Bone Disease After Kidney Transplantation

By Stuart M. Sprague and Michelle A. Josephson

Kidney transplantation is the optimal form of renal replacement therapy for many with end-stage kidney disease. However, kidney transplantation comes with a unique set of medical complications, important among them is bone disease. Posttransplant bone disorders are manifestations of pathologic processes occurring posttransplant that are superimposed on preexisting disorders of bone and mineral metabolism secondary to kidney failure and/or diabetes mellitus. As a consequence of early rapid bone loss, which is seen commonly within the first 3 to 6 months of transplant, the fracture risk posttransplant increases and has been reported as high as 5% to 44%. Posttransplant fractures occur more commonly at peripheral than central sites. Patients with a history of diabetes mellitus are at particular risk for fracture. Parathyroid hormone (PTH) and osteocalcin levels generally decrease after transplantation. Alkaline phosphatase and urinary collagen cross-links are unpredictable. Bone histology varies. No single biomarker unequivocally distinguishes between the various bone disorders found on biopsy examination. Immunosuppression is a major cause of posttransplant bone disorders. Glucocorticoids lead to decreased bone formation whereas the calcineurin inhibitors appear to cause increased bone turnover. Evaluating and managing posttransplant bone disease is an integral part of posttransplant medical care.

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**KIDNEY TRANSPLANTATION** is the optimal form of renal replacement therapy. Improvement in immunosuppressive therapy has increased allograft survival; however, this enhanced survival has led to the emergence of and appreciation of transplant complications such as bone disease. Bone and mineral disorders are a universal complication in patients with chronic kidney disease before transplantation. Several different pathogenetic mechanisms may be involved that may ultimately lead to one or more types of bone disease including osteitis fibrosa cystica as a result of secondary hyperparathyroidism, some form of low turnover bone disease (osteomalacia, dynamic bone disease, and aluminum bone disease), osteoporosis, osteosclerosis, and β2-microglobulin amyloidosis. In addition, hypogonadism, metabolic acidosis, and certain medications (loop diuretics, heparin, glucocorticoids, anti-epileptics, or cyclosporine) also may affect bone health. Superimposed on these underlying bone diseases are disorders of mineral metabolism, which occur after successful transplantation and include the effects of medications, persistence of underlying disorders, development of hyperphosphaturia, and the recurrence of varying degrees of renal insufficiency. These disorders of mineral metabolism and the associated bone disease lead to the development of fractures after transplantation.

**FRACTURES AFTER TRANSPLANTATION**

Patients with chronic kidney disease before transplantation are at increased risk for fracture, with vertebral fracture prevalence as high as 21% and the relative risk for hip fracture increased by 2- to 14-fold. Fracture risk is increased with older age, female sex, Caucasian race, duration of dialysis, diabetic nephropathy, peripheral vascular disease, low spine bone mineral density (BMD), and lower parathyroid hormone (PTH) levels. After successful kidney transplantation, studies report fracture rates between 5% and 44%. The causes of this wide range of reported fracture rates are many, including whether the fracture data was obtained by questionnaire or patient encounter. The variation likely also reflects differences in posttransplant timing of the studies. As shown in Figure 1 ($r = .7; P = .03$), the more time since transplantation, the higher the reported fracture rate. The spread also may be attributed to the fraction of transplant recipients with diabetes mellitus in the various studies. Patients with diabetes receiving a kidney-pancreas transplant have fracture rates as high as 40% and 49% posttransplantation. As shown in Table 1, the fracture risk is markedly higher for kidney and kidney-pancreas transplant recipients than the general population. The magnitude of the increased fracture risk faced by the transplant recipient also can be appreciated.
when comparing hospitalizations for fracture. Abbot et al\textsuperscript{17} found that in 33,479 transplant recipients who were 3 or less years posttransplant, the relative risk for being hospitalized for a fracture was 4.59 compared with the general population.

Risk factors identified for fracture include duration of hemodialysis before transplant,\textsuperscript{12} time since transplant,\textsuperscript{12} female sex (particularly if postmenopausal),\textsuperscript{10,12} BMD scores below the normal range,\textsuperscript{10} kidney failure from diabetes,\textsuperscript{10} history of fracture before transplant,\textsuperscript{10} and age greater than 45 years.\textsuperscript{4} In contrast, obesity was associated with a decreased risk for fracture.\textsuperscript{10} In addition, having a low BMD puts a recipient at increased risk for fracture, however, many patients with low BMDs do not experience a fracture, thus BMD does not discriminate between those who will and will not fracture.\textsuperscript{10} Posttransplant fractures occur both peripherally (feet and ankles) and centrally (in the ribs, hip, or vertebrae), whereas 6 studies have documented a higher fracture rate at peripheral sites.\textsuperscript{4,7-10,16} Patients with a history of diabetes mellitus are at particular risk for peripheral fractures.\textsuperscript{16}

