested an incidence rate of hip fracture of 5.0 and 7.5 per 1,000 person-years in those of BMD in persons without CKD.

In comparison to rates of 5.0 and 7.5 per 1,000 person-years in men and women in the general population, respectively.

Diagnosis

Imaging for Osteoporosis and the CKD-MBD

In the 2009 KDIGO mineral–bone guideline, recommendation 3.2.2 states, “In patients with CKD stages 3–5D with evidence of CKD-MBD, we suggest that BMD testing not be performed routinely, because BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy (2B).” This recommendation was largely based on cross-sectional studies showing no relationship between BMD and prevalent fractures. However, since that time, multiple prospective studies have consistently demonstrated that low BMD is indeed strongly associated with fracture risk in persons with CKD and that these associations are similar to those of BMD in persons without CKD.

Yenchek et al performed a large prospective analysis of older adults and showed that a lower femoral neck BMD was strongly associated with risk of fragility fractures, and that the relationship of BMD with fractures was similar in strength to those without CKD. Most of these study participants had CKD stage 3a. However, Iimori et al demonstrated similar findings among 485 dialysis patients in Japan. Considering these findings, in 2017, KDIGO updated the CKD-MBD guideline to state, as recommendation 3.2.1, “In patients with CKD G3a-G5D with evidence of CKD-MBD and/or risk factors for osteoporosis, we suggest BMD testing to assess fracture risk if results will impact treatment decisions (2B).”

It is our opinion that nearly all patients with CKD have evidence of CKD-MBD and therefore have a high risk of osteoporosis. Consequently, BMD testing is a critical component of the management of patients with CKD. Additionally, BMD testing should not only be interpreted in isolation but also with respect to whether osteoporosis is worsening across serial BMD measurements (also known as “least significant change”). However, while BMD can provide information on bone density, volume, and fracture risk, it does not provide information on bone turnover and mineralization, which is known to be abnormal in many patients with CKD and has direct treatment implications. There are other imaging modalities that provide information on bone turnover or architecture, such as positron-emission tomography (PET) or high-resolution peripheral quantitative computed tomography (HR-pQCT); however, these are not widely available and are primarily research tools.

Bone Turnover Biomarkers in Advanced CKD

It is our opinion that targeting abnormalities of bone turnover is one of the most important elements of managing the CKD-MBD; both high and low bone turnover can lead to low bone mass and fracture risk, yet the treatment strategies are diametrically opposite. The most commonly used bone turnover marker (BTM) in the clinical setting is intact parathyroid hormone (iPTH). Although there have been suggestions of using iPTH target levels of 150 pg/mL or 2-9 times the local laboratory reference range, the most recent KDIGO guideline does not recommend a specific iPTH because iPTH concentrations do not consistently reflect bone architecture and turnover seen on histology.

In the largest study to evaluate the diagnostic utility of iPTH for assessing bone turnover, Sprague et al evaluated iPTH concentrations in 492 dialysis patients who underwent bone biopsy and evaluation by histomorphometry. They found that the optimal iPTH cutoffs to determine low and high bone turnover were 108 and 323 pg/mL, respectively. However, although the iPTH concentrations were directly correlated with bone turnover across the study population, there was considerable heterogeneity in individual patients, with an area under the curve (AUC) of <0.73 for both low and high turnover states. Similarly, they found that the use of KDIGO cut points of 2 times to 9 times the normal range had a poor sensitivity in diagnosing the bone turnover state determined by histomorphometry. Nonetheless, iPTH concentrations above 9 times the normal reference range had high specificity for high-turnover disease (86%).
Thus, although iPTH is a useful BTM at the population level, it is not reliable as a sole indicator of bone turnover when applied to individual patients. However, when a dialysis patient has an extremely high iPTH concentration that exceeds the expected range, the specificity for high turnover bone disease is high. In such patients, we do not feel a bone biopsy is required, and drug therapy targeted at decreasing bone turnover is likely warranted. An example is in our clinical vignette, where the iPTH is quite suggestive of a high turnover state. The same may also be true for patients with very low iPTH levels—for example, consistently below 50 pg/mL, where the diagnosis of low turnover is likely; however, it should be recognized that the specificity of iPTH for low bone turnover is considerably worse than that of high turnover. Unfortunately, the vast majority of patients on dialysis will have iPTH concentrations between these extreme values.

