

# Bone Disease after Kidney Transplantation

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## Abstract

**Bone and mineral disorders occur frequently in kidney transplant recipients and are associated with a high risk of fracture, morbidity, and mortality. There is a broad spectrum of often overlapping bone diseases seen after transplantation, including osteoporosis as well as persisting high- or low-turnover bone disease. The pathophysiology underlying bone disorders after transplantation results from a complex interplay of factors, including preexisting renal osteodystrophy and bone loss related to a variety of causes, such as immunosuppression and alterations in the parathyroid hormone-vitamin D-fibroblast growth factor 23 axis as well as changes in mineral metabolism. Management is complex, because noninvasive tools, such as imaging and bone biomarkers, do not have sufficient sensitivity and specificity to detect these abnormalities in bone structure and function, whereas bone biopsy is not a widely available diagnostic tool. In this review, we focus on recent data that highlight improvements in our understanding of the prevalence, pathophysiology, and diagnostic and therapeutic strategies of mineral and bone disorders in kidney transplant recipients.**

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## Introduction

Bone disease post-transplantation is a major cause of morbidity in kidney transplant recipients, with a significantly higher risk of fractures as well as increased health care costs, hospitalization, and mortality (1). Post-transplantation bone disease is characterized by changes in bone quality and density as well as mineral metabolism, which contribute to increased fracture risk, and therefore, post-transplantation bone disease is significantly different from the range of chronic kidney disease and mineral bone disorders (CKD-MBDs) seen pretransplantation. In this review, we will discuss the epidemiology, pathophysiology, and types of post-transplantation bone disease, the role of imaging in predicting fracture risk, and therapeutic strategies to manage bone disease after transplantation.

## Epidemiology

The spectrum of bone diseases in kidney transplant recipients includes renal osteodystrophy, osteoporosis, bone fracture, and osteonecrosis. Earlier studies after transplantation indicate that bone mineral density (BMD) declines by 4%–10% in the first 6 months (2), with a further decrease of 0.4%–4.5% in lumbar BMD between 6 and 12 months (3). More recent publications of prospective trials that included patients managed with contemporary immunosuppression protocols have reported bone loss of only 0.1%–5.7% in the lumbar spine (4). After 1 year, BMD remains relatively stable with no further decline but at significantly lower levels than healthy controls (2). This reduction in BMD contributes to an increased risk of fractures. In the first 5 years after transplantation, 22.5% of kidney transplant recipients experience a fracture—an incidence that is four times

that in the general population (5). This risk remains significantly elevated even 10 years post-transplantation, suggesting that bone remains fragile after transplantation, despite improvement in parameters of mineral metabolism (1). Risk factors for bone loss and fractures are summarized in Table 1 (6). The fracture rate among kidney transplant recipients is 34% higher in the first 3 years after transplantation, but thereafter, the risk of fracture is lower than that in comparable patients who remain on dialysis (7). The most common fracture locations are the hip and ankle/foot (6), with hip fracture usually associated with osteoporosis. Because the distal skeleton is an atypical site for osteoporotic fracture, the relatively high frequency of ankle/foot fracture probably reflects the fact that both osteoporosis and renal osteodystrophy coexist post-transplantation. Outcomes for kidney transplant recipients who sustain a fracture are significantly worse, with a 60% increased risk in mortality compared with the general population (6). The US Renal Data System (USRDS) data show the importance of diabetes, with the risk of fracture among men with diabetes who underwent kidney-only transplantation being 31% higher than those who had received a simultaneous kidney-pancreas transplant (8), a finding consistent with recent microindentation studies showing that patients with diabetes have both reduced BMD and bone strength (9).

The rate of fracture has decreased in recent years, with the USRDS data showing the incidence of hip fracture to be 45% lower in patients transplanted in 2010 than in patients transplanted in 1997 (1), although it is still higher than in the general population (2). This trend partly reflects a significant reduction in cumulative glucocorticoid (GC) exposure, but this may not account for all of the reduction in fractures

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**Table 1. Risks factors associated with post-transplantation bone loss and fractures****Risk factors for osteoporosis**

## General factors

*Younger age at transplantation*  
*Poor nutrition*  
*Smoking*  
*Alcohol abuse*

## Endocrine/mineral factors

*Hypogonadal status*  
*Hypomagnesemia*

## Biologic abnormalities

*Functionally different alleles of the vitamin D receptor gene*

**Risk factors for fracture**

## Skeletal factors

*Lumbar osteoporosis or nonvertebral fractures*  
*Preexisting history of fracture*  
*Renal osteodystrophy*

## Risk of falls

*Postural instability*  
*Decreased visual acuity*  
*Peripheral vascular disease*  
*Peripheral neuropathy*  
*Orthostatic hypotension*  
*Drugs (hypnotics, antihypertension drugs)*

**Risk factors for both fracture and osteoporosis**

## General factors

*Age  $\geq 50$  yr old*  
*Women*  
*Body mass index  $< 23$  kg/m<sup>2</sup>*  
*Diabetes*  
*Time on dialysis*

## Transplantation factors

*Cumulative dose of corticosteroids*

## Biologic abnormalities

*Vitamin D deficiency*  
*Parathyroid hormone  $> 130$  ng/L*  
*High serum fibroblast growth factor 23 level*

(10); other factors may be important, including improved management of CKD-MBD pretransplantation and bone protection strategies, such as vitamin D and bisphosphonates in kidney transplant recipients, as well as changes in lifestyle and physical activity. Despite the reduction in hip fracture rates, outcomes after hip fracture are poor, with a recent analysis of 21,769 kidney transplant recipients in the United Kingdom indicating that a hip fracture was independently associated with a threefold increase in mortality risk (11).

**Pathophysiology of Post-Transplant Bone Disease**

Post-transplantation bone disease results from the evolution of preexisting CKD-MBD but also, the development, in some patients, of osteoporosis, and differentiating between these two often overlapping conditions is essential for subsequent management (2).

There is rapid loss of bone mass in the early post-transplant period that frequently affects trabecular bone because of decreased bone formation as a result of GC therapy (12).

