

**Summary:** Bone disease after kidney transplantation is associated with an increased risk of fractures, morbidity, and mortality. Its pathophysiology is complex, involving multiple contributors including pretransplant bone disease, immunosuppressive medications, and changes in the parathyroid–bone–kidney axis. Risk scores, bone turnover markers, and noninvasive imaging modalities are only able to partially predict the fracture risk in kidney transplant recipients. The optimal management of bone disease after kidney transplantation has not yet been established, with only a limited number of randomized clinical trials evaluating the efficacy of treatment regimens in kidney transplant recipients. This review focuses on the pathophysiology, evaluation, prevention, and treatment of post–kidney transplant mineral and bone disease as guided by recent evidence.

Semin Nephrol 41:168–179 © 2021 Elsevier Inc. All rights reserved.

**Keywords:** Kidney transplant, mineral bone disorder, MBD, fracture, osteoporosis

Chronic kidney disease (CKD) is associated with abnormalities in bone turnover, mineralization, and an increased risk of fractures.<sup>1</sup> Fractures in patients with advanced CKD and end-stage kidney disease may be associated with increased mortality compared with the general population.<sup>2,3</sup> Kidney transplantation (KT) is the treatment of choice for patients with end-stage kidney disease. It is associated with improved survival and quality of life compared with dialysis, but mineral bone disease and fractures remain an issue after transplantation.<sup>4,6</sup> Bone loss after transplantation is not unique to kidney transplant recipients (KTRs), and is seen in patients who receive other solid-organ transplants.<sup>6</sup>

However, bone disease after KT is unique in its pathophysiology because of its multifactorial contributors such as pretransplant bone disease, immunosuppressive medications, alterations in mineral metabolism, and changes in the parathyroid–bone–kidney axis.<sup>7</sup> In this article, we review the epidemiology, pathophysiology, fracture risk assessment, and evidence regarding treatment of bone disease after KT.

## EPIDEMIOLOGY

Bone mineral disorders and fractures are common in KTRs. Many studies have shown a significant decrease

\*Center for Transplantation Sciences, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, MA

†Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

‡Center for Molecular Medicine, Maine Medical Center Research Institute, Scarborough, ME

Financial disclosure: Supported in part by the Harold and Ellen Danser Endowed/Distinguished Chair in Transplantation at Massachusetts General Hospital (Boston, MA).

Conflict of interest statement: none.

Address reprint requests to Leonardo V. Riella, MD, PhD, Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02115. E-mail: [riella@mgh.harvard.edu](mailto:riella@mgh.harvard.edu)

0270-9295/ - see front matter

© 2021 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.semnephrol.2021.03.011>

in bone mineral density (BMD) in the first 6 months after KT, followed by stabilization or improvement after the first year.<sup>8–10</sup> KTRs have a more than four-fold risk of fractures compared with the general population, and a higher risk in the first 3 years after KT compared with patients on dialysis.<sup>11,12</sup>

Fractures in KTRs occur most commonly in peripheral locations, such as the ankle, and are associated with increased mortality.<sup>12,13</sup> Peripheral fractures are atypical for osteoporotic fractures, which suggests that their predominance likely reflects a significant contribution from renal osteodystrophy to fracture risk.<sup>7</sup> However, more recent data suggest that BMD loss and the incidence of fractures in KTRs is lower than what has been reported previously.<sup>14–17</sup> That may be related to changes in immunosuppression regimens combined with increased screening for osteoporosis and treatment for patients with fracture prevention therapies, as well as better management of hyperparathyroidism during CKD.<sup>17</sup>

## PATHOPHYSIOLOGY

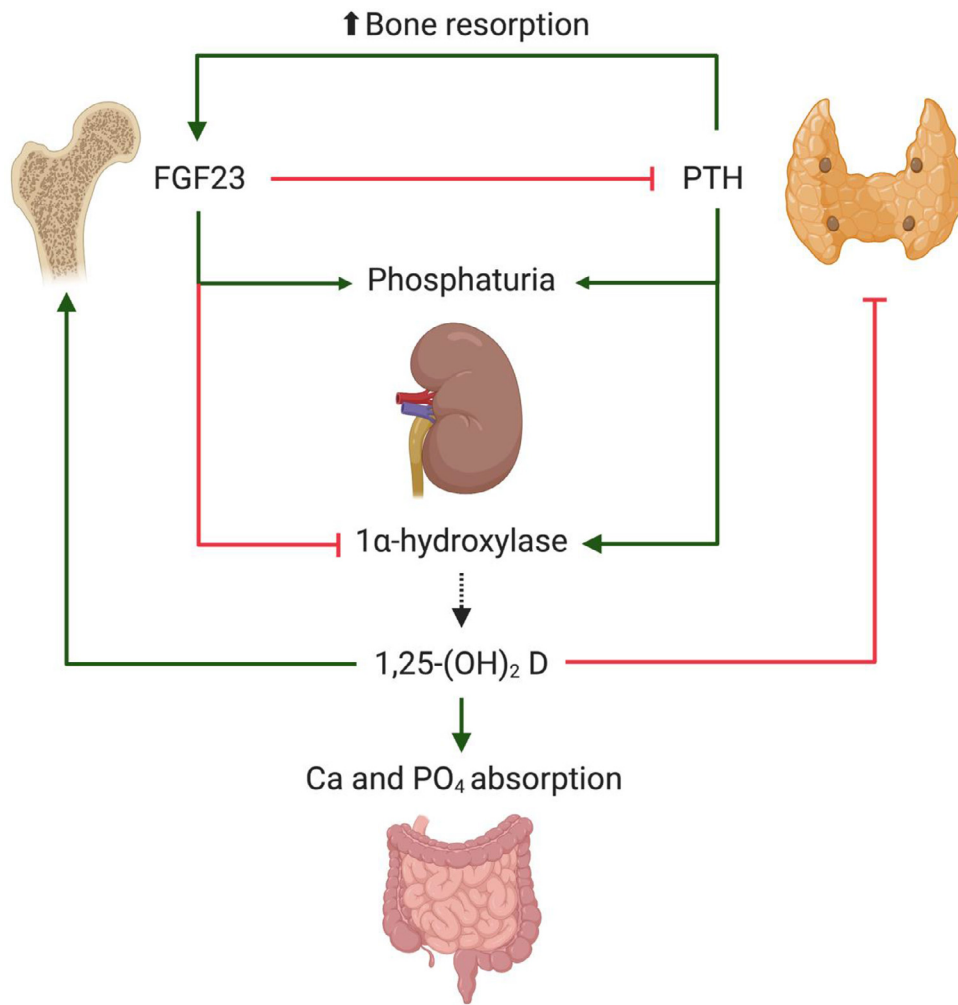
The pathophysiology of bone disease after KT involves pre-existing renal osteodystrophy, immunosuppressive medications, alterations in mineral metabolism, and changes in the parathyroid–bone–kidney axis.<sup>7</sup>

### Pretransplant Bone Disease

Bone disease before transplantation is associated with hypocalcemia, hyperphosphatemia, 1,25-(OH)<sub>2</sub> vitamin D deficiency, and abnormalities in bone turnover rate, likely related to parathyroid hormone (PTH). **Figure 1** shows the normal physiology of the parathyroid–bone–kidney axis, and **Figure 2** shows changes in CKD.

### Osteoporosis

Osteoporosis is characterized by bone fragility secondary to low bone mass and disruption of bone microarchitecture.



