In Practice

CKD–Mineral and Bone Disorder Management in Kidney Transplant Recipients

Hala M. Alshayeb, MD, Michelle A. Josephson, MD, and Stuart M. Sprague, DO

Kidney transplantation, the most effective treatment for the metabolic abnormalities of chronic kidney disease (CKD), only partially corrects CKD–mineral and bone disorders. Posttransplantation bone disease, one of the major complications of kidney transplantation, is characterized by accelerated loss of bone mineral density and increased risk of fractures and osteonecrosis. The pathogenesis of posttransplantation bone disease is multifactorial and includes the persistent manifestations of pretransplantation CKD–mineral and bone disorder, peritransplantation changes in the fibroblast growth factor 23–parathyroid hormone–vitamin D axis, metabolic perturbations such as persistent hypophosphatemia and hypercalcemia, and the effects of immunosuppressive therapies. Posttransplantation fractures occur more commonly at peripheral than central sites. Although there is significant loss of bone density after transplantation, the evidence linking posttransplantation bone loss and subsequent fracture risk is circumstantial. Presently, there are no prospective clinical trials that define the optimal therapy for posttransplantation bone disease. Combined pharmacologic therapy that targets multiple components of the disordered pathways has been used. Although bisphosphonate or calcitriol therapy can preserve bone mineral density after transplantation, there is no evidence that these agents decrease fracture risk. Moreover, bisphosphonates pose potential risks for adynamic bone disease.

INDEX WORDS: Posttransplantation bone disease; epidemiology; pathogenesis; screening; diagnosis; management.

CASE PRESENTATION

A 68-year-old white woman with a 37-year history of membranous glomerulonephritis and progressive chronic kidney disease (CKD) was found to have decreasing bone mineral density (BMD) 2 years after a pre-emptive living unrelated kidney transplantation. Dual-energy x-ray absorptiometry (DEXA) showed T scores of −3.1 and −1.9 at the lumbar spine and femoral neck, respectively. These values represented a decrease of 6% and 12.2%, respectively, compared with the study performed at the time of transplantation. Her induction immunosuppression therapy included high-dose prednisone and polyclonal antithymocyte globulin followed by maintenance therapy with cyclosporine, 75 mg, twice a day; azathioprine, 100 mg; and prednisone, 5 mg daily. Other pertinent medications included alendronate, 70 mg/wk, that was started 4 years prior to transplantation, and ergocalciferol, 50,000 U/wk. She was a nonsmoker. Age of menarche was 13 years, with spontaneous menopause in her late 40s. Skeletal history was significant for 3 foot fractures in childhood, one traumatic fracture 5 years prior to transplantation, and avascular necrosis of the left hip with a total hip replacement 8 months posttransplantation. She had 3 cellular rejection episodes during the first 10 months posttransplantation, all requiring intensified steroid dosing. OKT3 and polyclonal antithymocyte globulin also were used for the first and third rejection episodes, respectively. Physical examination showed a short frail-appearing woman with body mass index of 22 kg/m². Musculoskeletal examination was significant for a 1-inch left hip elevation. Pertinent laboratory data showed estimated glomerular filtration rate (eGFR) of 40 mL/min/1.73 m² and normal serum calcium, phosphorus, calcidiol, and calcitriol concentrations. Intact parathyroid hormone (PTH) level was elevated at 206 pg/mL, and other values were for bone-specific alkaline phosphatase (16: reference range, 9.1-27.5 U/L), osteocalcin (11.3: reference range, 0.4-8.7 ng/mL), and urine telopeptide (38: reference range, <65 nmol/mmol).

INTRODUCTION

Posttransplantation bone disease is a complex disorder and may lead not only to reduced bone quality or bone loss, which may result in fractures, but also to changes in mineral metabolism. Although considered to be within the spectrum of CKD–mineral bone disease, posttransplantation bone disease is markedly different from the mineral and bone disorders often seen in patients with CKD and end-stage kidney disease and is influenced by factors such as immunosuppressive therapy, kidney transplant function, hypophosphatemia, and disturbances in the fibroblastic growth factor 23 (FGF-23)-PTH–vitamin D axis.

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Received March 5, 2012. Accepted in revised form July 9, 2012.

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0272-6386/$36.00

http://dx.doi.org/10.1053/j.ajkd.2012.07.022

Am J Kidney Dis. 2012;xx(x):xxx
EPIDEMIOLOGY OF POSTTRANSPLANTATION BONE DISEASE

Posttransplantation osteoporosis is a common problem, with a prevalence of 11%-56% in long-term kidney transplant recipients. Bone loss is accelerated in the first 6-12 months after transplantation and predominantly involves trabecular bone. The reported rate of bone loss in the first 6 months ranges from 0.05%-14.5%; after 6 months, the rate varies from 0.01%-7.9%; and after 12 months, bone loss rates are reported to be 0.8%-9%. Bone loss in cortical bone, which is predominant in the femoral neck, is less pronounced. Almond et al found femoral neck bone loss to be 3.9% at 3 months in male transplant recipients. In contrast, Mikuls et al found minimal or no significant loss in the femoral neck during the first 6 months posttransplantation, and Smets et al showed that femoral BMD is stable after 6 months. Data regarding bone loss in long-term kidney transplant recipients (ie, >12 months posttransplantation) are conflicting, with some studies showing either less pronounced loss of bone or even a late increase in BMD, and others indicating ongoing bone loss.

Fracture rates after kidney transplantation have been reported to range from 5%-44%, with fracture episodes increasing over time after transplantation. Although posttransplantation fractures occur both peripherally and centrally, most studies demonstrate more fractures occurring at peripheral sites. Compared with dialysis patients on the waiting list, the relative risk of hip fracture in transplant recipients is 34% higher during the first 6 months posttransplantation and decreases by 0.8%–9% after 12 months, bone loss rates are reported to be 0.8%-9%. Posttransplantation diabetes is an important risk factor for posttransplantation fractures because diabetic patients receiving a kidney-pancreas transplant have fracture rates up to 49%. Posttransplantation fractures are associated with decreased survival, increased morbidity, and higher hospitalization rates compared with the general population. Risk factors for posttransplantation bone loss and fractures are summarized in Box 1. Decreased BMD posttransplantation does not necessarily predict the risk of fracture.

