Bone and Mineral Disease in Kidney Transplant Recipients

Pascale Khairallah¹ and Thomas L. Nickolas²

Abstract
After kidney transplantation, mineral and bone disorders are associated with higher risk of fractures and consequent morbidity and mortality. Disorders of calcium and phosphorus, vitamin D deficiency, and hyperparathyroidism are also common. The epidemiology of bone disease has evolved over the past several decades due to changes in immunosuppressive regimens, mainly glucocorticoid minimization or avoidance. The assessment of bone disease in kidney transplant recipients relies on risk factor recognition and bone mineral density assessment. Several drugs have been trialed for the treatment of post-transplant mineral and bone disorders. This review will focus on the epidemiology, effect, and treatment of metabolic and skeletal derangements in the transplant recipient.

Introduction
After kidney transplantation, disorders of mineral and bone metabolism are common and are important causes of morbidity and mortality (1–4). Post-transplantation mineral and bone disease (MBD) is defined by clinical features that are similar to, but distinct from, MBD occurring prior to transplantation. Hypophosphatemia, hypercalcemia, and hypovitaminosis D are highly prevalent (5–8). Over the past 2 decades, high-dose glucocorticoids have become less integral to maintenance immunosuppression regimens, resulting in relatively stable central skeleton (i.e., spine and hip) bone mineral density (BMD). In contrast, worsening BMD at the peripheral skeleton (i.e., forearm and leg) continues to be seen (9–11). This is associated with ongoing fractures that have important contributions to morbidity and mortality in post-transplant recipients (4,11). This review will focus on the epidemiology, pathogenesis, and potential therapeutics for disordered mineral and bone metabolism occurring after kidney transplantation.

Disorders in Calcium and Phosphorus
Hypercalcemia and hypophosphatemia are major mineral abnormalities occurring post-transplantation (12). Hypercalcemia affects up to 59%, 45%, and 21% of recipients at 3 and 12 months and 5 years, respectively (5,13). Serum calcium levels peak by 2 months post-transplant and remain elevated in 18% of recipients by 12 months post-transplant, and in 6%, levels remain high even by 10 years post-transplantation (14,15). Hypercalcemia is related to a combination of increased urinary calcium absorption secondary to hyperparathyroidism in a well-functioning kidney, vitamin D repletion, and calcium release from the skeleton (16). It is unclear from bone biopsy studies whether bone turnover is related to hypercalcemia (13,17).

Importantly, hypercalcemia may be associated with the development of calcifications in the allograft that consequently affect graft survival (18). Hypophosphatemia develops in up to 90% of post-transplant recipients (6,8). It typically develops in the first 3 months post-transplant and improves in approximately 86% of recipients by 12 months post-transplant (14,19,20). Hypophosphatemia develops secondary to high fibroblast growth factor 23 (FGF-23) levels (6), hyperparathyroidism-induced urinary phosphate wasting (6), and immunosuppressant effects (19). Beyond the first year post-transplantation, some recipients continue to experience urinary phosphate wasting despite normalization of serum phosphate levels (20).

Vitamin D Deficiency
Vitamin D deficiency, defined as 25-hydroxyvitamin D levels <30 ng/ml, is highly prevalent following transplantation, occurring in up to 80% of recipients by 3 months post-transplantation (6) and persisting in the short- and long-term periods post-transplantation (6,21). Vitamin D deficiency results in hypocalcemia and subsequent bone loss (22). Additionally, in vivo studies suggest that vitamin D has an immunoregulatory role, including diminished dendritic cell maturation and antigen-presenting capacity, enhanced regulatory T cell differentiation, improved pathogen clearance, and differentiation of immune inhibitory cell proliferation (22). Therefore, it is postulated that vitamin D deficiency in immunosuppressed individuals may reduce transplant tolerance, increase infections, and higher risk of malignancies (22). Major risk factors for persistent vitamin D deficiency post-transplantation include decreased allograft function and elevated FGF-23 levels (6). The Kidney Disease Improving Global Outcome (KDIGO) guidelines recommend that vitamin D
deficiency and insufficiency be corrected in CKD G1T-G5T using treatment strategies recommended for the general population (23).