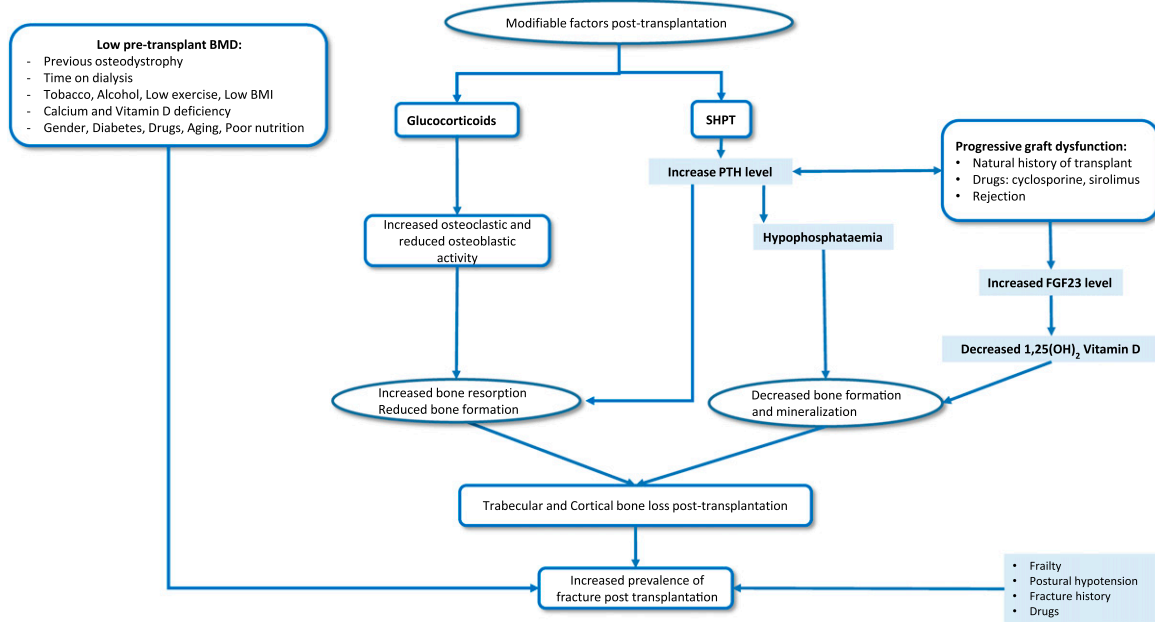
In contrast, before transplantation, bone loss preferentially affects the cortical bone mainly because of secondary hyperparathyroidism (SHPT). The evolution of post-transplantation bone disease is also modified by a variety of post-transplant factors, including the use of immunosuppressive drugs, the degree of graft dysfunction, and disturbances in mineral metabolism, including an increased level of fibroblast growth factor 23, ongoing SHPT, and vitamin D deficiency. Progressive loss of kidney function after transplantation increases the risk of worsening or *de novo* development of hyperparathyroidism with active vitamin D deficiency that leads to changes in bone histomorphometry similar to those observed before transplantation (2). Ethnicity may also affect the type of renal osteodystrophy seen after transplantation, because white patients on dialysis are more likely to have low bone turnover than blacks (13). In the following sections, we will discuss the effect of a number of factors in the development of post-transplantation bone disease as highlighted in Figure 1.

**Evolution of Preexisting Renal Osteodystrophy**

Preexisting renal osteodystrophy is a risk factor for fracture and adverse outcomes post-transplantation (14). The prevalence of histologic patterns of post-transplantation bone disease is not well defined, because there have been very few bone biopsy studies in kidney transplant recipients. Osteomalacia and adynamic bone disease (ABD) were the two most common types of renal osteodystrophy previously described (2); however, this may not represent the contemporary spectrum of renal osteodystrophy seen post-transplantation given the marked changes in both the management of CKD-MBD and immunosuppressive practice in recent years. In another cohort of 20 kidney transplant recipients, ABD was the most common lesion seen on bone biopsy 6 months post-transplantation (15), whereas in a different series of 57 kidney transplant recipients (biopsied at a mean interval of 53.5 months after transplantation), osteitis fibrosa (high-turnover bone disease) was the most common histomorphometric lesion seen, with ABD only affecting 5% of the kidney transplant recipients (16). This discrepancy in bone biopsy data may reflect the differing time after transplantation that the biopsy was taken, suggesting that bone disease continues to evolve for many years after transplantation.

**Osteoporosis and Effect of Immunosuppression on Bone**

Osteoporosis is defined as a reduction in bone mass with microarchitectural deterioration of bone tissue and subsequent increase in bone fragility and susceptibility to fracture. Osteoporosis has also been defined quantitatively using BMD and can be expressed as an SD score comparing an individual's BMD with that of a reference population as measured by dual x-ray absorptiometry (DXA). A T-score that is  $\leq -2.5$  (*i.e.*,  $\geq 2.5$  SDs below the mean BMD of a normal young-adult reference population) is indicative of osteoporosis. Although GC use remains the key risk factor for the development of osteoporosis after transplantation, there are other factors (summarized in Table 1) that contribute to the marked bone loss seen after transplantation.



**Figure 1. | Pathophysiology of bone loss and fractures before and after transplantation.** BMD, bone mineral density; BMI, body mass index; FGF23, fibroblast growth factor 23; 1,25(OH)<sub>2</sub>D, 1,25-dihydroxy vitamin D; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

GCs induce a net loss of BMD by reduction in bone formation and bone density, especially in the trabecular bone of the axial skeleton (12), which is related to the cumulative dose exposure in kidney transplant recipients (17). GCs have a profound inhibitory effect on bone formation by targeting osteoblast proliferation and differentiation while stimulating apoptosis of both osteoblasts and osteocytes. GCs also have indirect effects on the skeleton by inhibiting the synthesis of testosterone, estrogen, and adrenal androgens.

However, the increased risk of bone loss post-transplantation persists even in a steroid-free era. For instance, in a recent study of 47 kidney transplant recipients where GCs were withdrawn 3 days after transplantation, BMD declined significantly at the distal radius at 12 months, although lumbar and hip BMDs did not decline (18). This discrepancy between central and peripheral skeleton seems to be associated with differentially catabolic effects of parathyroid hormone (PTH) rather than GC dosage. It is worth noting that, in immunologically high-risk recipients, steroid-free immunosuppression may be associated with an increased risk of rejection and therefore, paradoxically, increase the risk of high-dose pulsed GCs.