PATHOGENESIS OF POSTTRANSPLANTATION BONE DISEASE

Renal Osteodystrophy

Renal osteodystrophy is common, with 90%-100% of kidney transplant recipients having histologic evidence of osteodystrophy and osteopenia. High-turnover bone disease as a result of persistent hyperparathyroidism has been reported in 25%-50% of bone biopsies in kidney transplant recipients with varying degree of severity. Adynamic bone disease (characterized by decreased numbers of osteoblasts and osteoclasts and reduced bone turnover) is a much more common problem and accounts for 5%-50% of the bone pathology observed in kidney transplant recipients prior to the introduction of bisphosphonate treatment. Adynamic bone disease may be exacerbated further by the use of bisphosphonates after transplantation. Mixed uremic bone disease (characterized by a mixture of elements of both high and low bone turnover with a mineralization defect) accounts for ~12% of bone pathology after kidney transplantation. Osteomalacia (characterized by prolonged mineralization lag time and increased volume of osteoid in association with low osteoclast and osteoblast activities) is uncommon bone pathology in kidney transplant recipients, with a prevalence <5% even when hypophosphatemia is present.

<table>
<thead>
<tr>
<th>Factors Associated With Posttransplantation Bone Loss and Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of dialysis prior to transplantation</td>
</tr>
<tr>
<td>Cumulative dose of glucocorticoid</td>
</tr>
<tr>
<td>Younger age at transplantation</td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
</tr>
<tr>
<td>Functionally different alleles of the VDR gene</td>
</tr>
<tr>
<td>High and low pretransplantation PTH levels</td>
</tr>
<tr>
<td>BMI &lt;23 kg/m²</td>
</tr>
<tr>
<td>High serum FGF-23 level</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone; VDR, vitamin D receptor. aBMD levels posttransplantation are lower in the Bb and BB genotype groups than the bb group. bHigh pretransplantation PTH level, >500 pg/mL; low pretransplantation PTH level, <195 pg/mL.
Immunosuppressive Agents

Glucocorticoids are a main contributor to bone loss posttransplantation, particularly to the rapid loss occurring in the first 6-12 months, because they inhibit bone formation and enhance bone resorption. Table 1 lists the multifactorial effects of glucocorticoids and other immunosuppressant agents on bone.

<table>
<thead>
<tr>
<th>Immunosuppressive Agent</th>
<th>Effect on Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>Effect on osteoblasts: decreases bone formation by inducing apoptosis, inhibiting function, and decreasing collagen synthesis. Effect on osteoclasts: increases bone resorption through osteoclast activation by upregulation of RANKL/OPG; systemic effects include decreased gastrointestinal absorption of calcium, increased renal calcium wasting, increased PTH, hypogonadism, myopathy, avascular necrosis</td>
</tr>
<tr>
<td>Calcineurin inhibitors: cyclosporine and tacrolimus</td>
<td>Controversial effect: in vitro appears to inhibit bone resorption; in vivo appears to increase bone resorption, leading to bone formation</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>No effect</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No effect</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Controversial effect; in vitro appears to inhibit osteoclast differentiation</td>
</tr>
<tr>
<td>Evirolimus</td>
<td>Controversial effect; in vitro appears to inhibit osteoclast formation, activity, and differentiation</td>
</tr>
</tbody>
</table>

Abbreviations: OPG, osteoprotegerin; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-κB ligand.

Table 1. Effects of Immunosuppressive Agents on Bone

Changes in Bone Remodeling Posttransplantation

The primary changes to bone remodeling after kidney transplantation are a decrease in bone formation and mineralization as a consequence of alterations in osteoblast function, decreased osteoblastogenesis, and increased osteoblast apoptosis coupled with persistent bone resorption, resulting in bone loss. Rojas et al prospectively studied 20 kidney allograft recipients, performing bone biopsies on the day of transplantation and within 21-120 days after transplantation. They showed that osteoid and osteoblast surfaces decreased within 35 days of transplantation, with prolongation of mineralization lag time, consistent with decreased bone turnover. Resorptive and osteoclast surfaces remained above normal. Forty-five percent of patients showed early osteoblast apoptosis and a decrease in osteoblast surface and number. Osteoblast apoptosis was observed more often in patients with both low turnover and mixed bone disease than in patients with high turnover. The few bone biopsy studies that evaluated patients with long-term relatively normal functioning kidney transplants showed either a purely adynamic lesion as the predominant pathology or decreased bone formation with prolonged mineralization lag time (low turnover) with features of persistent bone resorption.

Changes in Mineral Metabolism Post–Kidney Transplantation

Calcidiol deficiency and insufficiency are common in kidney transplant recipients, with reported prevalences of 30% and 81%, respectively. The cause is multifactorial and may be secondary to nutritional deficiency, malabsorption, and decreased sun exposure. Moreover, the regaining of functioning nephron mass and subsequent increase in CYP27b1 (1α-hydroxylase) activity results in increased metabolism of calcidiol to calcitriol, which subsequently causes a gradual decrease in PTH concentrations during the first 3-6 months posttransplantation. However, persistent hyperparathyroidism still exists in ~33% and 20% of patients at 6 and 12 months posttransplantation, respectively. Contributory factors include the degree of parathyroid gland hyperplasia and/or nodularity coupled with downregulation of both the vitamin D receptor (VDR) and calcium-sensing receptor pretransplantation, as well as persistent CKD after transplantation. Concentrations of the phosphaturic hormone FGF-23 decrease immediately posttransplantation, although they remain inappropriately elevated in respect to the prevailing serum phosphate concentration. By about 3 months posttransplantation, FGF-23 concentrations are decreased by 89% and by 12 months, FGF-23 concentrations are appropriate for the CKD stage of the transplant. Elevated FGF-23 level results in an inhibition of CYP27B1 and likely contributes to the low levels of calcitriol in the early posttransplantation period, which may contribute to the persistent hyperparathyroidism seen after transplantation. The elevated FGF-23 and PTH and low calcitriol concentrations likely contribute to the hypophosphatemia observed in many patients after transplantation. Calcium levels typically decrease in the very early posttransplantation period as a result of cessation of VDR
activators (VDRAs) and calcium-containing phosphate binders. However, after that initial decrease, calcium concentrations progressively increase, with hypercalcemia developing in a substantial number of patients during the first to third months posttransplantation.\textsuperscript{77,78} Hypercalcemia can be transient, resolving by 6-8 months posttransplantation in some patients,\textsuperscript{79} but lasting for many years in others.\textsuperscript{80} Hypercalcemia typically is associated with hyperparathyroidism and results from enhanced renal tubular reabsorption of calcium under the influence of PTH in the functioning transplant, the effects of calcitriol on the gastrointestinal absorption of calcium, and potentially by a direct effect of PTH in causing calcium efflux from the bone. Low bone turnover with relatively low PTH levels also may result in hypercalcemia because the bone is not able to act as a buffer for the circulating calcium pool.