There are a host of alternative BTM currently under investigation, including fibroblast growth factor 23 (FGF-23), PTH fragments, klotho, bone-specific acid phosphatase, tartrate-resistant acid phosphatase, and several others, but only a few are widely available clinically. Most of these are cleared from circulation by the kidney and are therefore uniformly elevated in the setting of diminished eGFR (Table 1). This makes set concentration targets suggesting high or low turnover in the general population unreliable in CKD or dialysis patients.

Alkaline phosphatase and bone-specific alkaline phosphatase (BSAP) are 2 biomarkers of bone formation that are not affected by GFR. Considering the effects of liver disease on alkaline phosphatase, BSAP has been more extensively studied for its utility as a marker of turnover in CKD, including in individuals treated with dialysis. Low concentrations of BSAP are consistently associated with low bone turnover and, depending on the assay and cut points, can be used to help determine the underlying turnover state. Sprague et al showed that BSAP had an AUC of 0.76 and 0.71 at predicting low and high turnover in dialysis patients, respectively. Thus, the BSAP AUC in isolation is similar to iPTH and likely is of limited use in individual patients.

Procollagen type 1 N-terminal propeptide (P1NP) and tartrate-resistant acid phosphatase (TRAP5b) are markers of bone formation and resorption that are not renally cleared and hold considerable promise. Unfortunately, these BTMs are not widely clinically available. In studies using multiple biomarkers to predict turnover, the positive predictive values often ranged from 50%-90% for high and low bone turnover states determined by histomorphometry. Ultimately, while useful at extreme levels, BTMs are not as reliable at assessing bone turnover by bone biopsy for most patients with CKD.

**Table 1. Markers of Bone Turnover**

<table>
<thead>
<tr>
<th>Biomarker Class</th>
<th>Renal Clearance</th>
<th>Hemodialysis Clearance</th>
<th>Association With Turnover Type*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone metabolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH</td>
<td>Yes</td>
<td>Yes (Fragments)</td>
<td>High</td>
</tr>
<tr>
<td>FGF-23</td>
<td>Yes</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>α-Klotho</td>
<td>Yes</td>
<td>No</td>
<td>Low</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Bone formation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSAP</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>P1NP/P1CP</td>
<td>No</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td><strong>Bone resorption</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NTX/CTX</td>
<td>Yes</td>
<td>Unknown</td>
<td>High</td>
</tr>
<tr>
<td>TRAP5b</td>
<td>No</td>
<td>No</td>
<td>High</td>
</tr>
</tbody>
</table>

Abbreviations: BSAP, bone-specific alkaline phosphatase; CTX, β-C-terminal telopeptide; FGF-23, fibroblast growth factor 23; NTX, cross-linked N-telopeptides of type I collagen; P1NP, procollagen type 1 C-terminal propeptide; P1NP, procollagen type 1 N-terminal propeptide; PTH, parathyroid hormone; TRAP5b, tartrate-resistant acid phosphatase.

*Higher concentrations of bone turnover markers are associated with high or low bone turnover.
Management

The management of osteoporosis in patients with advanced CKD or on dialysis fundamentally revolves around diagnosing and targeting abnormalities of mineralization and turnover with the goal of improving bone density, volume, and quality. In this section we will discuss the evidence for therapies that target mineralization and turnover, their potential side effects that are unique or more common in CKD, and how they may be efficacious in preventing osteoporosis and fractures.

Vitamin D, Vitamin D Receptor Agonists, and Calcimimetics

A key component of bone health is appropriate osteoblastic mineralization of osteoid, or newly laid down bone matrix that has not yet been calcified. Calcitriol is an important regulator of this process and thus drugs targeting the PTH/vitamin D axis have commonly been used to prevent abnormalities in bone mineralization and osteomalacia in patients with CKD. Studies evaluating the effects of vitamin D (cholecalciferol and ergocalciferol) and calcitriol on histologic mineralization parameters have been small, with conflicting findings regarding their effects on mineralization in dialysis patients. To date, there are no large clinical trials demonstrating benefits of vitamin D or calcitriol supplementation to prevent fractures in advanced CKD.