**Hyperparathyroidism**

Parathyroid hormone (PTH) levels improve quickly after transplantation (9,24). This improvement is due to involution of the parathyroid glands following the restoration of kidney function and the correction of most metabolic abnormalities that stimulate hyperparathyroidism (25). However, hyperparathyroidism completely resolves in only 30% and 57% of recipients within the first and second years post-transplantation, respectively (7). Drivers of persistent hyperparathyroidism include severe pretransplant hyperparathyroidism (26), poor allograft function, and low vitamin D levels (27). In some studies, hyperparathyroidism in the post-transplant period was associated with increased cortical and trabecular bone losses (9,28) and with higher fracture risk (29). Nevertheless, in recipients maintained on glucocorticoid-based regimens, PTH levels did not correlate with bone turnover (13) or BMD losses (24,30), emphasizing the complexity of bone disease post-transplantation.

**Bone Disease**

**The Changing Epidemiology of Bone Strength after Transplantation**

Bone strength is defined as the combination of bone density and quality. Bone density refers to the amount of bone mineral (hydroxyapatite) per centimeter squared of bone tissue (i.e., gmHA/cm²), and in the clinic, it is measured by dual energy x-ray absorptiometry. Bone quality refers to bone tissue material properties (i.e., microarchitecture, turnover, mineral content and structure, microcracks, collagen content, and structure) and is measured by tetracycline double-labeled bone biopsy with quantitative histomorphometry. Kidney transplant recipients come to transplant with significant impairments in bone strength, characterized by high rates of osteopenia and osteoporosis (32% and 15%, respectively) (31–33) and fractures (two- to 14-fold greater than that of the general population) (34–36). After kidney transplantation, the skeleton undergoes changes in the short and long term that are manifested by further impairments in bone strength. Historically, the first 12–18 months of transplantation were associated with dramatic decreases in bone density of up to 9% at the spine and hip (33,37,38). Over the long term, BMD was reported to stabilize between the third and fifth years post-transplant, increase by around 6% between the sixth and tenth years post-transplant, and increase by around 2% afterward (28). High rates of bone loss in the early transplant period were associated with high rates of fracture. Ball et al. (39) reported that hip fracture rates were three-fold higher among recipients than patients on dialysis during the first 3 years of transplantation; however, by the third post-transplant year, hip fracture incidence was equivalent between groups. Nikkel et al. (1) reported that 23% of recipients transplanted between 1988 and 1998 fractured within the first 5 years of transplantation. However, immunosuppression regimens have changed over the past several decades to favor either lower glucocorticoid doses or complete glucocorticoid withdrawal. Glucocorticoids are toxic to the skeleton, and exposure to glucocorticoids is an important risk factor for fracture. Thus, the epidemiology of bone disease and fractures after kidney transplantation has changed in parallel with the decreasing use of glucocorticoid-based immunosuppression. Several prospective studies conducted on recipients managed with low-dose or early glucocorticoid withdrawal regimens have reported that, over the first 12 months of transplantation, BMD at the central skeleton (i.e., spine and hip) remained stable or increased (9,10). In contrast, BMD at the peripheral skeleton (i.e., radius and tibia) decreased (9,10). Epidemiologic studies suggest that lower rates of bone loss have resulted in lower incidence of fractures. In a systematic review of fractures in kidney transplant recipients, Naylor et al. (11) reported that rates have been lower over the last decade, likely due to decreasing exposure to glucocorticoids. Using the United States Renal Data Systems (USRDS), Nikkel et al. (40) reported that patients discharged from the hospital without glucocorticoid-based immunosuppression compared with those with glucocorticoid-based immunosuppression experienced a 31% reduction in 5-year cumulative all-type fracture incidence, with yearly incidence rates of 5.8 and 8 per 1000 patient-years in recipients managed without and with glucocorticoids, respectively. In a Belgium cohort of 518 recipients managed with either glucocorticoid withdrawal or standard glucocorticoid-based immunosuppression followed for a median of 5.2 years, Evenepoel et al. (41) reported a cumulative fracture incidence rate of 7% with an incidence rate of 14.3 per 1000 patient-years. Even though there is lower fracture incidence among recipients, fractures remain an important cause of morbidity and mortality. In transplant recipients older than 55 years, incident fracture of the spine, hip, or extremity (i.e., hand, distal radius and ulna, and foot/ankle) was associated with 2.8-, 1.34-, and 1.85-fold higher mortality risk, respectively (4). Irrespective of mortality, the risk of graft loss was reported as 1.34- and 1.3-fold higher after a hip or extremity fracture, respectively (4).