**Figure 1.** Normal physiology of the parathyroid–kidney–bone axis. Parathyroid hormone (PTH) stimulates phosphaturia, calcium reabsorption, and 1,25-(OH)<sub>2</sub> vitamin D activation by 1 $\alpha$ -hydroxylase in the kidney. PTH also stimulates calcium release from bone, bone resorption, and secretion of fibroblast growth factor 23 (FGF23) by osteocytes and osteoblasts. FGF23 also stimulates phosphaturia but has an inhibitory effect on 1 $\alpha$ -hydroxylase activity and PTH secretion. 1,25-(OH)<sub>2</sub> vitamin D inhibits PTH synthesis and stimulates bone resorption, FGF23 secretion, and intestinal calcium and phosphate absorption. High serum calcium inhibits PTH secretion, while high phosphate stimulates PTH secretion (not shown). Created with BioRender.com (Toronto, Canada).

The diagnosis of osteoporosis is established by the occurrence of a fragility fracture or a T-score of 2.5 or less on dual-energy X-ray absorptiometry (DXA). Osteoporosis both before and after KT has been linked to an increased risk of fractures in KTRs.<sup>18,19</sup> Risk factors for osteoporosis in the general population such as older age and glucocorticoid use are common in KTRs.<sup>20</sup>

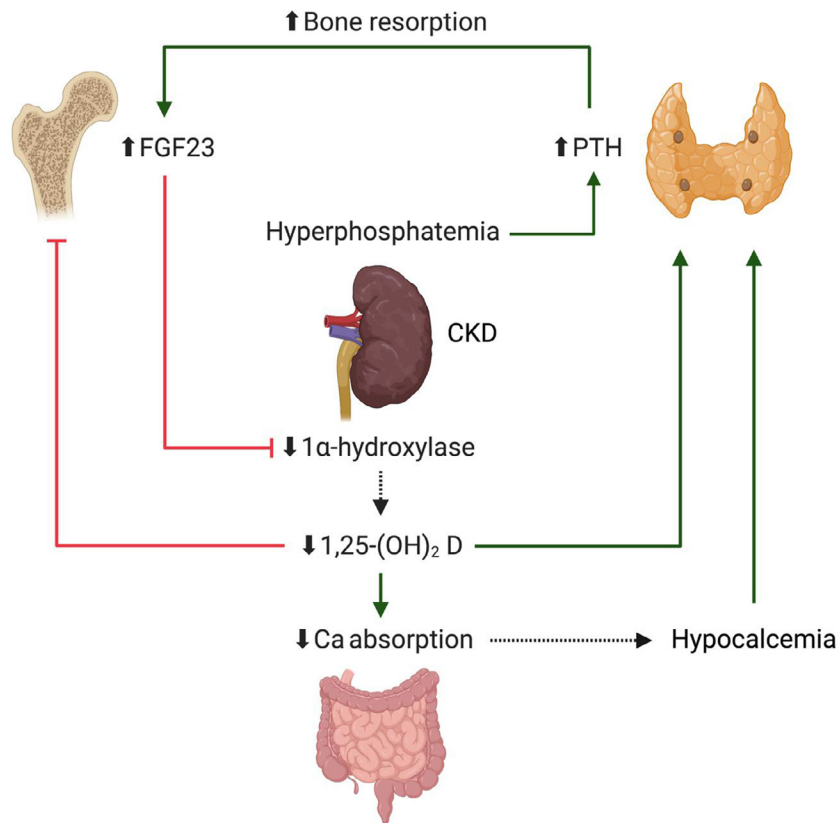
**Effects of Immunosuppression**

Glucocorticoids (GCs) affect bone strength through direct and indirect mechanisms. GCs increase osteoclastogenesis, reduce osteoblastogenesis, and increase apoptosis of osteoblasts and osteocytes. GCs also decrease calcium absorption and increase levels of receptor activator of nuclear factor- $\kappa$ B ligand, which results in increases in bone-resorbing osteoclasts.<sup>21</sup>

GCs used for rejection treatment or maintenance immunosuppression can have effects on bone health.<sup>22,23</sup> One study showed that each gram of GCs used for rejection treatment was associated with a cumulative decline in trabecular density.<sup>22</sup> For maintenance immunosuppression, analysis of US Renal Data System data showed a 31% reduction in fracture risk in patients on early corticosteroid withdrawal (CSW) protocols.<sup>23</sup> The effects of other immunosuppressive agents on bone disease is not clear.<sup>24</sup>

**Changes in Mineral Metabolism and Parathyroid –Bone–Kidney Axis**

Several changes in mineral metabolism and the parathyroid–bone–kidney axis occur after KT, related to the kidney’s restored ability to excrete phosphate, increased 1 $\alpha$ -hydroxylase activity, and restored effects of PTH



**Figure 2.** Parathyroid–kidney–bone axis in chronic kidney disease (CKD). In CKD, one of the earliest biomarkers of mineral bone disorder is an increase in fibroblast growth factor 23 (FGF23) levels, likely as compensation for the kidney’s reduced ability to excrete phosphorus. Increased FGF23 levels in combination with reduced kidney mass result in lower  $1\alpha$ -hydroxylase activity, reduced  $1,25\text{-(OH)}_2$  vitamin D levels, and less intestinal calcium absorption. Hyperphosphatemia develops as CKD progresses despite the phosphaturic effects of FGF23 and parathyroid hormone (PTH). Hypocalcemia, hyperphosphatemia, and low levels of  $1,25\text{-(OH)}_2$  vitamin D stimulate PTH secretion. Hyperparathyroidism may have adaptive effects in the short term but chronically has maladaptive effects on bone health. Created with BioRender.com (Toronto, Canada).

and fibroblast growth factor 23 (FGF23) as shown in Figures 3 and 4.<sup>21,25</sup>

### Persistent hyperparathyroidism

PTH levels decrease after KT, although the magnitude of decrease is variable across studies. The decrease in PTH levels likely is owing to changes in calcium, phosphorus, and  $1,25\text{-(OH)}_2$  vitamin D levels.<sup>21,26</sup> However, persistent hyperparathyroidism (PHPT) is common after KT, with a large prospective observational study reporting a prevalence of PHPT of more than 80% in the first year after KT in untreated patients. Although patients with higher pretransplant PTH values ( $>300$  pg/mL) experienced a greater decrease in PTH levels compared with patients with lower baseline PTH values (65–300 pg/mL), the proportion of patients with PHPT was the same in both groups. The mean PTH levels in both groups remained increased at 12 months after KT.<sup>21</sup>

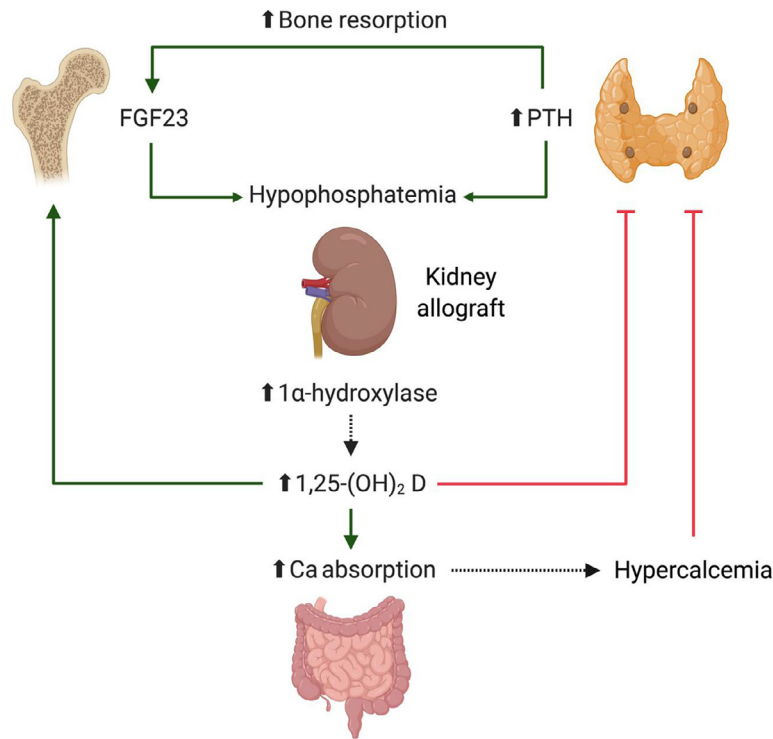
Higher PTH levels in KTRs are associated with decreased BMD at the total hip and femoral neck.<sup>22</sup> A study evaluating high-resolution peripheral quantitative