Calcineurin inhibitors have been shown to increase PTH and decrease magnesium. The increase in PTH results in an increase in osteoclastic activity, which may further increase the risk of osteoporosis (2).

### Changes in Mineral Metabolism Post-Transplantation

A number of key changes in mineral metabolism occur in the post-transplant period, although it is important to recognize that the relationships between mineral abnormalities and graft/patient outcomes are, as yet, associative

rather than causal, and one cannot assume that changes in mineral metabolism *per se* cause adverse outcomes. At present, the clinical utility of serum markers of bone turnover (PTH, bone-specific alkaline phosphatase [bALP], osteocalcin) is limited in terms of adequate sensitivity and specificity in predicting bone loss or bone structure and function.

PTH decreases by 50% 6 months after transplantation but remains high in nearly 45% of kidney transplant recipients 2 years post-transplantation (19) because of improvements in calcium, phosphorus, and 1,25-dihydroxy vitamin D [1,25(OH)<sub>2</sub>D] levels associated with improving kidney function (20). High PTH values correlate with significant bone loss at the hip (21), with PTH preferentially catabolic toward cortical rather than trabecular bone. In a single-center study of >140 kidney transplant recipients, persistent hyperparathyroidism (PTH > 130 ng/L) at 3 months was an independent risk factor for fracture, with a 7.5-fold increase in fracture risk (22). Furthermore, a recent analysis of 1609 kidney transplant recipients showed that persistent hyperparathyroidism was independently associated with worse graft survival (19). Despite this strong observational evidence linking high PTH levels to adverse outcomes, the optimal post-transplantation PTH level remains unknown.

**Calcium.** Serum calcium usually follows a biphasic pattern after kidney transplantation with an initial fall in calcium level in the first few weeks, probably secondary to the significant fall in PTH seen after transplantation. This is followed by a rise in serum calcium reflecting a combination of increased 1,25(OH)<sub>2</sub>D production from the allograft and persistent SHPT. Hypercalcemia has been reported in around 5%–15% of patients after transplantation and is most prevalent 3–6 months after transplantation, particularly in patients with high PTH (20). Persistently high

serum calcium and PTH levels are associated with interstitial microcalcification and poorer long-term graft outcomes (2).

**Phosphorous.** Hypophosphatemia is common in the early post-transplant period, and it occurs in  $\leq 50\%$  of incident kidney transplant recipients (20). It is usually self-limiting, reflecting an improvement in excretory kidney function, elevated PTH levels, and an increase in renal tubular sensitivity to PTH and fibroblast growth factor 23. Hypophosphatemia has been associated with severe alterations in bone turnover, such as a decrease in osteoblast activity and defective mineralization.

**Vitamin D.** Deficiency in 25-hydroxy vitamin D (25-OHD) is seen in 30% of kidney transplant recipients (23), and even if allograft function normalizes, 25-OHD levels often remain low. This persistent 25-OHD deficiency leads to hypocalcemia and abnormal bone mineralization (23). Furthermore, low 25-OHD levels may be associated with poor graft outcomes, including an increased risk of acute cellular rejection (24), possibly through the immunomodulatory effect of vitamin D on the immune system, which may be mediated through direct effects on T cells and also, indirectly *via* modification of dendritic cell function (23). A recent prospective study from France showed that low 25-OHD levels 3 months after transplantation were independently associated with a lower measured GFR and a higher risk for interstitial fibrosis at 12 months (25). There are no published randomized, controlled trials (RCTs) of native 25-OHD supplementation, but unpublished data from the VITA-D Study (26) seem to suggest that supplementation had no effect on either graft function or BMD.

## Evaluating Fracture Risk

### Role of DXA and Other Imaging in Fracture Risk

A DXA scan is a relatively accurate, noninvasive, cost-effective screening method for estimating bone mass, and it seems to help predict fracture risk in kidney transplant recipients. In a Swedish study of 238 kidney transplant recipients, 19% of patients had a fracture over a 12-year follow-up, and those with osteopenia and osteoporosis at the hip had a significantly increased risk of fracture compared with those with normal BMD (relative risks of 2.7 [95% confidence interval, 1.6 to 4.6] and 3.5 [95% confidence interval, 1.8 to 6.4], respectively) (27).

DXA is unable to assess microarchitectural structure of the bone and provides only a two-dimensional measurement of bone density. In contrast, high-resolution peripheral quantitative computed tomography (HR-pQCT) of the distal tibia and radius provides microarchitectural information and is able to quantify volumetric density of cortical and trabecular bone (28). Iyer *et al.* (18) have used HR-pQCT to show significant reductions in both cortical and trabecular bone densities after transplantation, which resulted in reduced estimated bone strength. Presently, HR-pQCT is a promising research tool, but there have been no studies to show whether it is a better predictor of fracture than DXA in kidney transplant recipients.

### Fracture Risk Assessment

The Fracture Risk Assessment Tool (FRAX) accurately estimates the 10-year probability of major osteoporotic

fractures in the general population and generates recommendations for therapy in patients at high risk of fracture. The FRAX does not require bone densitometry data to predict fracture risk and therefore, is a potentially attractive clinical decision aid. Recently, the FRAX has been shown to modestly predict fracture risk in kidney transplant recipients at a single center (29), but additional validation is required before it can be used as a bedside tool.

### Bone Biopsy

Bone biopsy with double-tetracycline labeling is the gold standard to accurately diagnose post-transplantation bone disease subtype, but it is not often performed. The Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guideline (30) states that it is reasonable to consider bone biopsy to guide treatment in the first 12 months post-transplant, but this recommendation is not graded because of a lack of evidence. Ideally, kidney transplant recipients who have persistent bone pain, fragility fractures, or severe osteoporosis need a bone biopsy to exclude ABD before initiation of antiresorptive therapy, because PTH levels are poorly predictive of underlying bone turnover (30). However, it is important to recognize that many patients find this invasive procedure unacceptable, and the processing and analysis of bone biopsies require significant expertise that precludes its widespread use. Furthermore, there are no published studies looking at the predictive value of bone biopsies in identifying kidney transplant recipients at risk of fracture. More studies are needed to clarify the clinical utility of bone biopsy on the practical management of post-transplantation bone disease and the effect of antiresorptive therapy on bone histology in this population.