**Bone Biopsy Studies—New Insights into Bone Disease in the Era of Lower-Dose Glucocorticoid Regimens**

Recent bone biopsy studies suggest that lower-dose glucocorticoid-based immunosuppression regimens are associated with less severe impairments in bone quality compared with those reported in older studies in patients managed with higher-dose glucocorticoid-based regimens. Older bone biopsy studies demonstrated more profound defects in bone volume. Monier-Faugere et al. (13) reported on 57 recipients followed for 5.6±0.8 years post-transplantation maintained on an average prednisone dose of 8.8±0.85 mg at the time of biopsy. Fifty-six percent had low trabecular bone volume, 60% had low bone turnover, and 87% had a mineralization defect (13). Cumulative prednisone dose described 36% and 20% of the heterogeneity in bone volume and turnover, respectively, and no clinical or demographic feature explained the mineralization defect. In recent studies, low bone turnover remains common, but bone volume is less severely impaired. In a placebo-controlled randomized clinical trial (RCT) of zoledronic acid given over the first year of kidney transplantation, 31 patients assigned to active
drug \((n = 15)\) or placebo \((n = 16)\) underwent bone biopsy pre-transplantation and 12-months post-transplantation. There were no effects of zoledronic acid on static or dynamic indices of histomorphometry; thus, we report the combined results. At baseline, 48% had low turnover and 63% had a mineralization defect. After transplantation, 68% had low turnover and 61% had a mineralization defect. The distribution among normal–, low–, and high–trabecular volume groups before and after transplantation changed from 61%, 15%, and 24% to 74%, 26%, and 0%, respectively \((P = 0.01)\). Furthermore, trabecular microarchitecture worsened, characterized by decreases in trabecular number and spacing \((10)\). In another study of 27 recipients managed with either glucocorticoid-sparing or glucocorticoid-based regimens, Keronen et al. \((17)\) reported that, pretransplantation, 63% had high turnover, 26% had low turnover, and 33% had a mineralization defect. Follow-up biopsy at 2 years post-transplantation demonstrated that 19% had high turnover, 52% had low turnover, and 44% had a mineralization defect. Trabecular bone volume did not change, and information on trabecular microarchitecture was not provided. In summary, these data suggest that minimizing glucocorticoid exposure after transplantation has fewer deleterious effects on trabecular bone quality. In contrast, transplantation itself is associated with lowering bone turnover.

Assessment of Bone Disease and Risk Classification of Fractures after Transplantation