Similarly, studies evaluating the effects of calcimimetics on mineralization based on bone biopsies have been small, with some showing increased mineralization while others showed no discernable effects. Separate from their secondary effects on calcitriol, calcimimetics activate the calcium sensing receptor, thereby suppressing PTH, a major driver of bone turnover. Thus, it has been hypothesized that calcimimetics can be useful in preventing and improving high bone turnover states in patients with CKD. The EVOLVE trial was the largest study of a calcimimetic versus placebo, evaluating 3,883 dialysis patients over 4 years. While cardiovascular disease was a primary outcome, it evaluated fractures as a secondary outcome. The EVOLVE trial failed to show a cardiovascular or fracture benefit in the primary analysis, but subgroup analysis revealed that cinacalcet may have been helpful in preventing fractures in the highest risk dialysis patients, the oldest participants, and those with prior history of fractures.

We recognize there is an absence of clinical trial data evaluating the effects of calcimimetics in persons with BTM concentrations at the extremes. However, in our clinical experience, we often use calcimimetics in dialysis patients with suspected high bone turnover. It is our opinion that in patients with biopsy evidence of high bone turnover, or with iPTH concentrations >9 times the normal reference range and a BSAP above the normal range, calcimimetics may play an important role in fracture prevention. More recently, an intravenous calcimimetic, etelcalcetide, has been approved for use in hemodialysis patients with secondary hyperparathyroidism. Large trials evaluating the effects of etelcalcetide on fractures and BMD are needed.

Antiresorptive Medications

Drugs approved by the US Food and Drug Administration (FDA) for the treatment of osteoporosis that have antiresorptive properties can be classified in 3 groups: bisphosphonates, receptor activator of nuclear factor κB ligand (RANKL) inhibitors, and hormone therapies (Table 2). These therapies may have particular benefits in persons with high bone turnover disease because they all decrease bone turnover. Most clinical trials of antiresorptive medications have excluded patients with advanced CKD, but the available data are most extensive for bisphosphonates. Subgroup analyses of phase 3 trials have suggested therapeutic benefits of bisphosphonates in patients with CKD 1-3b, as well as in patients who have undergone kidney transplantation. Unfortunately, the data on bisphosphonates in CKD 4-5D are extremely limited and largely describe treatment of hypercalcemia.

The main risks of bisphosphonate use in patients with advanced CKD or on dialysis include more rapid GFR decline and long-term effects within bone that may induce or exacerbate low turnover states. Notably, a recent analysis on the use of oral bisphosphonates in CKD suggested a 14% increased risk of CKD progression, though this is less of an issue for dialysis patients. Malluche et al are currently conducting a randomized, placebo-controlled trial evaluating bisphosphonate use versus usual care in persons on dialysis with BTM evidence of high bone turnover. This important study will provide not only early efficacy data, but also important safety and tolerability data in dialysis populations.

In our clinical experience, in dialysis patients with high bone turnover and worsening osteoporosis despite the use of calcimimetics and vitamin D receptor agonists, oral bisphosphonates at low doses have been well tolerated. Others have evaluated the use of intravenous bisphosphonates in patients on dialysis, suggesting there may be a role for these formulations as well. We aim to balance the risks with the tremendously high fracture burden and its consequences on quality of life in dialysis patients, and we advocate for the use of bisphosphonates in dialysis patients with BTM or bone biopsy evidence of high turnover disease and worsening osteoporosis (Fig 1).

However, this approach is opinion based and moves beyond the FDA indications for this class of medications. Thus, patients should be appropriately informed of the risks and the off-label use of this therapy in the process of shared decision making.
We recommend measuring baseline BTM levels and monitoring for changes to guide the duration of therapy—BSAP for bone formation and the NTX test (which measures the concentration of cross-linked N-telopeptides of type I collagen) for bone resorption. Notably, PTH concentrations often increase after bisphosphonate use as the medication diminishes bone turnover. Thus, in patients receiving bisphosphonates, PTH should be considered an unreliable indicator for underlying bone turnover. We also suggest that in patients with CKD 4-5 and progressive eGFR decline, bisphosphonates should likely be avoided, considering the risks of possibly exacerbating CKD progression.