Relationship Between Bone Loss and Vascular Calcifications

In CKD, observational studies have shown a strong inverse correlation between BMD and cardiovascular morbidity, cardiovascular mortality, as well as vascular calcification.\textsuperscript{81,82} Moreover, calcium apatite forms the crystal component of bone and has been found to accumulate in calcified blood vessels of many patients with CKD, and calcified plaques also were shown to express several bone matrix proteins that stimulate vascular smooth muscle cells to differentiate to osteoblasts. These findings support an important interaction of bone disorders and calcification of soft tissues.\textsuperscript{83,84} In the early post–kidney transplantation period, observational studies have shown progression of both coronary and aortic vascular calcifications,\textsuperscript{80,85} a finding that possibly is linked to the accelerated bone loss in the same period and should be evaluated further in prospective studies.

SCREENING AND DIAGNOSIS OF POSTTRANSPLANTATION BONE DISEASE

Biochemical

Posttransplantation monitoring for alterations in bone and mineral metabolism is helpful to target treatment more effectively. In the immediate posttransplantation period (up to 8 weeks), KDIGO (Kidney Disease: Improving Global Outcomes) guidelines recommend weekly monitoring of serum calcium and phosphorus concentrations until levels normalize.\textsuperscript{86} After the immediate posttransplantation period (>8 weeks), serum calcium, phosphorus, and PTH levels should be followed up according to KDIGO CKD–Mineral and Bone Disorders 2009 guidelines (Table 2).\textsuperscript{86} Additionally, serum vitamin D levels should be checked in the early posttransplantation period.\textsuperscript{86} Measurement of PTH and biomarkers of bone formation (bone-specific alkaline phosphatase and osteocalcin) and bone resorption (urinary collagen breakdown products and TRAP5b) does not correlate with bone loss or predict bone histology.\textsuperscript{87} However, monitoring the trends of biomarkers over time may be suggestive of the bone turnover rate because they typically respond within days or weeks after initiation of antiresorptive therapy, with a faster response rate in biomarkers of bone resorption than of bone formation.\textsuperscript{88} Therefore, they may provide some guidance about whether therapy should be focused on increasing or decreasing bone turnover in the absence of a biopsy.

Radiographic

DEXA scans are a relatively accurate noninvasive cost-effective screening method of estimating bone mass with low exposure of radiation.\textsuperscript{89} Results of DEXA scans are interpreted according to the World Health Organization (WHO) classification of osteoporosis.\textsuperscript{80} It is important to note that the WHO classification was developed to predict fracture risk based on data extrapolated from white postmenopausal women.

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min/1.73 m\textsuperscript{2})</th>
<th>Measurement of PTH (pg/mL)</th>
<th>Measurement of Alkaline Phosphatase (U/L)</th>
<th>Measurement of Calcium and Phosphorus (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1T</td>
<td>&gt;90</td>
<td>Every 12 mo</td>
<td>Not recommended</td>
<td>Every 6-12 mo</td>
</tr>
<tr>
<td>2T</td>
<td>60-90</td>
<td>Every 12 mo</td>
<td>Not recommended</td>
<td>Every 6-12 mo</td>
</tr>
<tr>
<td>3T</td>
<td>30-59</td>
<td>Every 12 mo</td>
<td>Every 12 mo</td>
<td>Every 6-12 mo</td>
</tr>
<tr>
<td>4T</td>
<td>15-29</td>
<td>Every 6-12 mo</td>
<td>Every 12 mo</td>
<td>Every 3-6 mo</td>
</tr>
<tr>
<td>5T</td>
<td>&lt;15</td>
<td>Every 3-6 mo</td>
<td>Every 12 mo</td>
<td>Every 1-3 mo</td>
</tr>
</tbody>
</table>

*Note:* Conversion factors for units: serum calcium in mg/dL to mmol/L, × 0.2495; serum phosphorus in mg/dL to mmol/L, × 0.323.

*Abbreviations:* CKD, chronic kidney disease; GFR, glomerular filtration rate; PTH, intact parathyroid hormone; MBD, Mineral and Bone Disorder.

Based on data from Kidney Disease: Improving Global Outcomes Transplant Work Group.\textsuperscript{86}
This initial standardization of DEXA limits its applicability to many populations, including the transplantation population, as shown by the poor correlation between BMD and fracture risk in posttransplantation patients. Furthermore, BMD provides no information regarding bone quality or turnover and measurements may be skewed because of extraskeletal calcifications, osteosclerosis, and osteomalacia. Thus, the indication for DEXA scanning after transplantation is unclear. Nevertheless, it has been recommended that when patients have GFR >30 mL/min/1.73 m², DEXA scans may be obtained at the time of transplantation or within the first 3 months after transplantation, particularly if patients are receiving glucocorticoids or have other risk factors for rapid bone loss. DEXA scans can be repeated at 12-month intervals if BMD decreases by >5% or otherwise every 2 years to determine response to therapy and make decisions about whether therapy can be discontinued. BMD testing is of no proven benefit in predicting fracture risk in patients with eGFR <30 mL/min/1.73 m² and should not be performed routinely in this patient population. Results of a DEXA scan should be interpreted in the setting of clinical history, risk factors, bone biomarkers, and a bone biopsy, if possible. When fractures are suspected, lateral spine radiographs can be obtained to screen for spinal fragility fractures, either with or instead of DEXA scans.