The 2017 KDIGO guidelines recommended BMD testing in kidney transplant recipients if the results will alter therapy. The guidelines did not mandate the need for a bone biopsy to start treatment, and they acknowledged that their guidance is limited to the first 12 months post-transplantation due to insufficient data to guide long-term recommendations \((23)\). Our approach is to consider a full clinical risk factor assessment for osteoporosis and fractures. Risk factors for post-transplant osteoporosis and fractures can be divided into pre- and post-transplant factors \((2,4,31,32,42,43)\) (Figure 1). Measurement of BMD by dual energy x-ray absorptiometry is the clinical gold standard to assess fracture risk. Using the World Health Organization T-score thresholds, limited but important prospective studies in kidney transplant recipients reported that osteopenia or osteoporosis at the spine and hip predicted fracture \((41,44)\). Prior to starting treatment, we assess bone turnover by circulating markers of bone formation and resorption, and then, we use that information to decide upon treatment options (Figure 2). Both the fracture risk assessment tool and trabecular bone score are reported to have discriminatory ability to predict fractures in kidney recipients \((45,46)\), but they need further validation in large and diverse cohorts of transplant recipients prior to their widespread application; therefore, they are not part of our algorithm.

**Figure 1.** Pretransplant and post-transplant risk factors for osteoporosis. BMI, body mass index.
Treatment of Bone Disease and Fractures after Kidney Transplantation

KDIGO recommends that patients with eGFR >30 ml/min per 1.73 m² and low BMD receive vitamin D, calcitriol, or bisphosphonates in the first 12 months after transplantation (23). However, there are now several classes of pharmacologic agents to treat osteoporosis and prevent fractures that may have applicability to kidney recipients. In the following section, we will review the evidence supporting therapeutic strategies.

Glucocorticoid Minimization

The skeletal effects of glucocorticoids are well established (47). Most transplant recipients remain on lifelong glucocorticoids, but many recipients can have glucocorticoid doses reduced to less than the threshold associated with skeletal toxicity (i.e., <7.5 mg daily) (48). Several longitudinal studies of patients on glucocorticoid-sparing immunosuppressive regimens demonstrated that BMD at the spine and hip remained stable or increased during the first post-transplant year (9,10,49). Furthermore, a USRDS analysis of 77,430 kidney transplant recipients reported that recipients discharged from the hospital without glucocorticoids compared with those with glucocorticoids had a lower risk of fracture (2% versus 3%, respectively; P<0.001): a 26% lower risk of fracture at 1 year post-transplantation and a 70% lower risk of fracture at 3 years post-transplantation (40). Thus, limiting exposure to glucocorticoids (in accordance with transplant center protocols) should be a key consideration in the management of transplant recipients, particularly those at high fracture risk defined by either prior fragility fracture at any level of BMD or low bone density (i.e., T score ≤−1.0) along with other clinical risk factors for fracture (e.g., older age, women, and diabetes).

Vitamin D and Analogs

Vitamin D deficiency is common following kidney transplantation (50). Treatment of kidney transplant recipients with cholecalciferol safely increases serum 25-hydroxy vitamin D levels and decreases PTH levels (51). Paricalcitol, a vitamin D receptor analog (VDRA), is similarly effective in decreasing PTH levels post-transplantation, although hypercalcemia and hypercalciuria are relatively frequent side effects (52,53). Transplant recipients randomized to calcium and a VDRA compared with recipients randomized to calcium or placebo had higher lumbar (total loss 5.0% versus 6.5%; P<0.002) and femoral BMD (total loss 4.0% versus 5.6%; P<0.001) at 6 months post-transplantation (54) and higher BMD at the femoral neck (5% increase versus 1% increase; P=0.03) and distal radius (3% increase versus 2% decrease; P=0.03) at 1 year post-transplantation (55). Supplementation for 6 months with paricalcitol compared with no supplementation decreased markers of bone turnover and increased BMD at the spine and femoral neck (53). Although a VDRA may be effective at improving BMD of kidney transplant recipients during

**Figure 2.** Risk-based approach to mineral and bone disease (MBD) management after kidney transplantation. *Bone turnover markers in clinical practice are limited to the following: parathyroid hormone (PTH) and bone-specific alkaline phosphatase (BSAP). Low turnover markers refer to PTH less than two times the upper limit of normal and BSAP less than the lower limit of the reference range. High turnover markers refer to PTH greater than two times the upper limit of normal and BSAP greater than the median of the reference range. If PTH and BSAP are discordant, then a bone biopsy is recommended to guide therapy. LLN, lower limit of normal; ULN, upper limit of normal; VDRA, vitamin D receptor analog.
the first year post-transplantation, no study has examined the effect of vitamin D supplementation on either BMD beyond the first year after transplantation or antifracture efficacy.