Denosumab is a drug with antiresorptive properties that can be used in the treatment of osteoporosis in advanced CKD with less risk of renal toxicity. Unfortunately, there are 3 important considerations when using denosumab in this patient population. First, denosumab use carries risks of severe hypocalcemia, which can be prolonged over weeks and can be observed even after a single dose. This side effect is more common in patients with advanced CKD or, in particular, on dialysis. Thus, close monitoring for this effect and aggressive, prolonged calcium supplementation may be needed. Second, data supporting efficacy for fracture prevention with denosumab in advanced CKD and in dialysis are limited. Last, many clinicians advocate for use of bisphosphonate therapy after completion of a denosumab course due to the risks of rebound osteoclast activity, loss of BMD, and vertebral fractures after stopping therapy with denosumab.

The feasibility of using bisphosphonates after denosumab should be considered and planned a priori. Therefore, we do not routinely use denosumab in our dialysis patients. However, in patients with progressive CKD 4-5, denosumab may be a reasonable treatment for high turnover states with low-dose bisphosphonate at the completion of therapy (possibly while on dialysis). If denosumab is used, we recommend measuring calcium frequently over the first 2 months after administration, and patients should be informed of the risks of needing urgent intravenous calcium infusions. Additionally, it is our practice to initiate calcium and calcitriol supplementation prophylactically before initiation of therapy, and tapering these medications as tolerated based on the changes in serum calcium after denosumab infusion.

Raloxifene represents an underutilized treatment option in women with advanced CKD and high bone turnover. Raloxifene is a selective estrogen receptor modulator (SERM) that has antiresorptive properties and has been FDA approved for use in the treatment of osteoporosis. Studies in CKD have demonstrated a favorable safety profile although studies in patients with advanced CKD or on dialysis are limited. Although estrogen therapy can increase the risk of thrombotic events, this risk is smaller when using SERMs. Nonetheless, we advise caution in patients with history of thromboembolic events including stroke and arteriovenous fistula thromboses.

**Anabolic Medications**

The prevalence of low bone turnover in patients with advanced CKD or maintenance dialysis may be over 50%,
suggesting that anabolic agents may play a critical role in the management of osteoporosis in these patients because anabolics will increase bone turnover.\(^5\) PTH analogues, including teriparatide and abaloparatide, stimulate bone turnover and are approved for the treatment of osteoporosis in the general population.\(^5\) Unlike bisphosphonates, these drugs do not appear to increase the risk of kidney function decline. Studies in mild to moderate CKD have suggested safety and efficacy of these agents in improving BMD.\(^5\) Unfortunately, studies in dialysis patients are few and of small sample sizes.\(^6\)

Nonetheless, in patients with histologic evidence of low bone turnover or iPTH concentrations < 2 times the laboratory reference range, and a BSAP below the normal range, we recommend consideration of these agents. One patient population that may uniquely benefit from these agents are patients with worsening osteoporosis after parathyroidectomy.\(^6\) These drugs were observed to increase the risk of osteosarcoma in preclinical animal studies during drug development, which resulted in the issuance of a black box warning when they were initially approved by the FDA.\(^6\) However, this risk has not been observed in large postmarketing studies in humans, and the FDA has recently removed the black box warning.\(^6\) Finally, most studies using these anabolic agents typically conclude with the addition of a bisphosphonate, which we feel remains necessary in patients on dialysis to prevent relapse bone loss when the anabolic agent is discontinued.

Romosozumab is a monoclonal antibody targeting sclerostin, a hormone produced by the osteocytes, and it was recently FDA approved for the treatment of osteoporosis.\(^6,6\) Romosozumab acts as an anabolic and an anti-resorptive concurrently, and may have potential in the treatment of the CKD-MBD, given the known abnormalities in sclerostin in CKD.\(^6,6\) However, romosozumab

---

**Figure 1.** Algorithm for the management of osteoporosis in patient on dialysis. \(^*\)Osteoporosis defined as T score \(\leq 2.5\), or fragility fractures. \(^\dagger\)We recommend achieving these targets using calcimetics, active vitamin D analogs, and phosphate binders. \(^\ddagger\)We do not recommend bone biopsy when life expectancy \(< 2\) years. \(^\circ\)PTH monitoring not recommended with bisphosphonates. \(\ast\)Worsening osteoporosis defined greater than least significant change in BMD on DXA. Abbreviations: BMD, bone mineral density; BSAP, bone-specific alkaline phosphatase; DXA, dual-energy x-ray absorptiometry; NTX, cross-linked N-telopeptides of type I collagen; PTH, parathyroid hormone.
Therapeutic Monitoring

Although contemporary clinical use of BTMs has been limited for definitively diagnosing bone turnover states in patients with CKD or on dialysis, they may have a role for monitoring response to therapies. The relationship of PTH and BSAP with bone turnover appears linear. Thus, once an individual’s bone turnover state is determined, monitoring changes in BTMs can be effective for determining dosing and duration of therapy. We suggest monitoring BSAP concentrations as a marker of bone formation that is not dependent on kidney clearance.