## Preventing and Managing Bone Disease Post-Transplantation

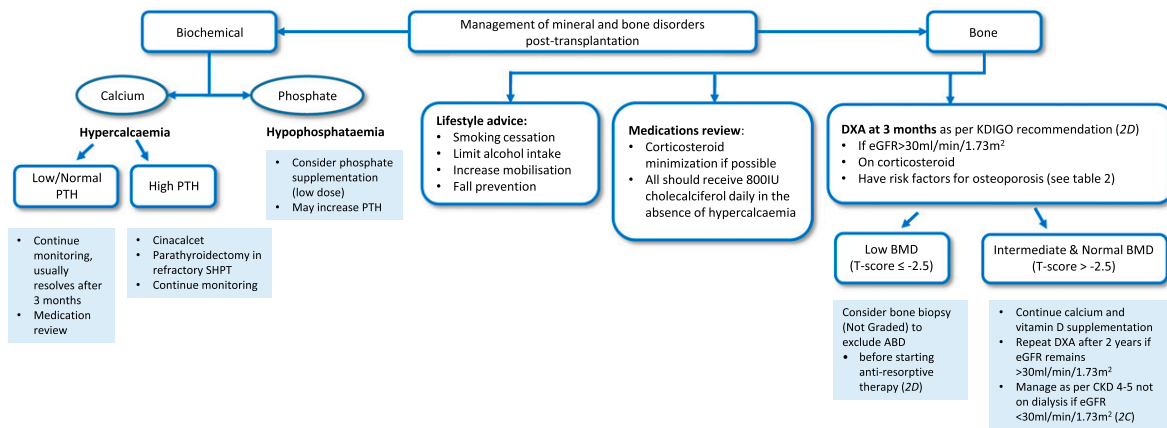
Figure 2 summarizes an approach to managing post-transplantation bone disease based on the KDIGO guidelines (30), although it is important to recognize that the evidence on which these recommendations are made is generally poor; therefore, management approach is inevitably opinion based. Specific interventions discussed below focus on recent data that help inform our understanding of these therapeutic strategies.

### Minimizing GCs

Reducing steroid exposure can minimize bone loss and should be especially considered for patients with known pretransplant osteopenia or osteoporosis (30). In a study of 87 kidney transplant recipients, BMD improved at the lumbar spine (by 4.7%) and the total hip (by 2.4%) after GC withdrawal 1-year post-transplantation compared with those who remained on GCs (31), and even late GC withdrawal has been shown to improve BMD (32). A recent analysis of the USRDS data found that early steroid withdrawal at hospital discharge was associated with a 31% fracture risk reduction and lower fracture-related hospitalization (10) without an increased risk of rejection in the steroid withdrawal arm.

### Vitamin D and Vitamin D Analogs

Supplementation with both active [1,25(OH)<sub>2</sub>D] and native (25-OHD) vitamin D can reduce loss of BMD in both



**Figure 2. | Management of mineral and bone disorders post-transplantation.** The strength of recommendation is indicated as level 1 (we recommend), level 2 (we suggest), or not graded, and the quality of the supporting evidence is shown as A (high), B (moderate), C (low), or D (very low). ABD, dynamic bone disease; BMD, bone mineral density; DXA, dual x-ray absorptiometry; KDIGO, Kidney Disease Improving Global Outcomes; PTH, parathyroid hormone; SHPT, secondary hyperparathyroidism.

the femoral and lumbar regions, but these studies have not been sufficiently powered to determine whether there is a beneficial effect on fracture rate (23). Furthermore, vitamin D has well described pleiotropic effects on the renin-angiotensin-aldosterone system and proteinuria (23) and immune-modulatory effects on T cells and dendritic cells, which may affect graft function (25).

Paricalcitol, a synthetic metabolically active vitamin D analog of calcitriol, has been shown to suppress PTH post-transplantation but was associated with a higher risk of hypercalcemia (33). In the same study, moderate renal allograft fibrosis was reduced in the paricalcitol group compared with the control group. Another randomized, crossover study has shown that paricalcitol also reduced bone remodeling as reflected by reduction of bALP and osteocalcin together with improvements in lumbar spine BMD (34). Interestingly, there was a reduction in eGFR associated with paricalcitol therapy, but it is not clear whether this reflects changes in creatinine secretion and generation or a direct effect on GFR.

**Calcimimetics**

Cinacalct is a calcimimetic agent that increases the sensitivity to calcium of the calcium-sensing receptor in the parathyroid gland and suppresses PTH. A recent RCT for the treatment of hypercalcemia and SHPT in 114 kidney transplant recipients (35) showed that cinacalct significantly reduced PTH and calcium with an increase in serum phosphorus levels without any effect on graft function compared with placebo. Although PTH has a catabolic effect on bone, reducing PTH with cinacalct, perhaps surprisingly, had no positive effect on BMD, possibly because of direct effects on a calcium-sensing receptor in bone that may offset any beneficial effects of lower PTH levels (36). Cinacalct therapy does result in significant hypercalciuria and may cause nephrocalcinosis, although this was not seen in a cohort of 34 kidney transplant recipients who underwent an allograft biopsy at 3 and 12 months post-transplantation (37). The direct effect of cinacalct on the bone histomorphometry in kidney transplant recipients has not

been studied in detail. In a small study of kidney transplant recipients who underwent bone biopsy before and after starting cinacalct, Borchhardt *et al.* (38) found that, although bone formation rates fell in seven of 10 patients, five of 10 patients had undetectable bone turnover after 18–24 months of cinacalct therapy. Notwithstanding the risk of ABD associated with cinacalct, one needs to recognize the risks associated with parathyroidectomy in kidney transplant recipients. These include irreversibly inducing ABD and a decline in eGFR after parathyroidectomy in the allograft, possibly as a result of the direct effects of PTH on renal hemodynamics (39).