Calcimimetics
Post-transplant MBD comprises biochemical (i.e., hyperparathyroidism, hypercalcemia, and hypophosphatemia) and skeletal (i.e., impaired bone strength) disorders. The pathogenesis of the biochemical disorders is related to the effects of circulating PTH and FGF-23 on kidney handling of phosphate and possible alterations in the kidney calcium-sensing receptors, mimicking a phenotype of familial hypocalciuric hypercalcaemia (6,16). Calcimimetics increase the sensitivity of the parathyroid gland calcium-sensing receptor to calcium, thereby suppressing PTH. A placebo-controlled RCT of cinacalcet following kidney transplantation demonstrated that 70% of the participants who received cinacalcet had normalization of calcium levels as compared with only 4% of the participants who received placebo (P<0.001) (56). Phosphate levels increased following cinacalcet treatment (P<0.001 as compared with placebo). PTH levels decreased by a mean of 128 pg/ml in the cinacalcet group, a change that was considerably greater than the 10.6-pg/ml decrease in PTH in the placebo group (P=0.002) (56). A prospective observational study of kidney transplant recipients with persistent hyperparathyroidism similarly demonstrated normalization of calcium as well as a rise in phosphate levels toward normal shortly following treatment initiation and for up to 12 months of follow-up. PTH levels did not improve until 9 months following initiation and did not normalize (57). The normalization of hypercalcemia and hypophosphatemia and the improvement in PTH levels with cinacalcet can be seen for up to 60 months of follow-up (58,59). When cinacalcet was discontinued following 12 months of therapy in ten kidney transplant recipients, calcium levels increased but remained within the normal range in eight of the recipients. PTH levels rose to pretreatment levels in two recipients only (60). Larger studies are required to inform nephrologists about the ideal time to discontinue cinacalcet in transplant recipients with secondary hyperparathyroidism. An RCT by Evenepoel et al. (56) assessed the effects of cinacalcet versus placebo on spine, hip, and one-third radius BMD in 154 (57 per group) patients. There were no between-group differences in percentage change in BMD at any skeletal site or in bone turnover markers. Kidney function assessed by eGFR was stable and similar between groups, and even though cinacalcet therapy resulted in hypercalciuria, this did not translate into higher risk of calcium deposits in the kidney (56). Borchardt et al. (61) performed bone biopsies in ten kidney transplant recipients at baseline and after 18–24 months of treatment with cinacalcet. Bone formation decreased in seven patients, with four patients progressing to adynamic bone disease. However, the decrease in bone formation was accompanied by an increase in osteoblast number, which is not a characteristic of adynamic bone disease, suggesting mini modeling similar to after parathyroidectomy rather than true shutdown of bone turnover. No study to date has evaluated the effect of cinacalcet on fractures in kidney recipients. In summary, cinacalcet is useful for controlling MBD biochemical abnormalities. However, no study has demonstrated a benefit on bone density, fractures, vascular calcifications, or nephrocalcinosis after transplantation. As such, it is not currently approved by the US Food and Drug Administration for the treatment of post-transplant MBD. Long-term benefits on important clinical outcomes have not been established for cinacalcet, and it may be useful as either a bridge to parathyroidectomy or ongoing therapy in patients with persistent MBD biochemical abnormalities but with contraindications to surgery.