Bone Biopsy

Bone biopsy is the gold standard for the identification and classification of posttransplantation bone disease. It involves histologic examination of undecalcified sections of bone from iliac crest with double tetracycline labeling. Biopsy is helpful to classify bone as having increased or decreased turnover, increased or decreased volume, or normal versus abnormal mineralization. Unfortunately, a biopsy is rarely obtained because of its invasive nature and the requirement of special expertise in obtaining and analyzing biopsy specimens. However, this should not prevent the use of bone biopsies. Bone biopsy should be considered to assist in the assessment and treatment of patients with multiple fractures or unexplained hypercalcemia. Furthermore, a biopsy may be helpful to rule out low turnover prior to the initiation of bisphosphonate therapy.

MANAGEMENT OF POSTTRANSPLANTATION BONE DISEASE

General Measures

Preventive measures for osteoporosis in the general population also apply to transplant recipients, including smoking cessation, decreased alcohol consumption, early mobilization after transplantation, fall risk reduction, and weight-bearing exercise. Cautious use of gonadal hormone replacement therapy for short periods in men and postmenopausal women with hypogonadism who do not have contraindications to hormone replacement therapy has been shown to slow the rate of bone loss in solid-organ transplant recipients. However, these therapies should not be considered first-line therapy because of increased risks of thrombotic events, cancer, and coronary artery disease. Various therapeutic strategies are listed in Tables 3 and 4, with the key therapeutic studies summarized in Tables 5 and 6.

Steroid Sparing and Steroid Withdrawal

The increasing use of steroid-sparing and steroid-withdrawal protocols has been associated with decreased bone loss, but with limited information for fracture risk. In a study of 57 simultaneous kidney-pancreas recipients who received steroid-sparing immunosuppression protocols, BMD measurements at 1 year showed improvement at the lumbar spine with stable BMD at the femoral neck. At 4 years, BMD had increased at both the lumbar spine and femoral neck. Steroid withdrawal 3 months after kidney transplantation was associated with decreased risk of osteoporosis, and steroid withdrawal 1 year after kidney transplantation was associated with improved BMD at the femoral neck, total hip, and lumbar spine. Unfortunately, there is no information about whether preservation of BMD results in fewer fractures, and data from observational studies for whether early corticosteroid withdrawal decreases fracture risk are conflicting. An observational study of 77,430 kidney transplant recipients with a median follow-up of 3.9 (range, 2.2-5.6) years showed that steroid withdrawal was associated with a 31% fracture risk reduction (hazard ratio, 0.69; 95% confidence interval, 0.59-0.81). Fracture incidence rates were significantly lower in recipients discharged without versus with steroid therapy (0.0058 vs 0.008 event/patient-year, respectively). However, in 175 solid-organ recipients with limited steroid exposure during the first 2-6 months after transplantation, Edwards et al found that 27% (32% kidney-pancreas recipients) developed fractures within 6 years. This fracture rate is similar to that previously reported in kidney-pancreas recipients who received steroids. The differences between these studies may be related to differences in the timing of steroid withdrawal. Further prospective comparative analyses are required to determine the impact of steroid-sparing regimens on subsequent fracture risk.
Calcium and Vitamin D Supplementation

Calcidiol deficiency is a prevalent problem in transplant patients. The effects of correcting calcidiol deficiency on BMD in transplant recipients remain controversial. Wissing et al. showed that although cholecalciferol supplementation (25,000 IU/mo) contributed to normalization of PTH levels, it did not prevent posttransplantation bone loss, whereas Sahin et al. showed that oral administration of 400 IU/d of cholecalciferol with 600 mg/d of calcium for 1 year resulted in improved PTH levels and a significant increase in femoral neck BMD. Thus, treatment of calcidiol deficiency with either cholecalciferol or ergocalciferol appears reasonable given the effects on improving calcium balance, decreasing PTH levels, and potential beneficial effects on immune and endocrine functions.

VDR Activators

VDRAs may influence posttransplantation mineral bone disease by several mechanisms. VDRA administration reverses the glucocorticoid-induced decrease in intestinal calcium absorption, directly suppresses PTH secretion, promotes differentiation of osteoblast precursors into mature cells, and increases the intestinal absorption of calcium and phosphorus. Several studies have shown that oral calcitriol decreases PTH concentrations in the posttransplantation period. Other studies show that calcitriol and other VDRAs improve BMD after kidney transplantation. However, these studies did not evaluate clinically important outcomes such as mortality, hospitalizations, or fractures. However, VDRA use has been associated with prolongation of transplant survival. We recommend the use of VDRAs to prevent bone loss in patients with osteopenia (T score, −1 to −2.5) or osteoporosis (T score less than −2.5) who have evidence of low turnover as confirmed by bone biopsy or suggested by bone biomarkers because bisphosphonate use should be avoided. VDRA use in this patient population has been shown to preserve BMD for up to 12 months. Furthermore, VDRAs should be considered in patients with normal BMD and no history of fragility fractures because bone loss is accelerated in the early posttransplantation period. In addition, the use of VDRAs to potentially prevent bone loss in patients with eGFR <30 mL/min and secondary hyperparathyroidism without hypercalcemia appears to be reasonable (Table 4). Frequent monitoring of serum calcium, phosphate, and PTH levels are warranted with the use of VDRAs.