computed tomography (HRpQCT), a new imaging modality that can provide three-dimensional images to better assess cortical and trabecular bone, showed that PTH had different associations with cortical and trabecular bone. Higher PTH levels in KTRs are associated with lower cortical area and thickness, while both PTH levels less than 100 and greater than 140 pg/mL were associated with decreased trabecular bone density.<sup>22</sup>

Pretransplant PTH levels do not correlate with the earlier-described findings. The bimodal nature of the association between post-KT PTH levels and fracture risk may reflect that both high- and low-turnover states are associated with fracture risk.<sup>26,27</sup> At this time, the goal PTH levels after KT to improve bone health and reduce fracture risk remain unknown.<sup>22</sup>

### FGF23 levels after transplantation

FGF23 is a hormone secreted by mature osteoblasts and osteocytes that regulate phosphorus homeostasis.<sup>28</sup> Its primary function is mediated by the receptor complex (Klotho–FGF-receptor-1c), which is present on parathyroid chief

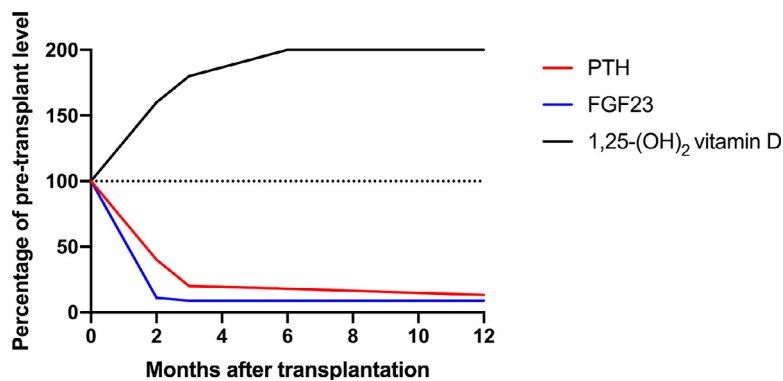


**Figure 3.** Parathyroid–kidney–bone axis after kidney transplantation (KT). After KT, the allograft has increased  $1\alpha$ -hydroxylase activity, is able to excrete phosphorus more efficiently, and is more responsive to parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). FGF23 and PTH levels decrease after KT, but PTH levels frequently remain above the normal range. Persistent hyperparathyroidism in this setting results in hypophosphatemia and increased bone resorption. Persistent hyperparathyroidism combined with increased  $1,25\text{-(OH)}_2$  vitamin D levels and increased intestinal calcium absorption results in hypercalcemia. Created with BioRender.com (Toronto, Canada).

cells and kidney proximal tubular cells.<sup>29</sup> It suppresses the expression of the sodium phosphate transporters in the proximal tubule, resulting in phosphaturia, and reduces levels of  $1,25\text{-(OH)}_2$  vitamin D by suppressing  $1\alpha$ -hydroxylase and activating 24-hydroxylase.<sup>25,29</sup> Its secretion is stimulated by PTH, and through a feedback loop FGF23 reduces PTH expression and secretion (Fig. 1).<sup>30</sup> There is limited evidence from animal models that increased dietary phosphate intake and increased serum inorganic phosphorus levels may be associated with increased FGF23 levels.<sup>31</sup>

Recent evidence has shown that iron deficiency and erythropoietin also play a role in the regulation of FGF23 production and cleavage.<sup>32</sup>

FGF23 levels increase early in the course of CKD, likely as compensation for the kidney’s reduced ability to excrete phosphorus.<sup>28,33</sup> After KT, FGF23 levels decrease rapidly despite PHPT.<sup>21</sup> In KTRs, increased FGF23 levels have been associated with lower serum phosphate and  $1,25\text{-(OH)}_2$  vitamin D levels, but do not seem to correlate with bone biopsy findings.<sup>21,34</sup>



**Figure 4.** Illustration of average changes in parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and  $1,25\text{-(OH)}_2$  vitamin D levels after kidney transplantation compared with pretransplant levels. Data for graph based on Wolf et al.<sup>21</sup> Created with GraphPad Prism 8.4.3. (Graphpad Software, San Diego, CA)

### Vitamin D levels after transplantation

Studies have shown that 25-OH vitamin D levels remain unchanged or decrease slightly after KT compared with pretransplant levels.<sup>21,26</sup> Studies have shown that 25-OH vitamin D deficiency is common in KTRs, with one study reporting 29% of KTRs having levels less than 10 ng/mL.<sup>35</sup> Lower levels of 25-OH vitamin D are associated with delayed mineralization on bone biopsy in KTRs.<sup>34</sup>

1,25-(OH)<sub>2</sub> vitamin D absolute levels increase significantly after KT, likely secondary to increased activity of 1 $\alpha$ -hydroxylase.<sup>21,26</sup> Studies have not shown a correlation between 1,25-(OH)<sub>2</sub> vitamin D levels and bone biopsy findings, but lower peritransplant levels of 1,25-(OH)<sub>2</sub> vitamin D (<7.5 ng/L) have been associated with fractures after KT.<sup>26,34</sup>

### Calcium homeostasis after transplantation

Calcium levels increase significantly after KT, likely related to increased 1 $\alpha$ -hydroxylase activity, PHPT, and allograft responsiveness to PTH. Hypercalcemia is most prevalent and mean calcium levels peak approximately 2 to 3 months after KT.<sup>21</sup> Patients with increased pretransplant PTH levels are more likely to develop hypercalcemia after KT.<sup>21,34</sup>

### Phosphorus homeostasis after transplantation

Phosphorus levels decrease rapidly after KT, reaching a nadir approximately 4 weeks after KT, after which levels begin to increase.<sup>21,26</sup> Patients with significantly increased PTH levels (>300 pg/mL) develop more hypophosphatemia after KT compared with patients with lower levels of PTH.<sup>21</sup> The decrease in phosphorus levels likely is related to improved glomerular filtration rate (GFR), PHPT, and allograft responsiveness to PTH and FGF23. Lower phosphorus levels are associated with bone biopsy findings of delayed mineralization in KTRs.<sup>34</sup>

### Fracture risk assessment

The available tools to assess fracture risk include clinical information, laboratory studies, noninvasive imaging, and bone biopsy. Clinical risk factors associated with increased fracture risk in KTRs are shown in [Table 1](#).<sup>11-13,18,19,22,23,26,27,36-38</sup>

### The World Health Organization Fracture Risk Assessment Tool

The Fracture Risk Assessment Tool (FRAX; World Health Organization, Geneva, Switzerland) estimates the 10-year risk of osteoporotic fractures in the general population. It initially was thought to not be useful in predicting fracture risk in KTRs because of the different