Parathyroidectomy
One RCT compared parathyroidectomy with cinacalcet in recipients ≥6 months from transplant who had secondary hyperparathyroidism, hypercalcemia, and hypophosphatemia (62). At 12 months after intervention, parathyroidectomy was superior to cinacalcet in reducing PTH and normalizing calcium. Beneficial skeletal effects of parathyroidectomy versus cinacalcet included increased BMD at the femoral neck and a reduction in bone resorption markers. There were no differences in vascular calcification changes. eGFR declined by 9 and 4 ml/min in the cinacalcet and parathyroidectomy groups, respectively, but the change was significant only in the cinacalcet group (P<0.01). Parathyroidectomy performed in an experienced center was associated with more severe hypocalcemia as compared with cinacalcet and was associated with health care economic cost benefit if treatment had been extended to >14 months. Parathyroidectomy can rarely be associated with complications, including wound-related complications and/or damage to nearby structures. Hence, parathyroidectomy should be preferred over cinacalcet in patients who require long-term management of MBD abnormalities, including persistent hypercalcemia, nephrocalcinosis/nephrolithiasis, or high bone turnover states resistant to medical therapies (63).

Bisphosphonates
Bisphosphonates are the most widely studied treatment for post-transplant bone disease. They increase BMD by suppressing bone turnover through inhibiting osteoclast function. Their suppressive effects on turnover and theoretical risk of inducing adynamic bone disease have led to considerable controversy regarding their use after kidney transplantation. Four small studies have used bone biopsy to determine if bisphosphonates are associated with adynamic bone disease in the early post-transplant period (10,64–66). The first study by Coco et al. (67) evaluated bone histomorphometry in six patients who received pamidronate for 12 months post-transplantation and 12 controls. All six patients who received pamidronate developed adynamic bone disease, as compared with half of the controls. It is important to note that three of the six patients who received pamidronate had adynamic bone disease at baseline. The findings of Coco et al. (67) were in contrast to those of Haas et al. (66), who found that no adynamic bone-disease developed in seven patients who received zoledronic acid compared with six controls in the first 6 months post-transplantation. A later study by Coco et al. (64) included a larger number of patients; 16 patients received risendronic acid in the first 12 months of transplantation compared with 13 controls. The study found no increased risk for
Table 1. Available treatments for the management of mineral and bone disease post-transplantation

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Parameters Affected by Therapy</th>
<th>Indications</th>
<th>Risks and Limitations</th>
</tr>
</thead>
</table>
| Vitamin D analogs (51–55) | Higher serum 25-hydroxy vitamin D levels  
Higher PTH levels  
Higher BMD at the spine, femoral neck, and radius within a year of transplantation | Vitamin D insufficiency  
Osteopenia  
Osteoporosis | Hypercalcemia  
Hypercalciuria  
No data beyond the first year post-transplantation  
No data regarding antifracture efficacy |
| Calcimimetics (56–59)  | Lower serum calcium levels  
Higher serum phosphate levels  
Lower PTH levels | Hypercalcemia  
Hypophosphatemia | Hypercalciuria  
Unknown ideal time to discontinue the drug  
No data showing effect on BMD  
No data regarding antifracture efficacy  
Not FDA approved for treatment of post-transplant MBD  
Surgical complications  
Hypocalcemia |
| Parathyroidectomy (62,63) | Lower serum calcium levels  
Higher serum phosphate levels  
Lower PTH levels  
Higher BMD at the femoral neck | Prolonged hypercalcemia/ hypercalcemia resistant to medical therapy  
Nephrolithiasis  
Nephrocalcinosis  
Severe hyperparathyroidism resistant to medical therapy  
Osteoporosis or worsening BMD with high turnover bone disease | AKI with intravenous bisphosphonates  
No antifracture efficacy  
No data beyond the first year post-transplantation  
Hypocalcemia  
Urinary tract infections  
No data regarding antifracture efficacy  
Rapid and significant bone loss and higher risk of vertebral fractures following discontinuation  
Daily subcutaneous injection  
No data regarding antifracture efficacy  
No data beyond the first 6 mo post-transplantation |
| Bisphosphonates (68,69) | Higher femoral neck and lumbar spine BMD in some studies—data controversial | Osteoporosis or worsening BMD with high turnover bone disease | No data regarding antifracture efficacy |
| Denosumab (73,74,77)  | Higher lumbar spine and total hip BMD | Osteoporosis or worsening BMD with high turnover bone disease | No data regarding antifracture efficacy  
No data beyond the first year post-transplantation |
| Teriparatide (80)      | Higher femoral neck BMD | Osteoporosis or worsening BMD with adynamic bone disease | No data regarding antifracture efficacy  
No data beyond the first 6 mo post-transplantation |

PTH, parathyroid hormone; BMD, bone mineral density; FDA, Food and Drug Administration; MBD, mineral and bone disease.