Table 3. Therapies for Posttransplantation Bone Disease

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism of Action</th>
<th>Effect on PTH</th>
<th>Effect on BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid sparing/withdrawal</td>
<td>Improve bone formation; improve calcium absorption; improve vitamin D metabolism</td>
<td>Possible decrease</td>
<td>Decreased loss</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Nutritional vitamin D replacement; improve calcium absorption</td>
<td>Decrease</td>
<td>Possible decreased loss</td>
</tr>
<tr>
<td>Calcitriol and VDRA</td>
<td>Directly decreases PTH synthesis and increases intestinal absorption of calcium</td>
<td>Decrease</td>
<td>Decreased loss</td>
</tr>
<tr>
<td>Phosphorus replacement</td>
<td>Increase serum phosphorus</td>
<td>Unclear</td>
<td>None</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Inhibit osteoclastic bone resorption</td>
<td>Possible increase</td>
<td>Decreased loss and possible net increase</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Inhibit osteoclastic bone resorption</td>
<td>None</td>
<td>Decreased trabecular bone loss</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>Allosterically modify CaSR, increasing sensitivity to extracellular calcium</td>
<td>Decrease</td>
<td>Decreased loss</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>Recombinant human PTH with anabolic bone effects</td>
<td>Unclear</td>
<td>May increase cortical bone</td>
</tr>
<tr>
<td>Denosumab</td>
<td>Humanized monoclonal antibody that blocks RANKL</td>
<td>Increase</td>
<td>Decreased loss; may increase</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>Surgical removal of parathyroid gland</td>
<td>Decrease</td>
<td>Decreased loss</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; CaSR, calcium sensing receptor; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-xB ligand; VDRA, vitamin D receptor activator.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Indications</th>
<th>Effect on BMD</th>
<th>Level of Evidence for Effect on BMD</th>
<th>Effect on Bone Fracture</th>
<th>Level of Evidence for Effect on Bone Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>Kidney transplant recipients with eGFR &gt;30 mL/min/1.73 m² who have osteopenia or osteoporosis in first 12 mo posttransplantation, after excluding low-turnover bone disease; kidney transplant recipients with eGFR &gt;30 mL/min/1.73 m² who have normal BMD and are at high risk of fractures (Box 1), after excluding low bone turnover</td>
<td>Improves femoral neck and lumbar spine BMD</td>
<td>Level I/A; validated from randomized trials</td>
<td>May decrease fracture risk</td>
<td>Level II-3/C; based on meta-analysis</td>
</tr>
<tr>
<td>VDRA</td>
<td>Persistent posttransplantation hyperparathyroidism with low calcium levels that cannot be treated with calcitriol; prevention of bone loss in kidney transplant recipients with eGFR &lt;30 mL/min/1.73 m² who have hyperparathyroidism without hypercalcemia; kidney transplant recipients with eGFR &gt;30 mL/min/1.73 m² who have osteopenia or osteoporosis in first 12 mo posttransplantation, and have low-turnover bone disease confirmed by biopsy or suggested by trend of bone biomarkers</td>
<td>Improves femoral neck and lumbar spine BMD</td>
<td>Level I/A; validated from randomized trials</td>
<td>May decrease fracture risk</td>
<td>Level II-3/C; based on meta-analysis</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Persistent posttransplantation hyperparathyroidism with hypercalcemia (off-label use)</td>
<td>Improves BMD</td>
<td>Level III/B; based on observational descriptive study</td>
<td>Unknown</td>
<td>NA</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>Persistent posttransplantation hyperparathyroidism with (1) parathyroid hyperplasia, (2) hypercalcemia, (3) unexplained or worsening transplant function, (4) symptomatic bone disease or spontaneous fracture, vascular calcification, calciphylaxis</td>
<td>Improves BMD</td>
<td>Level III/C; based on observational descriptive study</td>
<td>Unknown</td>
<td>NA</td>
</tr>
</tbody>
</table>

Note: Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667.

Abbreviations: BMD, bone mineral density; eGFR, estimated glomerular filtration rate; NA, not applicable; VDRA, vitamin D receptor activator.
alization by increasing osteoblast apoptosis, impairing osteoblast activity, and inhibiting osteoblast proliferation. Therapy for hypophosphatemia should not be overaggressive because phosphate replacement can result in hypocalcemia by physiochemical binding, persistent hyperparathyroidism, hyperphosphatemia, and calcitriol deficiency and increase the risk of nephrocalcinosis and acute phosphate nephropathy. Until more data become available regarding the risks and/or benefits, we recommend cautious phosphate repletion when serum levels are less than 1-1.5 mg/dL or patients are symptomatic.

**Bisphosphonates**

Bisphosphonates induce osteoclastic apoptosis, reduce osteoclastic activity, and result in decreased bone resorption. Studies have shown that oral (risedronate, alendronate, and ibandronate) and intravenous (ibandronate, zolecronic acid, and pamidronate) bisphosphonates preserve BMD in the lumbar spine and femoral neck in the early posttransplantation period. However, there is a lack of evidence that bisphosphonates decrease fracture risk in kidney transplant recipients. This may be secondary to the unpowered nature of these studies. Furthermore, because bone biopsies are not performed routinely after kidney transplantation and levels of PTH and bone turnover biomarkers are not reflective of bone histology, it is clinically challenging to avoid bisphosphonate use in patients with pre-existing adynamic bone disease. This inadvertent use of bisphosphonates could be detrimental and partially responsible for the lack of decrease in the incidence of fractures after bisphosphonate treatment. A small retrospective cohort study of self-reported fractures in