**Table 1.** Risk Factors Associated With Fractures After Kidney Transplantation

|   |  |
|---|--|
| Pretransplant risk factors                                    |  |
| Age, >50 y  |  |
| Female  |  |
| BMI <18   |  |
| Diabetes mellitus, types 1 and 2                              |  |
| Diabetic nephropathy as cause of ESKD                         |  |
| Pretransplant dialysis  |  |
| Longer time on dialysis                                       |  |
| Pretransplant osteopenia and osteoporosis                     |  |
| Hospitalization for fracture before transplant                |  |
| Transplant risk factors                                       |  |
| Deceased donor kidney transplant                              |  |
| Post-transplant osteopenia and osteoporosis                   |  |
| Proton pump inhibitor use                                     |  |
| Reduced physical activity                                     |  |
| Low peritransplant levels of 1,25-(OH) <sub>2</sub> vitamin D |  |
| PTH levels >130 pg/mL at 3 months after KT                    |  |
| Corticosteroid-based maintenance immunosuppression            |  |
| Cumulative glucocorticoid dose                                |  |

Abbreviations: BMI, body mass index; ESKD, end-stage kidney disease; KT, kidney transplantation; PTH, parathyroid hormone.

pathophysiology of bone disease compared with the general population. However, initial data suggest that the FRAX score correlates well with observed rates of fractures in KTRs and further studies are warranted to validate this score in KTRs.<sup>39</sup>

### PTH, vitamin D, and bone turnover biomarkers

There is no strong evidence that pretransplant PTH levels correlate with bone turnover markers or fracture risk after KT, and therefore they should not be used as part of the fracture risk assessment.<sup>22,40</sup> As discussed earlier, the relationship between PTH after KT and fracture risk may be bimodal, but it is clear that PTH values greater than 130 pg/mL at 3 months after KT, as well as lower peritransplant levels of 1,25-(OH)<sub>2</sub> vitamin D (<7.5 ng/L), are associated with an increased risk of fracture after KT.<sup>26,27</sup>

Several bone turnover markers have been evaluated in the post-KT setting. Higher PTH levels in KTRs were associated with increased levels of several bone turnover markers, including bone-specific alkaline phosphatase, procollagen of type 1 N-terminal propeptide, and collagen type 1 cross-linked C-telopeptide (CTX-1). The levels of most bone turnover markers tend to decrease in the first 3 months after KT.<sup>21</sup> There was no significant association between bone turnover marker levels and bone loss on DXA, but higher bone turnover marker levels have been associated with decreases in cortical area, thickness, and density on HRpQCT.<sup>22</sup> Bone-specific alkaline phosphatase and CTX-1 levels also have been shown to correlate with biopsy findings of increased turnover and bone resorption, respectively, in KTRs.<sup>34,41</sup> However, there is no evidence at this time that bone turnover markers (especially CTX-1, procollagen of type 1



N-terminal propeptide) help predict fracture risk in KTRs.<sup>26</sup> Sclerostin is a bone anti-anabolic protein that currently is being evaluated as a biomarker of bone disease in KTRs.<sup>42</sup>

### Noninvasive Imaging

A DXA scan is a useful imaging modality that measures BMD and helps diagnose osteoporosis. The T-score at the femoral neck has been shown to decrease after KT, but does not seem to correlate with bone biopsy findings.<sup>26,43</sup> There is evidence from retrospective studies that osteopenia and osteoporosis are associated with increased fracture risk in KTRs.<sup>19</sup> Important limitations to DXA imaging include that it provides a two-dimensional image and cannot differentiate between high- and low-turnover states.

Trabecular bone score (TBS) is a new method to evaluate trabecular microarchitecture using a gray-scale textural analysis of DXA images that has been shown to predict osteoporotic fractures in postmenopausal women independently of BMD.<sup>44,45</sup> Recent data suggest it may be a useful noninvasive measure of bone strength in KTRs and that it can reclassify KTRs with normal BMD as being at increased risk for fractures.<sup>46</sup> Older age and pre-KT dialysis are associated with lower TBS scores at baseline. A proposed reason for the discrepancy between DXA and TBS, despite both being derived from the same images, is that vascular calcifications affect DXA but not TBS.<sup>46</sup> TBS in combination with the FRAX score may be helpful in predicting fracture risk in KTRs, but has yet to be validated in this population.<sup>47</sup>

HRpQCT is a new imaging modality that can provide three-dimensional imaging of bones and has shown changes in trabecular and cortical bone in KTRs. It has been incorporated into many studies looking at bone disease in KTRs. Although promising, it remains a research tool and is not widely available for clinical use at this time.<sup>22</sup>

### Bone Biopsy

Bone biopsy is the gold standard for identifying the histopathology underlying bone disease. Although the static parameters (eg, trabecular number and thickness) that it provides may be replaced by the earlier-mentioned imaging methods, biopsy remains the only tool able to evaluate bone formation and mineral opposition rates.<sup>44</sup> Studies looking at bone biopsy specimens in KTRs have shown that they are abnormal in the majority of patients. It was initially thought that most KTRs have low bone turnover disease on biopsy, but this has not been consistent across studies.<sup>34,48,49</sup> There are no studies that have evaluated the correlation between bone biopsy findings and fracture risk. Because of its invasive nature and limited expertise in histomorphometry, bone biopsy is not performed routinely in assessing bone disease in KTRs.<sup>24</sup>

## PREVENTION AND TREATMENT

The Kidney Disease: Improving Global Outcomes 2017 guidelines recommend considering treating KTRs with vitamin D, calcitriol, alfacalcidol, or antiresorptive agents in the first 12 months after KT if they have low BMD and an estimated GFR greater than 30 mL/min per 1.73 m<sup>2</sup>. They suggest using phosphorus, calcium, PTH, and vitamin D levels to guide treatment, but do not provide more specific recommendations.<sup>50</sup> Here, we provide a review of the data behind the use of different preventive and treatment strategies for bone disease in KTRs.

### Pretransplant Mineral Bone Disorder Management

A recent retrospective study showed that KTRs in more recent years had a lower fracture risk and were more likely to have pre-KT 25-OH vitamin D levels greater than 30 µg/L and pre-KT PTH in the range of two to nine times the upper limit of normal.<sup>40</sup> Based on that and the Kidney Disease: Improving Global Outcomes 2017 guidelines, it is reasonable to target 25-OH vitamin D levels greater than 30 µg/L and a PTH level between two and nine times the upper limit of normal.<sup>40,50</sup>

### Reducing Glucocorticoid Use

The effects of various CSW protocols on BMD and fracture risk have shown different degrees of improvement across studies. For early CSW, one randomized clinical trial (RCT) showed that it was associated with a significant increase in BMD at the lumbar spine (LS) compared with the corticosteroid maintenance (CSM) protocol, while a more recent single-arm observational study showed it was associated with stable BMD in the central skeleton, but decreased BMD in the peripheral skeleton.<sup>22,51</sup> For late CSW, RCTs have shown that it is associated with an increase in BMD at the LS and total hip compared with the CSM protocol.<sup>52,53</sup> The discrepancies seen between some of the early CSW studies may be owing to the data being focused on BMD at the central skeleton and a reduction in the total amount of steroids used post-transplantation over time.

An analysis of 7 years of US Renal Data System data showed a 31% fracture risk reduction in KTRs on early CSW protocols.<sup>23</sup> Early CSW are appealing for the prevention of bone disease after KT, but cannot be used in all KTRs, especially in patients at high risk for allograft rejection.