**Recombinant PTH**

Recombinant PTH (teriparatide) is an anabolic agent, which can improve BMD in patients with GC-induced and postmenopausal osteoporosis. In a 6-month double-blind RCT of 26 kidney transplant recipients (40), patients who received daily teriparatide injection did not show an improvement of BMD in the lumbar spine or distal radius compared with those in the placebo group. However, there was stabilization of femoral neck BMD in the teriparatide-treated group. Teriparatide is expensive, and in view of the lack of supporting data from RCTs in kidney transplant recipients, its therapeutic role is unclear, although theoretically, it may be an attractive agent for those with severe osteoporosis who also have evidence of ABD.

**Antiresorptive Agents**

Bisphosphonates and denosumab are the two commonly used antiresorptive agents for osteoporosis. Both therapies can potentially induce low bone turnover, and therefore, it is important to consider a bone biopsy before initiating therapy in those at high risk of ABD, such as those who have had a previous parathyroidectomy (30).

Bisphosphonates accumulate at sites of active bone resorption, where they enter osteoclasts and inhibit farnesyl pyrophosphate synthase, which results in osteoclast apoptosis, thereby inhibiting bone resorption. They bind potently to mineralized bone, with a half-life of ≤10 years, and the fraction not taken up by bone (40%–60%) is

Table 2. Overview of all randomized, controlled trials of bisphosphonates in kidney transplant recipients

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Kovac <i>et al.</i> (41)	12	Yes	2 g Calcium carbonate and 0.25 $\mu$ g calcitriol daily	Alendronate add-on therapy was started within 1 mo post-transplant	6	BMD: BMD increment in lumbar spine in the alendronate group and decrement in the control group but not statistically significant. Biochemistry: No difference in both groups in calcium, phosphate, PTH, and BsAP	Small sample size, open label study
Giannini <i>et al.</i> (42)	40	Yes	980 mg Calcium daily for the first 6 mo, then 0.50 $\mu$ g/d oral calcitriol and 500 mg/d calcium carbonate	Alendronate add-on therapy was started 6 mo post-transplantation	12	BMD: The changes in bone density remained similar in both groups after adjustment for the cumulative intake of corticosteroids in patients treated with alendronate versus calcitriol and patients treated with calcium only. No difference in fracture rate. Biochemistry: No difference in both groups in calcium and BsAP. PTH levels increased in the alendronate group and slightly decreased in the control group	Small sample size, lag time since transplantation for starting alendronate, open label study

**Table 2. (Continued)**

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Grotz <i>et al.</i> (43)	80	Yes	At least 1 g dietary calcium daily (or 500 mg calcium supplement daily for dairy intolerance)	Ibandronate was started preoperatively	12	BMD (treatment versus control group): BMD at the lumbar spine and the hip with ibandronate. Significant reduction in BMD was observed in the control group. Two vertebral bone fractures occurred in each group. Biochemistry: No difference in both groups in calcium, phosphate, BsAP, or PTH. Graft function: Fewer acute rejection episodes with ibandronate ( $P < 0.01$ ). Graft function after 1 yr was similar in both groups	Small sample size, double-blind study, no supplementation with vitamin D
Jeffery <i>et al.</i> (44)	117	Yes	1 g Dietary calcium plus additional 500 mg calcium carbonate daily	No information about the time lag when the bisphosphonate was given after transplantation	12	BMD: Similar significant increase in BMD in both groups at the lumbar spine and femur compared with baseline. Biochemistry: No difference in both groups in PTH	Both arms received relatively high doses of steroids

Table 2. (Continued)

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Haas <i>et al.</i> (45)	20	Yes	1 g Calcium citrate daily	Zoledronate started immediately post-transplantation	6	BMD: Lumbar spine BMD improved significantly in the zoledronate group but deteriorated significantly in the control group. Significant decrease in femoral neck BMD in the placebo group but not in patients receiving zoledronate. No increased risk of ABD in the zoledronate-treated group (only three patients) compared with placebo. High-turnover bone disease resolved similarly in both groups. Biochemistry: Osteocalcin and type 1 collagen peptides were significantly lower in patients receiving zoledronate. No difference in both groups in calcium, phosphorus, iPTH, and ALP	Small sample size, double-blind study, no vitamin D supplementation



**Table 2. (Continued)**

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Coco <i>et al.</i> (46)	72	Yes	Oral calcitriol and calcium carbonate (dosage unknown)	Pamidronate started 48 h post-transplantation	12	BMD (treatment versus control group): Percentage decrease in vertebral BMD from baseline was less in the pamidronate group compared with the placebo group. No change in hip BMD. No difference in fracture rate. Biochemistry: No difference in both groups in calcium, phosphate, BsAP, or PTH. Bone biopsies: Low-turnover bone disease in 50% of patients at baseline. At 6 mo, all patients in the pamidronate group had ABD, whereas 50% of the control group continued to have or developed low bone turnover	Small sample size, double-blind study
Schwarz <i>et al.</i> (47)	20	Yes	1 g Calcium citrate daily	Zoledronate started 2 wk post-transplantation	36	BMD: Both groups exhibited an improvement of BMD, without statistical differences between groups. Two fractures in each group. Biochemistry: No difference in both groups in osteocalcin, BsAP, CTX, calcitonin, and iPTH	Small sample size, no vitamin D supplementation, exclusion of ABD (on bone biopsy)

Table 2. (Continued)

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Walsh <i>et al.</i> (48)	125	Unknown	500 mg Calcium carbonate and 400 IU cholecalciferol daily	Pamidronate started preoperatively	12	BMD: Significant increase in lumbar BMD with pamidronate, whereas the placebo group had worsening BMD. No difference in femoral neck BMD. Two vertebral fractures in the pamidronate group and four vertebral fractures in the control group. Biochemistry: No difference in calcium, phosphate, BsAP, or PTH between both groups	Double-blind study
Torregrosa <i>et al.</i> (49)	101	Unknown	1500 mg Calcium carbonate and 400 IU cholecalciferol daily	Risedronate versus placebo: No information about the time lag when risedronate was given after transplantation	12	BMD: Patients in the control group showed a significant worsening of BMD. Lumbar BMD at baseline was significantly lower in the control group and remained stable during the study. Femoral BMD of those treated with risedronate was significantly increased at 6-mo follow-up but not at 12 mo. Incidence of vertebral fracture was lower in the risedronate group. Biochemistry: No difference between groups in calcium, phosphate, and PTH	