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groz et al (^{12}) (2001)</td>
<td>80</td>
<td>Prospective placebo controlled; kidney recipients received either ibandronate or placebo at 3, 6, and 9 mo posttransplantation vs control group</td>
<td>Less bone loss, spinal deformation, and loss of body height in the ibandronate group during first y posttransplantation</td>
</tr>
<tr>
<td>Fan et al (^{12,113}) (2000, 2003)</td>
<td>26</td>
<td>Prospective placebo controlled; kidney recipients received either IV pamidronate or placebo at time of transplantation and 1 mo later; 17 patients had second DEXA at 4 y</td>
<td>Preserved BMD at lumbar spine and femoral neck in pamidronate group vs increased loss of BMD in placebo group during first y posttransplantation; preserved BMD at femoral neck in 4 y in pamidronate-treated group</td>
</tr>
<tr>
<td>Haas et al (^{116}) (2003)</td>
<td>43</td>
<td>Prospective placebo controlled; kidney recipients received either zoledronic acid or placebo at baseline and within 3-6 mo after transplantation</td>
<td>Improved BMD in lumbar spine, stable BMD in femoral neck, no increased risk of adynamic bone disease in the zoledronic acid–treated group</td>
</tr>
<tr>
<td>Coco et al (^{52}) (2003)</td>
<td>20</td>
<td>Prospective, controlled; kidney recipients received either pamidronate at 1, 2, 3, 6 mo plus daily vitamin D/Ca (^{1,2}) vs vitamin D/Ca (^{2})</td>
<td>Preserved BMD in vertebral spine at 6 and 12 mo with increased risk of adynamic bone disease in pamidronate-treated group (all patients in pamidronate group vs 50% in control group)</td>
</tr>
<tr>
<td>Jeffery et al (^{111}) (2003)</td>
<td>117</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline received either daily alendronate and Ca (^{1,2}) or calcitriol and Ca (^{2})</td>
<td>Improved BMD in lumbar spine and femoral neck in both groups, superior effect of alendronate on spine BMD</td>
</tr>
<tr>
<td>El-Agroudy et al (^{110}) (2005)</td>
<td>60</td>
<td>Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate or alfacalcidol or calcitonin vs control</td>
<td>Alfacalcidol and alendronate improved BMD at both lumbar spine and femoral neck, while calcitonin improved BMD in lumbar spine only</td>
</tr>
<tr>
<td>Nowacka-Cleciura et al (^{114}) (2006)</td>
<td>66</td>
<td>Prospective, controlled; kidney recipients with osteopenia or osteoporosis at baseline received either alendronate or risendronate or were drug free</td>
<td>Improved BMD in femoral neck in bisphosphonate-treated group at 12 mo</td>
</tr>
<tr>
<td>Torregrosa et al (^{118}) (2007)</td>
<td>84</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline treated either weekly risendronate + daily vitamin D/Ca (^{1,2}) or vitamin D/Ca (^{2}) only</td>
<td>Increased BMD in lumbar spine at 1 y in risendronate-treated group</td>
</tr>
<tr>
<td>Abediazar &amp; Nahkivani (^{117}) (2011)</td>
<td>43</td>
<td>Prospective, controlled; kidney recipients with osteopenia at baseline were randomly assigned to either weekly alendronate + daily vitamin D or daily vitamin D only</td>
<td>Alendronate increased BMD in distal radius and lumbar spine at 1 y</td>
</tr>
</tbody>
</table>

Abbreviations: BMD, bone mineral density; Ca \(^{1,2}\), calcium; DEXA, dual-energy x-ray absorptiometry; IV, intravenous.
solid-organ transplant recipients treated with steroid-sparing protocols showed that bisphosphonate use was associated with lower risk of self-reported fractures. However, Coco et al demonstrated that pamidronate use was associated with preservation of BMD at both the femoral neck and lumbar spine, although there was an increase in biopsy-proven adynamic bone disease after 6 months compared to placebo. It is unknown whether the increase in adynamic bone was detrimental or the increase in BMD decreased the fracture risk.

In contrast, Haas et al found that patients who received 2 doses of zoledronic acid within 3 months of transplantation did not develop adynamic bone disease on bone biopsies performed after 6 months. Zoledronic acid also was associated with an increase in lumbar spine and stabilization of femoral BMD. The differences between studies may be related to differences in bisphosphonate compounds, the relatively lower dosing of the zoledronic acid, or the timing of the bone biopsies relative to treatment. Conley et al demonstrated that bisphosphonate use initiated after the first year after transplantation was associated with preservation of BMD at the femoral neck, yet no association was observed between femoral neck bone loss and fractures, either with or without bisphosphonate therapy. Palmer et al performed a meta-analysis of 24 trials evaluating the use of bisphosphonates, VDRAs, and calcitonin in preventing posttransplantation bone loss. All the interventions improved BMD; however, none of the therapies was found to prevent fracture. The latter finding may be because none of these trials was powered to detect a reduction in fracture risk. Head-to-head comparison in 2 studies showed that bisphosphonates were superior to calcitriol in preserving BMD. The use of either bisphosphonates or calcitriol provided substantial and clinically significant prevention of reducing the risk of fracture.

### Table 6. Studies Reporting Effects of Cinacalcet Use in Treatment of Posttransplantation Hyperparathyroidism and Hypercalcemia