### Vitamin D and Its Analogs

Vitamin D is known to have effects on bone mineralization, intestinal absorption of calcium and phosphate, proteinuria, and the immune system.<sup>54</sup> There are no placebo-controlled RCTs evaluating the effects of cholecalciferol or calcitriol supplementation on BMD or

fracture risk. In a trial comparing calcitriol with alendronate in KTRs, both groups had a statistically significant increase in BMD at 12 months, but there was no statistically significant difference between the two groups.<sup>55</sup> Paricalcitol is a vitamin D–receptor agonist similar to calcitriol that has less of a stimulatory effect on intestinal calcium and phosphate absorption.<sup>56</sup> In a cross-over RCT, paricalcitol treatment was associated with a significant reduction in PTH and bone turnover marker levels, and a small increase in LS BMD compared with no treatment. The study also found a small reduction in proteinuria and estimated GFR during paricalcitol treatment, which was thought to be related to either increased generation or reduced tubular secretion of creatinine as opposed to a true reduction in GFR.<sup>57</sup> More studies are needed to determine the effects of paricalcitol on fracture risk, GFR, and long-term allograft outcomes.

### **Anabolic agents**

Teriparatide is a recombinant human PTH that has anabolic effects on the human skeleton and has been shown to increase BMD and reduce fracture rates in postmenopausal women.<sup>58</sup> One small RCT randomized 26 KTRs to receive daily subcutaneous teriparatide injections for 6 months versus placebo. Both groups received calcium and vitamin D supplementation. The results showed that BMD at the femoral head decreased in the placebo group but remained stable in the teriparatide group. However, there were no differences in the BMD at LS and distal radius/ulna or histomorphometric parameters between the two groups. The risk of fracture was not evaluated in the study.<sup>49</sup> At this time, the role of teriparatide in treating bone disease in KTRs remains unclear.

### **Calcimimetics**

Cinacalcet inhibits PTH secretion by increasing the sensitivity of the calcium-sensing receptor to calcium in the parathyroid glands. One RCT of 114 KTRs with PHPT and hypercalcemia comparing cinacalcet with placebo showed that patients in the cinacalcet group had a statistically significant decrease in corrected calcium and PTH levels compared with the placebo group, but the effect disappeared when cinacalcet was discontinued for 4 weeks. There was no significant difference in BMD change between the two groups. Fracture risk was not assessed in the study.<sup>59</sup>

Another RCT that randomized 30 patients to subtotal parathyroidectomy or cinacalcet found that patients who had a subtotal parathyroidectomy were more likely to be normocalcemic, had a greater reduction in PTH levels, and an increase in femoral neck BMD than patients treated with cinacalcet.<sup>60</sup> More studies are needed to

determine the long-term effects of cinacalcet on bone health and fracture risk in KTRs. At this time, cinacalcet is not approved for the treatment of hyperparathyroidism in KTRs but is considered clinically in patients with persistent hypercalcemia owing to increased PTH after transplantation.<sup>50</sup>

### **Denosumab**

Denosumab is a monoclonal antibody against receptor activator of nuclear factor- $\kappa$ B ligand that decreases bone resorption and has been shown to be effective in increasing BMD and reducing fractures in postmenopausal women.<sup>61,62</sup> One advantage of denosumab is that it is not cleared by the kidney and can be used safely in patients with reduced estimated GFR without an increased risk of adverse events.<sup>62-64</sup> However, a risk of rebound fractures has been reported when denosumab is discontinued, so switching to a bisphosphonate after denosumab discontinuation is frequently performed.<sup>65</sup> One open-label RCT comparing denosumab with placebo in KTRs showed that denosumab treatment was associated with an increase in BMD at the LS and total hip and lower bone turnover marker levels compared with the control group. Urinary tract infections, diarrhea, and asymptomatic hypocalcemia were more common in the denosumab group. The study did not assess fracture risks.<sup>66</sup> Denosumab is a promising treatment for bone disease in KTRs, but studies evaluating its effect on fracture risk in these patients are needed.

### **Bisphosphonates**

Bisphosphonates are antiresorptive agents that inhibit osteoclast farnesyl pyrophosphate synthase, resulting in osteoclast apoptosis and reduced bone resorption.<sup>7,43</sup> Several trials evaluating the efficacy of different bisphosphonates in KTRs have been performed and are summarized in [Table 2](#).<sup>14,43,55,67-77</sup> The trials listed showed that bisphosphonates were not associated with adverse allograft outcomes in KTRs with an estimated GFR greater than 30 mL/min per 1.73 m<sup>2</sup>. Most trials showed that bisphosphonates were associated with stable or improved BMD at various sites, although they may not have much additional benefit in patients already on calcium and vitamin D supplementation. Different studies have shown variable outcomes in terms of risk of adynamic bone disease (ABD). One study reported that all patients on pamidronate developed ABD, while another study reported no new cases of ABD in patients on risedronate. Several studies also showed a nonsignificant trend toward reduced fracture risk in KTRs. Trials powered to detect a difference in fracture risk and evaluating the risk of ABD in KTRs are needed.<sup>14,43,55,67-77</sup>

**Table 2.** Randomized Controlled Trials of Bisphosphonates in Kidney Transplant Recipients

| Study                          | Subjects, n | Treatment in Both Groups  | Additional Treatment  | Follow Up Period, mo | Findings  | Notes   |
|--------------------------------|-------------|---|---|----------------------|---|---|
| Kovac et al <sup>75</sup>      | 12          | PO calcium carbonate 2,000 mg/d and calcitriol 0.25 µg/d  | PO alendronate 10 mg/d  | 6                    | Patients in alendronate group had an increase in LS BMD at 6 months, while patients in the control group had a decrease in LS BMD. However, LS BMD at 6 months was not significantly different between the two groups.  | Small sample size<br>Open-label study<br>No description of randomization<br>Fracture risk not evaluated   |
| Giannini et al <sup>76</sup>   | 40          | First 12 months: PO calcium 980 mg/d (dietary)<br>Last 12 months: PO calcium carbonate 500 mg/d and calcitriol 0.5 µg/d   | PO alendronate 10 mg/d (started at 12 months)                                     | 24                   | Patients in alendronate group had a statistically significant increase in BMD at the spine, FN, and total femur compared with control group. BTMs decreased significantly in alendronate group, but did not change significantly in control group.  | Small sample size<br>Open-label study<br>Patients were followed up for 12 months before and after alendronate initiation                              |
| Jeffrey et al <sup>55</sup>    | 117         | 1,000 mg of dietary calcium plus PO calcium carbonate 500 mg/d  | PO alendronate 10 mg/d versus PO calcitriol 0.25 µg/d                             | 12                   | Each group had a significant increase in LS and femur BMD compared with pretreatment BMD, but there was no difference in the BMD increase between the two groups.   | Open-label study<br>Significant difference in baseline eGFR and time from transplantation between the two groups<br>All patients were on cyclosporine |
| Grotz et al <sup>70</sup>      | 80          | PO 1,000 mg dietary calcium or calcium 500 mg supplement daily (if unable to tolerate dairy)<br>PO cholecalciferol 10,000 IU if 25-OH vitamin D level <15 ng/mL | IV ibandronate (1 mg before KT and 2 mg at 3, 6, and 9 months after KT)           | 12                   | Patients in ibandronate group had a higher BMD at the LS, FN, and midfemoral shaft compared with control group. One vertebral and one arm fracture occurred in each group. Less incidence of acute rejection in ibandronate group but no difference in graft function at 12 months.       |   |
| Smerud et al <sup>74</sup>     | 129         | PO calcitriol 0.25 µg/d and calcium 500 mg twice daily  | IV ibandronate 3 mg every 3 months for 12 months                                  | 12                   | Compared with placebo group, treatment with ibandronate was associated with improved BMD at the femur and ultradistal radius, and lower levels of P1NP, OC, and BALP. There was no difference in LS BMD between the two groups. One vertebral fracture was reported in each group.        |   |
| Walsh et al <sup>67</sup>      | 125         | PO calcium carbonate 500 mg and cholecalciferol 400 IU/d  | IV pamidronate 1 mg/kg (perioperatively then at 1, 4, 8, and 12 months post-KT)   | 24                   | Patients in the pamidronate group had a significant increase in BMD at the LS and TH compared with the control group, in which BMD decreased in both. There were no differences in FN BMD or levels of BALP or CTX-1. Two fractures occurred in pamidronate group and 6 in control group. | All patients were on cyclosporine   |
| Torregrosa et al <sup>69</sup> | 39          | PO calcium 1,000 mg and cholecalciferol 800 IU/d  | IV pamidronate 30 mg (one dose at 7-10 days then a second dose 3 months after KT) | 12                   | Patients in the pamidronate group had stable BMD at the LS, while the control group had a statistically significant decrease in LS BMD. There were no differences in fracture incidence or in BMD at the FN or TH between the two groups.   | Small sample size<br>All patients had osteopenia and were on cyclosporine   |
| Coco et al <sup>73</sup>       | 72          | PO calcitriol and calcium (doses not reported)  | IV pamidronate 60 mg within 48 hours of KT  | 12                   | Treatment with pamidronate was associated with less decrease in LS BMD but no significant difference in TH BMD or BTMs compared   | Not placebo controlled<br>More women and patients with  |