**Table 2. (Continued)**

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Torregrosa <i>et al.</i> (50)	39	Unknown	1 g Calcium and 800 IU cholecalciferol daily	Pamidronate started within 2 wk post-transplantation	12	BMD: Lumbar spine BMD remained stable in the pamidronate group but fell in the placebo group. Biochemistry: No difference between groups in terms of calcium, phosphate, and PTH. Normalization of the PINP concentration in the pamidronate group only	Placebo-controlled study, small sample size
Smerud <i>et al.</i> (51)	129	Yes	0.25 μg Calcitriol and 1 g calcium carbonate daily	Ibandronate started within 4 wk post-transplantation	12	BMD: No difference in the lumbar BMD between groups. Improvement in hip and forearm density in treated patients. One vertebral bone fracture in the ibandronate group and one vertebral bone in the control group. Biochemistry: No difference in PTH between groups. Decrease in BsAP and osteocalcin in the ibandronate group	Double-blind study

Table 2. (Continued)

Authors	No. of Patients	Corticosteroid <sup>a</sup>	Standard Treatment for Both Groups	Additional Treatment	Period of Follow-Up (mo)	Key End Points	Comments
Coco <i>et al.</i> (52)	42	Yes	0.25 $\mu$ g Calcitriol daily	Risedronate started as soon as renal function improved to SCr < 2.0 mg/dl after transplant	12	BMD: No significant change in lumbar spine in both groups. Two vertebral bone fractures in the risedronate group. Biochemistry: No difference in calcium, phosphate, BsAP, or PTH between groups. Bone biopsies: Risedronate-treated men had increased osteoid formation, whereas control men had increased resorption characteristics	Small sample size, double-blind study

BMD, bone mineral density; PTH, parathyroid hormone; BsAP, bone-specific alkaline phosphatase; ABD, adynamic bone disease; iPTH, intact parathyroid hormone; ALP, alkaline phosphatase; CTX, C-terminal telopeptides type 1 collagen; PINP, procollagen type 1 N-terminal propeptide; SCr, serum creatinine.

<sup>a</sup>All of the studies using corticosteroid used prednisolone, except for the study by Haas *et al.* (45), which used methylprednisolone.

excreted by a combination of glomerular filtration and active tubular transport. Therefore, impaired graft function can have a significant effect on the pharmacokinetics and half-life of bisphosphonates. However, treatment is well tolerated in kidney transplant recipients with a GFR >30 ml/min per 1.73 m<sup>2</sup>, with no significant adverse effects compared with placebo/no treatment (30).

The key RCTs using bisphosphonates in kidney transplant recipients are summarized in Table 2 (41–52). Most of the studies show that bisphosphonate therapy preserves or increases BMD in the lumbar spine and femoral neck in the early post-transplantation period. It is worth noting that the risk of ABD as a result of bisphosphonate therapy has not been a consistently observed phenomenon. For example, Coco *et al.* (46) studied the effect of pamidronate combined with low-dose calcium and calcitriol on preservation of bone mass at 6 and 12 months compared with placebo. Pamidronate was associated with preservation of vertebral BMD but an increased risk of low bone turnover on bone biopsy. In contrast, more recent data from the same group showed that risedronate did not affect BMD and that it was not associated with an increased risk of developing ABD in kidney transplant recipients (52). This difference between bisphosphonate effects could be related to differences in potency in their mechanisms of action or may reflect the difference in the enzyme-suppressive activity of second (pamidronate) and third generation (risedronate) bisphosphonates.

A recent study by Smerud *et al.* (51) showed no benefit with ibandronate compared with calcium and calcitriol supplementation alone on lumbar BMD, but ibandronate did modestly increase hip and forearm BMD. It also suppressed bone turnover markers, including procollagen type 1 N-terminal propeptide, osteocalcin, and bALP. This finding is in striking contrast to earlier studies, which seemed to show a beneficial effect of bisphosphonates on lumbar BMD. This is likely to be because of significantly less GC exposure in the study by Smerud *et al.* (51) as well as the fact that the control group received calcitriol and calcium supplementation. Indeed, a number of studies in which vitamin D therapy was part of standard care in the control group failed to show a benefit of bisphosphonates on BMD after kidney transplantation. This suggests that widespread bisphosphonate use may have less of an effect on BMD in the contemporary era of reduced rejection rates, reduced steroid exposure, and widespread use of vitamin D and that the value of bisphosphonate therapy will be targeted use in high-risk recipients.

Denosumab, a humanized monoclonal antibody against the receptor activator of NF- $\kappa$ B ligand, decreases bone resorption, significantly increases BMD, and decreases the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. It is also effective at reducing fracture risk in patients with impaired kidney function, including those with CKD stage 4 (53). Denosumab is not renally cleared, which makes it more attractive than bisphosphonates in patients with significant graft dysfunction, although there are little data of its use in the transplant population.

## Conclusions

Complex abnormalities of mineral homeostasis and bone remodeling occur post-transplantation, resulting in loss of bone density, increased risk of fracture, and increased overall risk of mortality. All transplant recipients should be evaluated for mineral bone disorder and monitored for ongoing bone loss. Management of post-transplantation bone disease is challenging but should initially focus on biochemical abnormalities associated with bone mineral disorder. Cinacalcet seems to be effective in correcting biochemical abnormalities associated with hyperparathyroidism, but it has no effect on BMD, and there are no outcome data with regard to its effect on fracture risk. Similarly, although DXA seems to predict fracture risk and bisphosphonates generally have a positive effect on BMD after transplantation, there are little data to show that bisphosphonates effect clinical end points, such as fracture. Reducing cumulative GC exposure combined with calcium and vitamin D supplementation alone prevents bone loss after transplantation. Antiresorptive therapy, such as bisphosphonates, should only be reserved for those patients at high risk of fracture with evidence of significant bone loss, despite optimal supportive therapy.