Adynamic bone disease or mineralization defects. Most recently, Marques et al. (10) performed the largest and most informative trial to date, further demonstrating that zoledronic acid did not result in the development of adynamic bone disease. It is important to note that in Marques et al. (10), bone turnover in both the placebo and treatment groups decreased, suggesting that the natural history of bone turnover in the first year of transplantation is to decrease.

The effects of bisphosphonates on skeletal outcomes are unclear. A 2016 meta-analysis of 12 studies that included 621 kidney transplant recipients who received a bisphosphonate (including pamidronate, alendronate, clodronate, ibandronate, zoledronic acid, and risedronate) concluded that bisphosphonates were associated with improvement in femoral neck BMD (mean difference 0.055 g/cm²; 95% confidence interval [95% CI], 0.01 to 0.10) and lumbar spine BMD (0.053 g/cm²; 95% CI, 0.03 to 0.07). The improvements in femoral neck and lumbar spine BMD were more pronounced when patients were started on bisphosphonates within the first 6 months following transplantation. However, rates of fractures were similar between groups. Bisphosphonate therapy was safe, with no adverse kidney effects noted (68). A 2019 Cochrane review searched for RCTs and quasi-RCTs evaluating treatments for bone disease among kidney transplant recipients (69). Bisphosphonates administered for a median of 12 months post-transplantation were not associated with significant increases in BMD at the spine or hip. Furthermore, there was low-certainty evidence that they prevented fractures (relative risk, 0.62; 95% CI, 0.38 to 1.01). Data on the use of bisphosphonates are limited to the first 12 months post-transplantation as no study evaluated BMD, histomorphometric changes, or fracture rates beyond that time period. These studies provide conflicting evidence as to whether bisphosphonates ameliorate bone disease in kidney transplant recipients.
Intravenous but not oral bisphosphonates have been associated with AKI (70,71); thus, many nephrologists are apprehensive to administer them to their patients. In such cases, referral to a kidney MBD expert or to endocrinology may be necessary. It is reasonable for nephrologists to administer oral bisphosphonates to transplant recipients at risk for fracture, as long as their limitations and risks are discussed with patients prior to initiating therapy.

Denosumab

Denosumab is a potent antiresorptive agent. It is an mAb against the receptor activator of the NF-κB ligand, and it inhibits osteoclast proliferation and development. In contrast to bisphosphonates, denosumab is not cleared by the kidney; therefore, there is no risk of oversuppressing bone turnover due to drug accumulation in CKD (72). Only one prospective, randomized trial by Bonani et al. (73) evaluated the use of denosumab versus placebo in de novo kidney transplant recipients. At 1 year following treatment, lumbar spine and total hip BMD significantly increased in the denosumab group compared with the placebo group (5%; \(P<0.001\) and 2%; \(P=0.04\), respectively). Urinary tract infections occurred more frequently in the denosumab-treated group, as did hypocalcemia events, although the latter events were asymptomatic and transient. Hypocalcemia events can be averted by ensuring adequate vitamin D repletion before denosumab initiation. The study was too small to assess effects on fractures. Randomized controlled trials evaluating the effect of denosumab beyond the first year of transplantation are lacking. However, a retrospective study of solid organ transplant recipients 6.4±6.3 years post-transplantation determined that denosumab use for 1.65±0.7 years resulted in improvements in lumbar spine and proximal femur BMD T scores in kidney transplant recipients (74). A phase 2 trial in long-term kidney recipients is currently enrolling (NCT03660554). Given the antiresorptive consequences of using denosumab, caution should be used in patients suspected of having adynamic bone disease. Furthermore, studies in postmenopausal women demonstrated rapid and significant bone loss (75) and higher risk of vertebral fractures (76) following denosumab discontinuation. Similarly, Kobel et al. (77) reported in follow-up to Bonani et al. (73) that significant bone loss at the spine and hip occurred after discontinuation of denosumab. Current recommendations are to initiate a several-year course of potent bisphosphonate therapy to preserve BMD and prevent vertebral fractures after denosumab discontinuation (78,79).