(continued on next page)



Table 2 (Continued)

| Study                          | Subjects, n | Treatment in Both Groups                                   | Additional Treatment   | Follow Up Period, mo | Findings   | Notes   |
|--------------------------------|-------------|--|--|----------------------|--|---|
|                                |             |  | followed by 30 mg at 1, 2, 3, and 6 months   |                      | with control group<br>ABD was present in 50% of all patients at baseline<br>At 6 months, 100% of patients in pamidronate group had ABD compared with 50% in control group<br>One vertebral fracture occurred in pamidronate group and two occurred in control group  | GN as etiology of ESKD in pamidronate group   |
| Torregrosa et al <sup>68</sup> | 101         | PO calcium carbonate 1,500 mg and cholecalciferol 400 IU/d | PO risedronate 35 mg/wk (duration not specified)                                     | 12                   | Patients in the risedronate group had a higher LS BMD at all points and a higher FN BMD at 6 months only compared with the control group<br>Four vertebral fractures occurred in risedronate group and six in control group  | Open-label study<br>Findings at LS confounded by significantly lower baseline LS BMD in control group |
| Coco et al <sup>43</sup>       | 42          | PO calcitriol 0.25 µg/d                                    | PO risedronate 35 mg/wk for 12 months  | 12                   | There were no differences in BMD or BTMs between the two groups overall<br>Risedronate treatment was associated with a decrease in bone activity on biopsy but no patients developed ABD<br>Two vertebral fractures occurred in risedronate group and none in control group<br>The effect of risedronate on BMD and bone activity on biopsy may differ between men and women | Small sample size<br>More women and higher BMI in control group                                       |
| Haas et al <sup>71</sup>       | 20          | PO calcium citrate 1,000 mg/d                              | IV zoledronic acid 4 mg (first dose within 2 weeks and second dose at 3 months)      | 6                    | Patients in zoledronic acid group had a significant increase in LS and stable FN BMD, while control group had a significant decrease in both LS and FN BMD   | Small sample size   |
| Schwarz et al <sup>77</sup>    | 20          | PO calcium citrate 1,000 mg/d for the first 6 months       | IV zoledronic acid 4 mg (first dose given 2 weeks and second dose 3 months after KT) | 36                   | Each group had a significant increase in FN BMD at 3 years compared with 6 months, but there was no significant difference in the BMD increase between the two groups<br>There was no statistically significant difference in LS BMD or levels of BTMs between the two groups at 3 y   | Small sample size<br>All patients were on cyclosporine  |
| Marques et al <sup>14</sup>    | 32          | PO cholecalciferol 50,000 IU/mo                            | IV zoledronic acid 5 mg (one dose at the time of KT)                                 | 12                   | Patients in zoledronic acid group had a significant increase in LS and FN BMD by DXA compared with control group<br>There was no significant difference in the incidence of ABD or levels of BALP and sclerostin between the two groups  | Small sample size<br>Living donor KTRs only<br>Fracture risk not evaluated                            |

Abbreviations: ABD, adynamic bone disease; BALP, bone-specific alkaline phosphatase; BMD, bone mineral density; BMI, body mass index; BTM, bone turnover marker; CTX-1, collagen type 1 cross-linked C-telopeptide; DXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FN, femoral neck; GN, glomerulonephritis; IV, intravenous; KT, kidney transplantation; KTR, kidney transplant recipient; LS, lumbar spine; OC, osteocalcin; PO, orally; P1NP, procollagen of type 1 N-terminal propeptide; TH, total hip.

## CONCLUSIONS

Bone disease after KT is the result of pretransplant renal osteodystrophy and post-transplant bone loss related to multiple factors including glucocorticoid use and PHPT. Risk scores, bone turnover markers, and noninvasive imaging modalities have been studied in an attempt to risk-stratify the KTR risk for fractures, but these only partially help in predicting fracture risk. Wide practice variation exists in whom to obtain DXA imaging and in the frequency of testing.<sup>78</sup> At this time, there is insufficient high-quality data to make evidence-based recommendations about the timing and frequency of monitoring BMD and PTH levels after kidney transplantation. Further studies are needed to validate an accurate fracture risk prediction tool to help guide management. Several studies have evaluated regimens for the treatment and prevention of post-KT bone disease. Denosumab, bisphosphonates, and active vitamin D analogs have shown improvement in BMD, but no improvement in fracture risk, although many studies likely were underpowered to evaluate their effects on fracture risk. Further research is needed to evaluate the efficacy of these treatment options on fracture prevention.

Based on the limited available evidence, we recommend measurement of PTH, phosphorus and 25-OH vitamin D levels at 3 months after KT. We also recommend DXA imaging in the first 6 months after KT in patients at higher risk for fractures including patients on CSM immunosuppression regimens, those treated for rejection, those with PTH levels greater than 130 pg/mL, or with pretransplant osteopenia or osteoporosis. We do not routinely recommend bone biopsy given its invasive nature and lack of evidence that it correlates with fracture risk in KTRs. Bone biopsy can be considered in patients with recurrent fractures.

We recommend treatment of pretransplant renal osteodystrophy targeting a PTH level of two to nine times the upper limit of normal in addition to post-transplant 25-OH vitamin D supplementation to a target level greater than 30 µg/L and minimizing GC exposure because these interventions may be associated with improved BMD and reduced risk of fracture. In patients who develop post-transplant fractures or osteoporosis on DXA imaging, we recommend targeting PTH levels less than 130 pg/mL with active vitamin D analogs or cinacalcet, depending on serum calcium levels, and consideration of treatment with a bisphosphonate or denosumab.