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kruse et al</td>
<td>14</td>
<td>Prospective; cinacalcet dose 30 mg daily for 3 mo</td>
<td>No effect on PTH; 11.8% decrease in serum Ca; no effect on phosphorus; some reduction in kidney function</td>
</tr>
<tr>
<td>Serra et al</td>
<td>11</td>
<td>Prospective; cinacalcet dose 30 mg daily titrated for normocalcemia for 10 wk</td>
<td>21.8% decrease in PTH; 9.5% decrease in serum Ca; 17% increase in serum phosphorus</td>
</tr>
<tr>
<td>Serra et al</td>
<td>12</td>
<td>Prospective; cinacalcet dose 30 mg daily titrated for normocalcemia for 12 wk</td>
<td>30% decrease in PTH; 11.7% decrease in serum Ca; 20% increase in serum phosphorus</td>
</tr>
<tr>
<td>Serra et al</td>
<td>10</td>
<td>Prospective; cinacalcet dose 30-60 mg daily for 2 wk</td>
<td>60% decrease in PTH; decreased renal phosphorus excretion in the first 8 h by 30%-40%; normalization of serum phosphorus; decrease in FGF-23</td>
</tr>
<tr>
<td>Leca et al</td>
<td>10</td>
<td>Prospective; cinacalcet dose 30 mg daily titrated to a maximum of 60 mg for 6 mo</td>
<td>50% decrease in PTH; 12.7% decrease in serum Ca; 18.5% increase in phosphorus</td>
</tr>
<tr>
<td>Srinivas et al</td>
<td>11</td>
<td>Prospective; cinacalcet dose 30 mg daily for 3-12 mo</td>
<td>Downward trend in PTH; 14.6% decrease in serum Ca; 12% increase in serum phosphorus</td>
</tr>
<tr>
<td>Szwarc et al</td>
<td>9</td>
<td>Prospective; cinacalcet dose 30 mg daily titrated to normocalcemia for 6 mo</td>
<td>22% decrease in PTH; 12% decrease in serum Ca; trend to increase in serum phosphorus</td>
</tr>
<tr>
<td>El-Amm et al</td>
<td>18</td>
<td>Retrospective; cinacalcet dose 30-180 mg of cinacalcet for 6 mo</td>
<td>42% decrease in PTH; 8% decrease in serum Ca; 11% increase in serum phosphorus</td>
</tr>
<tr>
<td>Bergua et al</td>
<td>9</td>
<td>Prospective; cinacalcet dose 30 mg, titrated for normocalcemia for up to 12 mo</td>
<td>40% decrease in PTH; 14% decrease in serum Ca; trend to increase in serum phosphorus</td>
</tr>
<tr>
<td>Gomez et al</td>
<td>48</td>
<td>Retrospective; cinacalcet dose 30-180 mg for 1 y</td>
<td>42% decrease in PTH; 9% decrease in serum Ca</td>
</tr>
<tr>
<td>Cho et al</td>
<td>8 in cinacalcet group, 15 controls</td>
<td>Retrospective; case-control study; cinacalcet therapy for &gt;12 mo; outcome BMD changes from baseline to 12, 24, and 36 mo posttransplantation</td>
<td>Increased BMD in femoral neck at 36 mo posttransplantation</td>
</tr>
<tr>
<td>Copley et al</td>
<td>31</td>
<td>Retrospective; cinacalcet dose 30-240 mg daily for ≥3 mo</td>
<td>21.8% decrease in PTH; 6.8% decrease in serum Ca; 10% increase in serum phosphorus</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMD, bone mineral density; Ca, calcium; FGF-23, fibroblast growth factor 23; PTH, parathyroid hormone.
bone loss in both the femoral neck and lumbar spine in comparison to control, whereas calcitonin did not improve femoral neck BMD. Stein et al. performed a meta-analysis of 11 trials evaluating 780 solid-organ transplant recipients (42% kidney recipients) who received either bisphosphonates or VDRAs within the first 12 months posttransplantation. This analysis showed that use of bisphosphonates or VDRAs was associated with reduced fractures. Differences in the outcomes between Palmer et al. and the Stein et al. meta-analyses are related to differences in the methodology, study populations, timing of therapy, and most importantly, frequency of reported fractures in both analyses because in the Palmer et al. review, only 11 of 24 studies (34/514 patients) had reported fracture data, whereas in the Stein et al. study, 134 fracture incidents were reported. These data support the notion that preventive therapy with either bisphosphonates or VDRAs likely is better than no therapy in terms of preventing posttransplantation bone loss and possibly fractures.

In our opinion, bisphosphonates are well tolerated, reasonably safe, and effective for the prevention and management of posttransplantation bone loss when dosed appropriately and used for limited periods after excluding low bone turnover. There have not been direct studies comparing the antiresorptive efficacy of different bisphosphonates or intravenous versus oral bisphosphonates in the posttransplantation period. Intravenous bisphosphonates can be used as an alternative in patients who cannot tolerate the oral regimen or who are nonadherent. It should be noted that studies of bisphosphonate use in the posttransplantation period have not been powered to detect fracture risk reduction. Bisphosphonates should be avoided in patients with eGFR <30 mL/min/1.73 m² secondary to the prolonged half-life, potential risk of adynamic bone disease and subsequently increased fracture risk, or the possibility of acute worsening in kidney function. In patients with eGFR >30-35 mL/min/1.73 m², bisphosphonates can be used cautiously in the first 12 months posttransplantation for patients with osteopenia or osteoporosis or patients with normal BMD who are at high risk of fractures (Table 4), especially if on a steroid-based immunosuppression protocol, after excluding low bone turnover. There is no consensus about duration of therapy. Because bone loss is pronounced mainly in the first year posttransplantation and BMD begins to recover in many patients after the first year, 12-18 months of therapy should be sufficient for most patients.

Calcimimetics

Calcimimetics allosterically increase sensitivity of the calcium-sensing receptor in the parathyroid gland to calcium and suppress PTH. Cinacalcet has been shown to be beneficial in correcting hypercalcemia and hyperparathyroidism in multiple trials in kidney transplant recipients (Table 6). In a multicenter retrospective analysis of transplant recipients with secondary hyperparathyroidism, Copley et al. showed that cinacalcet use was associated with a 21.8% decrease in PTH level, 6.8% decrease in serum calcium level, and 10% increase in serum phosphorus level. Findings in all the other studies are consistent with this observation. None of these studies had a control group or was able to differentiate between persistent secondary hyperparathyroidism or autonomous tertiary hyperparathyroidism; none provided measures of parathyroid gland size or information about whether these patients were resistant to VDRA therapy. In a study that discontinued cinacalcet therapy after 6 months, both calcium and PTH concentrations rebounded to elevated levels after withdrawal, whereas in another study in which cinacalcet therapy was stopped after 12 months, most patients maintained lower concentrations of calcium and PTH. This raises questions about whether the persistent hyperparathyroidism would resolve without intervention in some patients, as well as how long calcimimetic intervention is necessary. Cho et al. demonstrated that cinacalcet therapy also was associated with improved BMD 36 months post–kidney transplantation, with a significant reduction in calcium levels in patients with persistent secondary hyperparathyroidism. Observations regarding the effects of calcimimetics on kidney transplant function are contradictory. Some studies indicate that it may be associated with a slight decrease in kidney function, whereas others show no difference in serum creatinine levels. There have been 3 case reports in the literature in which cinacalcet may be associated with nephrocalcinosis and transplant failure. However Courbebaisse et al. evaluated 71 kidney recipients with hypercalcemic hyperparathyroidism in which 34 patients received cinacalcet between months 3 and 12 after kidney transplantation. Cinacalcet use was associated with more significant reductions in PTH level, hypocalemia, increased serum phosphorus level, hypercalcemia, and hypophosphatemia in comparison to the noncinacalcet group, with no adverse effects on GFR or kidney transplant calcium phosphate deposition.