Teriparatide

Teriparatide is a recombinant peptide of the first 34 amino-terminal residues of PTH. It is an osteoanabolic agent used to treat osteoporosis and prevent fractures in both age-related and glucocorticoid-induced osteoporosis (72). Only one randomized, double-blind, placebo-controlled trial has evaluated the efficacy of teriparatide in post-transplant bone disease (80). Twelve patients received teriparatide for 6 months, while 12 patients received placebo. BMD at the lumbar spine and the distal forearm did not differ between groups throughout the study period. Femoral neck BMD remained stable in the teriparatide group, whereas it decreased significantly in the placebo group. Bone biopsies were performed in six participants in each group. None of the histomorphometric parameters differed between the groups at baseline or at the end of the study. Of five patients with adynamic bone disease at the beginning of the study, teriparatide resulted in three patients converting to higher turnover states (80). Teriparatide is expensive, is cumbersome to use as a daily subcutaneous injection, and is without a significant proven benefit or superiority over current therapies. Consequently, its role is likely to be limited to patients with adynamic bone disease who are not candidates for other agents.

MBD post-transplantation is a complex syndrome including hypercalcemia, hypophosphatemia, hyperparathyroidism, and decreased bone quality and strength. MBD is ultimately associated with high risk of morbidity and mortality. MBD biochemical abnormalities require therapeutic interventions but will resolve in the majority of patients after the first year of transplantation, and then, long-term management should prioritize parathyroidectomy for persistent abnormalities in patients who are surgical candidates (Figure 2, Table 1). In regard to the skeleton, observational research has proven that high doses of glucocorticoids are linked to greater bone loss and fractures in recipients. Unfortunately, other than minimizing glucocorticoids, no other treatment has been definitively proven to be associated with MBD improvements or fracture risk reduction. As KDIGO points out, “data are insufficient to guide treatment after the first-year post-transplantation” (23) because even the few studies that showed some therapeutic benefit lacked long-term data. Future research in this area should focus on long-term evaluation of current therapies (i.e., beyond the first year post-transplantation) on the treatment of prevalent kidney transplant recipients and on the effects of treatment on fracture rates and cardiovascular calcification and events. In the meantime, using algorithms, such as the one we propose (Figure 2), can guide fracture risk assessment and the treatment of biochemical and skeletal derangements, possibly improving post-transplant outcomes.

Disclosures

P. Khairallah reports serving on the National Kidney Foundation (NKF) Spring Clinical Meetings Program Committee for 2021, serving as a member of NKF, and serving as a member of the International Society of Nephrology. T.L. Nickolas reports consultancy agreements with Pharmacosmos; receiving research funding from Amgen and Pharmacosmos. Columbia University (T.L. Nickolas’s institution) has licensed patents on Neutrophil Gelatinase Associated Lipocalin to Abbott Diagnostics and Alere.

Funding

None.

References


74. Brunova J, Kratochvilova S, Stepinkova J: Osteoporosis therapy with denosumab in organ transplant recipients. Front Endocrinol (Lausanne) 9: 162, 2018


78. Anastasilakis AD, Papapoulos SE, Polyzos SA, Appelman-Dijkstra NM, Makras P: Zoledronate for the prevention of bone loss in


Published online ahead of print. Publication date available at www.cjasn.org.