## REFERENCES

- Kim SM, Long J, Montez-Rath M, Leonard M, Chertow GM. Hip Fracture in patients with non-dialysis-requiring chronic kidney disease. *J Bone Miner Res.* 2016;31:1803-9.
- Robertson L, Black C, Fluck N, Gordon S, Hollick R, Nguyen H, et al. Hip fracture incidence and mortality in chronic kidney disease: the GLOMMS-II record linkage cohort study. *BMJ Open.* 2018;8:e020312.
- Lo LWT, Yanling X, Chou ACC, Sen Howe T, Allen JC, Koh JSB. End-stage renal failure is an independent risk factor for 1-year mortality after hip fracture surgery. *Geriatr Orthop Surg Rehabil.* 2018;9:2151459318770561.
- Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. *J Am Soc Nephrol.* 1998;9:2135-41.
- Russell JD, Beecroft ML, Ludwin D, Churchill DN. The quality of life in renal transplantation—a prospective study. *Transplantation.* 1992;54:656-60.
- Yu T-M, Lin C-L, Chang S-N, Sung F-C, Huang S-T, Kao C-H. Osteoporosis and fractures after solid organ transplantation: a nationwide population-based cohort study. *Mayo Clin Proc.* 2014;89:888-95.
- Bouquegneau A, Salam S, Delanaye P, Eastell R, Khwaja A. Bone disease after kidney transplantation. *Clin J Am Soc Nephrol.* 2016;11:1282-96.
- Rajapakse CS, Leonard MB, Bhagat YA, Sun W, Magland JF, Wehrli FW. Micro-MR imaging-based computational biomechanics demonstrates reduction in cortical and trabecular bone strength after renal transplantation. *Radiology.* 2012;262:912-20.
- Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral mineral density after renal transplantation. *N Engl J Med.* 1991;325:544-50.
- Naylor KL, Garg AX, Hodsmann AB, Rush DN, Leslie WD. Long-term changes in bone mineral density in kidney transplant recipients. *Transplantation.* 2014;98:1279-85.
- Vautour LM, Melton LJ, Clarke BL, Achenbach SJ, Oberg AL, McCarthy JT. Long-term fracture risk following renal transplantation: a population-based study. *Osteoporos Int.* 2004;15:160-7.
- Abbott KC, Oglesby RJ, Hypolite IO, Kirk AD, Ko CW, Welch PG, et al. Hospitalizations for fractures after renal transplantation in the United States. *Ann Epidemiol.* 2001;11:450-7.
- Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N. Risk of fractures after renal transplantation in the United States. *Transplantation.* 2009;87:1846-51.
- Marques IDB, Araújo MJCLN, Gracioli FG, Dos Reis LM, Pereira RMR, Alvarenga JC, et al. A randomized trial of zoledronic acid to prevent bone loss in the first year after kidney transplantation. *J Am Soc Nephrol.* 2019;30:355-65.
- Evenepoel P, Claes K, Meijers B, Laurent MR, Bammens B, Naesens M, et al. Natural history of mineral metabolism, bone turnover and bone mineral density in de novo renal transplant recipients treated with a steroid minimization immunosuppressive protocol. *Nephrol Dial Transplant.* 2020;35:697-705.
- Nair SS, Lenihan CR, Montez-Rath ME, Lowenberg DW, Chertow GM, Winkelmayer WC. Temporal trends in the incidence, treatment and outcomes of hip fracture after first kidney transplantation in the United States. *Am J Transplant.* 2014;14:943-51.
- Naylor KL, Jamal SA, Zou G, McArthur E, Lam NN, Leslie WD, et al. Fracture incidence in adult kidney transplant recipients. *Transplantation.* 2016;100:167-75.
- Lee ES, Lim J-H, Cho J-H, Jung H-Y, Choi J-Y, Park S-H, et al. Pre-transplant osteoporosis and osteopenia are risk factors for fractures after kidney transplantation. *Transplant Proc.* 2019;51:2704-9.
- Akaberi S, Simonsen O, Lindergård B, Nyberg G. Can DXA predict fractures in renal transplant patients? *Am J Transplant.* 2008;8:2647-51.
- Kerschan-Schindl K. Prevention and rehabilitation of osteoporosis. *Wien Med Wochenschr.* 2016;166:22-7.