Finally, we do not use the NTX test to diagnose the degree of bone turnover, but it may be useful for following changes in bone resorption by evaluating trends over time in individual patients. In patients being treated with an antiresorptive agent without adequate reduction in BTMs, calcimimetics can be considered in conjunction, although this drug class has not been well studied in combination therapy approaches and serum calcium concentrations must be closely monitored. Finally, the duration of therapy—whether it be with an antiresorptive or anabolic agent—is not well defined and likely needs to be individualized. We suggest serial DXA monitoring every 2 years and feel it is reasonable to stop antiresorptive or anabolic therapy when significant improvements are seen in BMD or on histomorphometry.

Future Directions

Many fundamental research questions remain unanswered in the management of osteoporosis in the advanced CKD. In terms of diagnosis, observational studies that identify imaging techniques and blood biomarkers that better quantify bone turnover would be of immense benefit given the invasive nature and limited availability of bone biopsies. New normal ranges of renally cleared BTMs are needed at any given GFR level. Further studies using non–renally-cleared BTMs will also be helpful in managing turnover abnormalities across the spectrum of CKD. As the number of bone biopsies at individual centers tends to be small, larger, multicenter bone biopsy studies are likely necessary to determine these target ranges for clinically available BTMs. Finally, randomized trials using antiresorptive and anabolic medications are needed in dialysis populations to demonstrate safety and efficacy, particularly for clinically meaningful outcomes like fractures.

Review of Clinical Vignette and Conclusion

After discussing the patient’s osteoporosis with his endocrinologist, a decision was made that given the degree of PTH elevation, high bone turnover disease was highly likely. Oral alendronate at 35 mg weekly was started and will continue for 2 years. Serial measurements of BSAP and NTX were performed and decreased by approximately 50%. After 2 years, a repeat DXA scan revealed improvements in BMD at multiple anatomic sites, and the alendronate was stopped. The patient appreciated the improvements in BMD and the fact that he had not fractured any other bones.

In conclusion, osteoporosis is highly prevalent in persons with advanced CKD, including those treated with kidney replacement therapy. Fractures represent a major threat to the well-being and quality of life of this population. As physicians, we are tasked with helping to mitigate these risks, despite the absence of robust randomized trials to support our decisions. With the increasing armamentarium of osteoporosis drugs now available, we have the power to decrease fracture rates in our patients going forward.

Article Information

Authors’ Full Names and Academic Degrees: Charles Ginsberg, MD, MAS, and Joachim H. Ix MD, MAS.

Authors’ Affiliations: Division of Nephrology-Hypertension, Department of Medicine, University of California-San Diego (CG, JHI); Nephrology Section, Veterans Affairs San Diego Healthcare System (JHI), San Diego, California.

Address for Correspondence: Charles Ginsberg, MD, MAS, 9452 Medical Center Dr, L3E206, La Jolla, CA 92037. Email: cginsberg@health.ucsd.edu

Support: Dr Ginsberg and Dr Ix are supported by the National Institute of Diabetes, Digestive, and Kidney Diseases K23DK118197 and Loan Repayment Program (Ginsberg) as well as R01DK101720 and K24 DK110427 (Ix). These funders had no role in defining the content of this review.

Financial Disclosures: Dr Ix has served as a member of the Data Safety Monitoring Board for Sanofi International, and has served on advisory boards for Ardelyx, AstraZeneca, Jnana Pharmaceuticals, and Bayer. Dr Ginsberg declares that he has no relevant financial interests.

Acknowledgements: We would like to thank Dr Hartmut Malluche for providing information on his randomized trial evaluating biomarker guided therapy in patients on maintenance dialysis.

Peer Review: Received February 18, 2021, in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form June 18, 2021.

References


comparable ROD diagnosis as full 7.5mm wide samples. Bone. 2020;138:115460. doi:10.1016/j.bone.2020.115460
60. Cejka D, Kodras K, Bader T, Haas M. Treatment of hemodialysis-associated adynamic bone disease with