## Disclosures

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## References

1. Sukumaran Nair S, 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* 14: 943–951, 2014
2. Malluche HH, Monier-Faugere M-C, Herberth J: Bone disease after renal transplantation. *Nat Rev Nephrol* 6: 32–40, 2010
3. Brandenburg VM, Politt D, Ketteler M, Fassbender WJ, Heussen N, Westenfeld R, Freuding T, Floege J, Ittel TH: Early rapid loss followed by long-term consolidation characterizes the development of lumbar bone mineral density after kidney transplantation. *Transplantation* 77: 1566–1571, 2004
4. Weisinger JR, Carlini RG, Rojas E, Bellorin-Font E: Bone disease after renal transplantation. *Clin J Am Soc Nephrol* 1: 1300–1313, 2006
5. Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N: Risk of fractures after renal transplantation in the United States. *Transplantation* 87: 1846–1851, 2009
6. Naylor KL, Li AH, Lam NN, Hodsman AB, Jamal SA, Garg AX: Fracture risk in kidney transplant recipients: A systematic review. *Transplantation* 95: 1461–1470, 2013
7. Ball AM, Gillen DL, Sherrard D, Weiss NS, Emerson SS, Seliger SL, Kestenbaum BR, Stehman-Breen C: Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 288: 3014–3018, 2002
8. Nikkel LE, Iyer SP, Mohan S, Zhang A, McMahan DJ, Tanriover B, Cohen DJ, Ratner L, Hollenbeak CS, Rubin MR, Shane E, Nickolas TL; CURE Group (The Columbia University Renal Epidemiology Group): Pancreas-kidney transplantation is associated with reduced fracture risk compared with kidney-alone transplantation in men with type 1 diabetes. *Kidney Int* 83: 471–478, 2013
9. Farr JN, Drake MT, Amin S, Melton LJ 3rd, McCready LK, Khosla S: In vivo assessment of bone quality in postmenopausal women with type 2 diabetes. *J Bone Miner Res* 29: 787–795, 2014
10. Nikkel LE, Mohan S, Zhang A, McMahan DJ, Boutroy S, Dube G, Tanriover B, Cohen D, Ratner L, Hollenbeak CS, Leonard MB, Shane E, Nickolas TL: Reduced fracture risk with early corticosteroid withdrawal after kidney transplant. *Am J Transplant* 12: 649–659, 2012