21. Wolf M, Weir MR, Kopyt N, Mannon RB, Von Visger J, Deng H, et al. A prospective cohort study of mineral metabolism after kidney transplantation. *Transplantation*. 2016;100:184-93.
22. Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, et al. Kidney transplantation with early corticosteroid withdrawal: paradoxical effects at the central and peripheral skeleton. *J Am Soc Nephrol*. 2014;25:1331-41.
23. Nikkel LE, Mohan S, Zhang A, McMahon DJ, Boutroy S, Dube G, et al. Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. *Am J Transplant*. 2012;12:649-59.
24. Drüeke TB, Evenepoel P. The bone after kidney transplantation. *Clin J Am Soc Nephrol*. 2019;14:795-7.
25. Wolf M, Molnar MZ, Amaral AP, Czira ME, Rudas A, Ujszaszi A, et al. Elevated fibroblast growth factor 23 is a risk factor for kidney transplant loss and mortality. *J Am Soc Nephrol*. 2011;22:956-66.
26. Schreiber PW, Bischoff-Ferrari HA, Boggian K, Bonani M, van Delden C, Enriquez N, et al. Bone metabolism dynamics in the early post-transplant period following kidney and liver transplantation. *PLoS One*. 2018;13:e0191167.
27. Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, et al. Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant*. 2013;13:2653-63.
28. Ix JH. New insights to fibroblast growth factor 23 in kidney transplant. *J Am Soc Nephrol*. 2011;22:799-801.
29. Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. *Nature*. 2006;444:770-4.
30. Wolf M. Mineral (mal)adaptation to kidney disease—Young Investigator Award Address: American Society of Nephrology Kidney Week 2014. *Clin J Am Soc Nephrol*. 2015;10:1875-85.
31. Saito H, Maeda A, Ohtomo S-I, Hirata M, Kusano K, Kato S, et al. Circulating FGF-23 is regulated by 1 $\alpha$ ,25-dihydroxyvitamin D3 and phosphorus in vivo. *J Biol Chem*. 2005;280:2543-9.
32. Edmonston D, Wolf M. FGF23 at the crossroads of phosphate, iron economy and erythropoiesis. *Nat Rev Nephrol*. 2020;16:7-19.
33. Ix JH, Shlipak MG, Wassel CL, Whooley MA. Fibroblast growth factor-23 and early decrements in kidney function: the Heart and Soul Study. *Nephrol Dial Transplant*. 2010;25:993-7.
34. Neves CL, dos Reis LM, Batista DG, Custodio MR, Gracioli FG, de Martin R, et al. Persistence of bone and mineral disorders 2 years after successful kidney transplantation. *Transplantation*. 2013;96:290-6.
35. Sadlier DM, Magee CC. Prevalence of 25(OH) vitamin D (calcidiol) deficiency at time of renal transplantation: a prospective study. *Clin Transplant*. 2020;21:683-8.
36. Naylor KL, Zou G, Leslie WD, Hodsmann AB, Lam NN, McArthur E, et al. Risk factors for fracture in adult kidney transplant recipients. *World J Transplant*. 2016;6:370-9.
37. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, et al. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA*. 2002;288:3014-8.
38. Lenihan CR, Sukumaran Nair S, Vangala C, Ramanathan V, Montez-Rath ME, Winkelmayer WC. Proton pump inhibitor use and risk of hip fracture in kidney transplant recipients. *Am J Kidney Dis*. 2017;69:595-601.
39. Naylor KL, Leslie WD, Hodsmann AB, Rush DN, Garg AX. FRAX predicts fracture risk in kidney transplant recipients. *Transplantation*. 2014;97:940-5.
40. Perrin P, Kiener C, Javier R-M, Braun L, Cognard N, Gautier-Vargas G, et al. Recent changes in chronic kidney disease-mineral and bone disorders and associated fractures after kidney transplantation. *Transplantation*. 2017;101:1897-905.
41. Chavassieux P, Portero-Muzy N, Roux J-P, Garnero P, Chapurlat R. Are biochemical markers of bone turnover representative of bone histomorphometry in 370 postmenopausal women? *J Clin Endocrinol Metab*. 2015;100:4662-8.
42. Tartaglione L, Pasquali M, Rotondi S, Muci ML, Leonangeli C, Farcomeni A, et al. Interactions of sclerostin with FGF23, soluble klotho and vitamin D in renal transplantation. *PLoS One*. 2017;12:e0178637.
43. Coco M, Pullman J, Cohen HW, Lee S, Shapiro C, Solorzano C, et al. Effect of risedronate on bone in renal transplant recipients. *J Am Soc Nephrol*. 2012;23:1426-37.
44. Coco M, Pullman JM. Noninvasive imaging of bone microarchitecture in patients receiving renal transplant: can it replace histology? *Clin J Am Soc Nephrol*. 2017;12:562-4.
45. Hans D, Goertzen AL, Krieg M-A, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. *J Bone Miner Res*. 2011;26:2762-9.
46. Luckman M, Hans D, Cortez N, Nishiyama KK, Agarawal S, Zhang C, et al. Spine trabecular bone score as an indicator of bone microarchitecture at the peripheral skeleton in kidney transplant recipients. *Clin J Am Soc Nephrol*. 2017;12:644-52.
47. Malakoutian T, Mirzaei A, Shiroudbakhsi A, Amini Kadijani A, Tehrani-Banihashemi A, Zabihiyeganeh M. The added value of trabecular bone score in fracture risk assessment of kidney transplant recipients. *Iran J Kidney Dis*. 2020;14:300-7.
48. Monier-Faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. *J Am Soc Nephrol*. 2000;11:1093-9.
49. Cejka D, Benesch T, Krestan C, Roschger P, Klaushofer K, Pietschmann P, et al. Effect of teriparatide on early bone loss after kidney transplantation. *Am J Transplant*. 2008;8:1864-70.
50. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl*. 2017;7:1-59.
51. Aroldi A, Tarantino A, Montagnino G, Cesana B, Cocucci C, Ponticelli C. Effects of three immunosuppressive regimens on vertebral bone density in renal transplant recipients: a prospective study. *Transplantation*. 1997;63:380-6.
52. Ing SW, Sinnott LT, Donepudi S, Davies EA, Pelletier RP, Lane NE. Change in bone mineral density at one year following glucocorticoid withdrawal in kidney transplant recipients. *Clin Transplant*. 1997;25:E113-23.
53. Farmer CKT, Hampson G, Abbs IC, Hilton RM, Koffman CG, Fogelman I, et al. Late low-dose steroid withdrawal in renal transplant recipients increases bone formation and bone mineral density. *Am J Transplant*. 2006;6:2929-36.
54. McGregor R, Li G, Penny H, Lombardi G, Afzali B, Goldsmith DJ. Vitamin D in renal transplantation - from biological mechanisms to clinical benefits. *Am J Transplant*. 2014;14:1259-70.
55. Jeffery JR, Leslie WD, Karpinski ME, Nickerson PW, Rush DN. Prevalence and treatment of decreased bone density in renal transplant recipients: a randomized prospective trial of calcitriol versus alendronate. *Transplantation*. 2003;76:1498-502.
56. Brown AJ, Finch J, Slatopolsky E. Differential effects of 19-nor-1,25-dihydroxyvitamin D(2) and 1,25-dihydroxyvitamin D(3) on intestinal calcium and phosphate transport. *J Lab Clin Med*. 2002;139:279-84.
57. Trillini M, Cortinovis M, Ruggenti P, Reyes Loaeza J, Courville K, Ferrer-Siles C, et al. Paricalcitol for secondary hyperparathyroidism in renal transplantation. *J Am Soc Nephrol*. 2015;26:1205-14.

58. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344:1434-41.
59. Evenepoel P, Cooper K, Holdaas H, Messa P, Mourad G, Olgaard K, et al. A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant*. 2014;14:2545-55.
60. Cruzado JM, Moreno P, Torregrosa J V, Taco O, Mast R, Gómez-Vaquero C, et al. A randomized study comparing parathyroidectomy with cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. *J Am Soc Nephrol*. 2016;27:2487-94.
61. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Sidthanti S, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010;25:72-81.
62. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361:756-65.
63. Iseri K, Watanabe M, Yoshikawa H, Mitsui H, Endo T, Yamamoto Y, et al. Effects of denosumab and alendronate on bone health and vascular function in hemodialysis patients: a randomized, controlled trial. *J Bone Miner Res*. 2019;34:1014-24.
64. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res*. 2011;26:1829-35.
65. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guañabens N, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. *Bone*. 2017;105:11-7.
66. Bonani M, Frey D, Brockmann J, Fehr T, Mueller TF, Saleh L, et al. Effect of twice-yearly denosumab on prevention of bone mineral density loss in de novo kidney transplant recipients: a randomized controlled trial. *Am J Transplant*. 2016;16:1882-91.
67. Walsh SB, Altmann P, Pattison J, Wilkie M, Yaqoob MM, Dudley C, et al. Effect of pamidronate on bone loss after kidney transplantation: a randomized trial. *Am J Kidney Dis*. 2009;53:856-65.
68. Torregrosa J-V, Fuster D, Gentil M-A, Marcen R, Guirado L, Zaragoza S, et al. Open-label trial: effect of weekly risedronate immediately after transplantation in kidney recipients. *Transplantation*. 2010;89:1476-81.
69. Torregrosa J-V, Fuster D, Monegal A, Gentil MA, Bravo J, Guirado L, et al. Efficacy of low doses of pamidronate in osteopenic patients administered in the early post-renal transplant. *Osteoporos Int*. 2011;22:281-7.
70. Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, et al. Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol*. 2001;12:1530-7.
71. Haas M, Leko-Mohr Z, Roschger P, Kletzmayer J, Schwarz C, Mitterbauer C, et al. Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int*. 2003;63:1130-6.
72. Cruz DN, Brickel HM, Wysolmerski JJ, Gundberg CG, Simpson CA, Kliger AS, et al. Treatment of osteoporosis and osteopenia in long-term renal transplant patients with alendronate. *Am J Transplant*. 2002;2:62-7.
73. Coco M, Glicklich D, Faugere MC, Burris L, Bognar I, Durkin P, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. *J Am Soc Nephrol*. 2003;14:2669-76.
74. Smerud KT, Dolgos S, Olsen IC, Åsberg A, Sagedal S, Reisæter AV, et al. A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. *Am J Transplant*. 2012;12:3316-25.
75. Kovac D, Lindic J, Kandus A, Bren AF. Prevention of bone loss with alendronate in kidney transplant recipients. *Transplantation*. 2000;70:1542-3.
76. Giannini S, D'Angelo A, Carraro G, Nobile M, Rigotti P, Bonfante L, et al. Alendronate prevents further bone loss in renal transplant recipients. *J Bone Miner Res*. 2001;16:2111-7.
77. Schwarz C, Mitterbauer C, Heinze G, Woloszczuk W, Haas M, Oberbauer R. Nonsustained effect of short-term bisphosphonate therapy on bone turnover three years after renal transplantation. *Kidney Int*. 2004;65:304-9.
78. Naylor KL, Zou G, Leslie WD, McArthur E, Lam NN, Knoll GA, et al. Frequency of bone mineral density testing in adult kidney transplant recipients from Ontario, Canada: a population-based cohort study. *Can J Kidney Health Dis*. 2016;3:2.