Prospective studies, such as the 2 ongoing studies (Treatment of Autonomous Hyperparathyroidism in Post Renal Transplant Recipients [ClinicalTrials.gov number NCT00975000] and A Prospective, Randomized Trial to Compare Subtotal Parathyroidectomy Versus Cinacalcet in the Treatment of Persistent Secondary Hyperparathyroidism Post Renal Transplantation...
tion [NCT01178450]), are required to evaluate the role of cinacalcet therapy and whether it is beneficial over parathyroidectomy.

**Parathyroidectomy**

On average, 0.5%-5% of transplant recipients with persistent hyperparathyroidism ultimately will require parathyroidectomy.\(^1\)\(^3\)\(^7\)\(^8\)\(^1\)\(^3\)\(^8\)\(^1\)\(^5\)\(^8\) Indications include symptomatic or severe hypercalcemia, symptomatic bone disease or spontaneous fracture, vascular calcification, calciphylaxis, or persistent hyperparathyroidism for more than 1 year after transplantation. Parathyroidectomy results in an abrupt decrease in serum PTH and calcium concentrations and an increase in serum phosphorus level. In some studies, parathyroidectomy has been reported to be associated with worsening transplant function.\(^1\)\(^3\)\(^8\)\(^1\)\(^5\)\(^9\) However, at least one study showed that parathyroidectomy did not affect transplant survival at 3 years.\(^1\)\(^3\)\(^9\) In a retrospective analysis of parathyroidectomy for tertiary hyperparathyroidism in kidney transplant recipients, BMD significantly improved in both the hip and spine.\(^1\)\(^4\)\(^0\) The effects of parathyroidectomy on fracture risk and whether medical treatment with calcimimetics is an appropriate alternative to surgery await further clinical studies.

**Teriparatide**

Teriparatide is a recombinant human PTH (comprising amino acids 1-34) that has anabolic bone effects when administered intermittently in the general population. Teriparatide is shown to reduce fracture risk in postmenopausal women receiving glucocorticoids.\(^1\)\(^3\)\(^2\) One study showed that teriparatide administered for 6 months was safe but did not alter BMD compared with the placebo group; however, the study was underpowered.\(^1\)\(^3\)\(^3\) In 2 reports, one a single case and the other a case series of 5 kidney transplant recipients with a history of pretransplantation parathyroidectomy who developed refractory hypocalcemia in their early posttransplantation course, teriparatide therapy led to faster normalization of calcium levels, permitted earlier suspension of intravenous calcium supplementation, and reduced calcitriol requirements.\(^1\)\(^3\)\(^4\)\(^1\)\(^3\)\(^5\)

**Potential New Therapies**

Denosumab is a fully humanized monoclonal antibody that inhibits the formation, function, and survival of osteoclasts, preventing interaction of RANKL (receptor activator of nuclear factor-κB ligand) with RANK. The use of denosumab causes a reduction in osteoclast formation and thus decreased bone resorption and an increase in BMD. In a study of osteoporosis in postmenopausal women, denosumab was found to be safe and was associated with improved BMD and decreased fracture risk.\(^1\)\(^3\)\(^6\) even in a cohort of patients with varying degrees of kidney function.\(^1\)\(^6\)\(^0\) Odanacatib is a selective, potent, and reversible inhibitor of cathepsin K that inhibits bone loss in mice.\(^1\)\(^6\)\(^1\) The antiresorptive properties of odanacatib have been evaluated in phase 1 and 2 clinical trials, and phase 3 studies currently are underway. Both these agents have the potential to prevent posttransplantation fractures. However, there presently are no studies evaluating their use in the transplantation population.

**CONCLUSIONS**

In summary, complex abnormalities of mineral homeostasis and bone remodeling in the posttransplantation period result in loss of BMD, with an increase in bone fragility and fractures. Although decreases in BMD may predict fracture risk in many different patient populations, low BMD in kidney transplant recipients does not appear to differentiate patients at risk of fracture. Other metabolic factors influence both BMD and quality, resulting in decreased bone strength, which predisposes the transplant recipient to increased fracture risk. All transplant recipients should be evaluated for metabolic disorders and monitored for ongoing bone loss. Management of posttransplantation bone disease is challenging, but initially should focus on correcting metabolic disorders. The use of bone biopsy may add important information to aid in the choice of treatment. Although multiple studies have shown that different interventions may slow bone loss and improve BMD, no therapy has yet been shown to reduce fracture risk. With the lack of sufficient prospective studies evaluating currently available therapies, clinical judgment must serve as the guiding principle to evaluate the risk-benefit of specific therapies for preventing bone loss and fractures.

**CASE REVIEW**

The index case presented a common scenario encountered in the transplant clinic. She was a postmenopausal kidney transplant recipient who had lumbar spine osteoporosis and worsening femoral osteopenia with stage 3 CKD, mild hyperparathyroidism, and prior vitamin D deficiency. She had multiple risk factors that increased her risk of bone loss and fractures, including advanced age, female sex, early menopause, high cumulative dose of steroids, effects of cyclosporine on osteogenesis, and persistent hyperparathyroidism. A bone biopsy was performed (Fig 1), which was diagnostic for adynamic bone disease.

Pretransplantation osteodystrophy, in addition to advanced CKD (eGFR, 40 ml/min/1.73 m\(^2\)), long-term steroid use, and long-term use of bisphosphonate therapy (alendronate for 6 years), likely contributed to her adynamic bone disease. Based on biopsy results,
alendronate therapy was discontinued, nutritional vitamin D treatment was continued, and low-dose calcitriol therapy was initiated. Unfortunately, there is little evidence to support the use of the other currently available therapies; thus, no other specific treatment was instituted.

ACKNOWLEDGEMENTS

Support: None.
Financial Disclosure: The authors declare that they have no relevant financial interests.

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Figure 1. Bone biopsy in index case shows low bone turnover, defective mineralization, and decreased bone volume. Low-power view shows (A) loss of connectivity, thinned trabeculae, and now marrow fibrosis; (B-D) minimal osteoid accumulation, markedly decreased, osteoblasts, osteoclasts, or evidence of resorption; and (E, F) minimal tetracycline uptake; thus, a low bone formation rate.
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