11. Ferro CJ, Arnold J, Bagnall D, Ray D, Sharif A: Fracture risk and mortality post-kidney transplantation. *Clin Transplant* 29: 1004–1012, 2015
12. 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* 11: 1093–1099, 2000
13. Malluche HH, Mawad HW, Monier-Faugere M-C: Renal osteodystrophy in the first decade of the new millennium: Analysis of 630 bone biopsies in black and white patients. *J Bone Miner Res* 26: 1368–1376, 2011
14. Neves CL, dos Reis LM, Batista DG, Custodio MR, Gracioli FG, Martin RC, Neves KR, Dominguez WV, Moyses RM, Jorgetti V: Persistence of bone and mineral disorders 2 years after successful kidney transplantation. *Transplantation* 96: 290–296, 2013
15. Cruz EAS, Lugon JR, Jorgetti V, Draibe SA, Carvalho AB: Histologic evolution of bone disease 6 months after successful kidney transplantation. *Am J Kidney Dis* 44: 747–756, 2004
16. Lehmann G, Ott U, Stein G, Steiner T, Wolf G: Renal osteodystrophy after successful renal transplantation: A histomorphometric analysis in 57 patients. *Transplant Proc* 39: 3153–3158, 2007
17. 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* 325: 544–550, 1991
18. Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, McMahon DJ, Boutroy S, Liu XS, Ratner LE, Cohen DJ, Guo XE, Shane E, Nickolas TL: Kidney transplantation with early corticosteroid withdrawal: Paradoxical effects at the central and peripheral skeleton. *J Am Soc Nephrol* 25: 1331–1341, 2014
19. Lou I, Foley D, Odorico SK, Levenson G, Schneider DF, Sippel R, Chen H: How well does renal transplantation cure hyperparathyroidism? *Ann Surg* 262: 653–659, 2015
20. Wolf M, Weir MR, Kopyt N, Mannon RB, Von Visger J, Deng H, Yue S, Vincenti F: A prospective cohort study of mineral metabolism after kidney transplantation. *Transplantation* 100: 184–193, 2016
21. Akaberi S, Lindergård B, Simonsen O, Nyberg G: Impact of parathyroid hormone on bone density in long-term renal transplant patients with good graft function. *Transplantation* 82: 749–752, 2006
22. Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, Muller C, Olagne J, Moulin B: Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant* 13: 2653–2663, 2013
23. 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* 14: 1259–1270, 2014
24. Lee JR, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T: Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. *Transplantation* 98: 292–299, 2014
25. Bienaimé F, Girard D, Anglicheau D, Canaud G, Souberbielle JC, Kreis H, Noël LH, Friedlander G, Elie C, Legendre C, Prié D: Vitamin D status and outcomes after renal transplantation. *J Am Soc Nephrol* 24: 831–841, 2013
26. Thiem U, Heinze G, Segel R, Perkmann T, Kainberger F, Mühlbacher F, Hörl W, Borchhardt K: VITA-D: Cholecalciferol substitution in vitamin D deficient kidney transplant recipients: A randomized, placebo-controlled study to evaluate the post-transplant outcome. *Trials* 10: 36, 2009
27. Akaberi S, Simonsen O, Lindergård B, Nyberg G: Can DXA predict fractures in renal transplant patients? *Am J Transplant* 8: 2647–2651, 2008
28. Nishiyama KK, Pauchard Y, Nikkel LE, Iyer S, Zhang C, McMahon DJ, Cohen D, Boyd SK, Shane E, Nickolas TL: Longitudinal HR-pQCT and image registration detects endocortical bone loss in kidney transplantation patients. *J Bone Miner Res* 30: 554–561, 2015
29. Naylor KL, Leslie WD, Hodsman AB, Rush DN, Garg AX: FRAX predicts fracture risk in kidney transplant recipients. *Transplantation* 97: 940–945, 2014
30. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 113: S1–S130, 2009
31. 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* 25: E113–E123, 2011
32. Farmer CKT, Hampson G, Abbs IC, Hilton RM, Koffman CG, Fogelman I, Sacks SH: Late low-dose steroid withdrawal in renal transplant recipients increases bone formation and bone mineral density. *Am J Transplant* 6: 2929–2936, 2006
33. Amer H, Griffin MD, Stegall MD, Cosio FG, Park WD, Kremers WK, Heilman RL, Mazur MJ, Hamawi K, Larson TS, Kumar R: Oral paricalcitol reduces the prevalence of posttransplant hyperparathyroidism: Results of an open label randomized trial. *Am J Transplant* 13: 1576–1585, 2013
34. Trillini M, Cortinovis M, Ruggenti P, Reyes Loaeza J, Courville K, Ferrer-Siles C, Prandini S, Gaspari F, Cannata A, Villa A, Perna A, Gotti E, Caruso MR, Martinetti D, Remuzzi G, Perico N: Paricalcitol for secondary hyperparathyroidism in renal transplantation. *J Am Soc Nephrol* 26: 1205–1214, 2015
35. Evenepoel P, Cooper K, Holdaas H, Messa P, Mourad G, Olgaard K, Rutkowski B, Schaefer H, Deng H, Torregrosa JV, Wuthrich RP, Yue S: A randomized study evaluating cinacalcet to treat hypercalcemia in renal transplant recipients with persistent hyperparathyroidism. *Am J Transplant* 14: 2545–2555, 2014
36. Peacock M, Bolognese MA, Borofsky M, Scumpia S, Sterling LR, Cheng S, Shoback D: Cinacalcet treatment of primary hyperparathyroidism: Biochemical and bone densitometric outcomes in a five-year study. *J Clin Endocrinol Metab* 94: 4860–4867, 2009
37. Courbebaisse M, Diet C, Timsit M-O, Mamzer M-F, Thervet E, Noel L-H, Legendre C, Friedlander G, Martinez F, Prié D: Effects of cinacalcet in renal transplant patients with hyperparathyroidism. *Am J Nephrol* 35: 341–348, 2012
38. Borchhardt KA, Diarra D, Sulzbacher I, Benesch T, Haas M, Sunder-Plassmann G: Cinacalcet decreases bone formation rate in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Nephrol* 31: 482–489, 2010
39. Parikh S, Nagaraja H, Agarwal A, Samavedi S, Von Visger J, Nori U, Andreoni K, Pesavento T, Singh N: Impact of post-kidney transplant parathyroidectomy on allograft function. *Clin Transplant* 27: 397–402, 2013
40. Cejka D, Benesch T, Krestan C, Roschger P, Klaushofer K, Pietschmann P, Haas M: Effect of teriparatide on early bone loss after kidney transplantation. *Am J Transplant* 8: 1864–1870, 2008
41. Kovac D, Lindic J, Kandus A, Bren AF: Prevention of bone loss with alendronate in kidney transplant recipients. *Transplantation* 70: 1542–1543, 2000
42. Giannini S, D'Angelo A, Carraro G, Nobile M, Rigotti P, Bonfante L, Marchini F, Zaninotto M, Dalle Carbonare L, Sartori L, Crepaldi G: Alendronate prevents further bone loss in renal transplant recipients. *J Bone Miner Res* 16: 2111–2117, 2001
43. Grotz W, Nagel C, Poeschel D, Cybulla M, Petersen KG, Uhl M, Strey C, Kirste G, Olschewski M, Reichelt A, Rump LC: Effect of ibandronate on bone loss and renal function after kidney transplantation. *J Am Soc Nephrol* 12: 1530–1537, 2001
44. 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* 76: 1498–1502, 2003
45. Haas M, Leko-Mohr Z, Roschger P, Kletzmayer J, Schwarz C, Mitterbauer C, Steininger R, Grampp S, Klaushofer K, Dellling G, Oberbauer R: Zoledronic acid to prevent bone loss in the first 6 months after renal transplantation. *Kidney Int* 63: 1130–1136, 2003
46. Coco M, Glicklich D, Faugere MC, Burris L, Bognar I, Durkin P, Tellis V, Greenstein S, Schechner R, Figueroa K, McDonough P, Wang G, Malluche H: Prevention of bone loss in renal transplant recipients: A prospective, randomized trial of intravenous pamidronate. *J Am Soc Nephrol* 14: 2669–2676, 2003
47. 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* 65: 304–309, 2004
48. Walsh SB, Altmann P, Pattison J, Wilkie M, Yaqoob MM, Dudley C, Cockwell P, Sweny P, Banks LM, Hall-Craggs M, Noonan K, Andrews C, Cunningham J: Effect of pamidronate on bone loss

- after kidney transplantation: A randomized trial. *Am J Kidney Dis* 53: 856–865, 2009
49. Torregrosa J-V, Fuster D, Gentil M-A, Marcen R, Guirado L, Zarraga S, Bravo J, Burgos D, Monegal A, Muxí A, García S: Open-label trial: Effect of weekly risedronate immediately after transplantation in kidney recipients. *Transplantation* 89: 1476–1481, 2010
50. Torregrosa J-V, Fuster D, Monegal A, Gentil MA, Bravo J, Guirado L, Muxí A, Cubero J: Efficacy of low doses of pamidronate in osteopenic patients administered in the early post-renal transplant. *Osteoporos Int* 22: 281–287, 2011
51. Smerud KT, Dolgos S, Olsen IC, Åsberg A, Sagedal S, Reisæter AV, Midtvedt K, Pfeffer P, Ueland T, Godang K, Bollerslev J, Hartmann A: A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. *Am J Transplant* 12: 3316–3325, 2012
52. Coco M, Pullman J, Cohen HW, Lee S, Shapiro C, Solorzano C, Greenstein S, Glicklich D: Effect of risedronate on bone in renal transplant recipients. *J Am Soc Nephrol* 23: 1426–1437, 2012
53. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, Ebeling PR, Franek E, Yang YC, Egbuna OI, Boonen S, Miller PD: Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res* 26: 1829–1835, 2011

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