**BMD**

Patients with chronic kidney disease have an increased prevalence of low BMD at the spine, hip, and distal radius. Risk factors for a low BMD include female sex, Caucasian race, amenorrhea, lower weight or body mass index, increased PTH level, duration of hemodialysis, and previous kidney transplantation. Recipients of either kidney or combined kidney-pancreas allografts rapidly lose bone after transplantation.\textsuperscript{16-36} Decreases in BMD, measured by dual x-ray absorptiometry scans, have been observed as early as 3 to 6 months after transplant. Almond et al\textsuperscript{34} found a 3.93% decrease in femoral neck BMD in male transplant recipients at 3 months. Julian et al\textsuperscript{32} observed a lumbar spine BMD decrease of 6.8% at 6 months. Investigators who have obtained serial BMD scans at both the lumbar spine (mainly trabecular bone) and femoral neck (predominately cortical bone) have found bone loss at both sites.\textsuperscript{18,25,27,28,33-36} In contrast to these findings, a few investigators have not documented BMD loss after transplantation and have attributed their results to differing effects of immunosuppression (cyclosporine had a beneficial effect compared with azathioprine,\textsuperscript{20} deflazacort was associated with less bone loss than prednisone,\textsuperscript{23,24} and tacrolimus-treated patients gained bone, whereas cyclosporine-treated patients lost bone\textsuperscript{31}) or the influence of the vitamin D receptor genotype bb.\textsuperscript{21} Risk factors for posttransplant bone loss have been identified, but not all studies implicate the same ones. These risks include total glucocorticoid exposure,\textsuperscript{12,20,22,37,38} dialysis duration

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**Table 1. Age and Gender-Specific Initial Fracture Estimated Relative Risk Compared with General Population in Kidney and Kidney-Pancreas Transplant Recipients Surviving at Least 30 Days**

<table>
<thead>
<tr>
<th>Age In Years</th>
<th>Women K TX Recipients-RR</th>
<th>Men K TX Recipients-RR</th>
<th>Women KP TX Recipients-RR</th>
<th>Men KP TX Recipients-RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>18.51</td>
<td>4.74</td>
<td>38.63</td>
<td>13.19</td>
</tr>
<tr>
<td>45-64</td>
<td>34.03</td>
<td>4.88</td>
<td>54.91</td>
<td>80.73</td>
</tr>
</tbody>
</table>

Abbreviations: K, kidney alone; TX, transplant; RR, estimated relative risk; KP, kidney-pancreas.

Data from reference 6.
Some investigators have identified increasing time since transplantation as a risk and yet others examining BMD trends 2 or more years posttransplant have not shown continued bone loss. In 12 such studies several years posttransplant, 3 did not show a significant decrease, 22,36,41 6 noted improvements in BMD, 19,27,38,42-44 one showed a slight improvement in the lumbar spine accompanied by a small decline at the femoral neck, 45 and 2 found that although some patients improve, some patients worsen. 46,47 The researchers of one of these last 2 studies found that allograft recipients with declining bone density scores differed from those with stable bone densities. The former had biomarkers indicating a high turnover bone state whereas the latter did not. 46 However, despite the improvements in BMD that some studies have shown after the first year posttransplantation, most studies show that BMDs measured up to 12 years posttransplantation remain low. 11,30,36,40,44,46-57

BONE BIOMARKERS

As shown in Figure 2, the majority of studies evaluating PTH trends posttransplant show that PTH levels decrease after transplantation. 22,24,31,35,41,43,55,58-63 Of these 13 studies, 8 note that despite the decrease, levels remain increased. 22,35,41,55,58-60,63 At least one study found that an increased PTH concentration was associated with decreasing bone density, although this has not been observed uniformly. 51,64

As depicted in Figure 2, alkaline phosphatase levels have an unpredictable trend posttransplantation. 22,24,31,35,41,43,58,61,65-69 Of 6 cross-sectional studies, 2 noted that levels were higher than normal posttransplant, 52,70 whereas 4 found no difference from control. 51,54,71,72 Steroid use has been associated with an alkaline phosphatase decrease. 13,66 Whether alkaline phosphatase helps predict the risk for bone loss is unclear. One study found no correlation between alkaline phosphatase levels and bone loss at the lumbar spine, 43 but another found that increased alkaline phosphatase levels correlated with low femoral neck BMDs. 13

At least 5 studies have shown osteocalcin decreases with time posttransplantation (Fig 2). 35,58,63,65,68 Several studies have found an association between trends in osteocalcin and PTH levels. 54,59,73-75 Most cross-sectional studies note that osteocalcin is increased posttransplant, 24,52,54,71,72,74 whereas one found it to be normal. 47 At least one study noted an association between osteocalcin and decreasing BMD scores, 64 although another did not. 47

Urinary collagen cross-links have been found to either decrease or remain unchanged after transplantation (Fig 2). 24,35,41,61,65 Two cross-sectional studies found the levels to be increased, 52,54 whereas one noted levels within the normal range. 71 In one study the urinary collagen cross-links trends correlated with PTH levels as well as with alkaline phosphatase levels. 61 Cruz et al 46 found that increased levels of urinary collagen cross-links and serum osteocalcin levels were associated with decreases in BMD.

BONE HISTOLOGY

Performing bone biopsy examinations after transplantation is rare in day-to-day clinical practice. Studies that have evaluated bone biopsy examinations have revealed that bone histomorphometry results could not have been predicted from other less invasive clinical tests. The bone biopsy results of at least 373 kidney transplant recipients, on no specific therapy for bone loss, 21,32,44,49,51,76-82 revealed that the lesions found in transplant patients varied widely. Sanchez et al 79 performed biopsy examinations on children and adolescents and found 66% to have normal bone histology posttransplant, however, in most series only a mi-
nority of patients have normal bone histology after transplantation. Although many patients have low bone turnover on biopsy examination, many other patients display a high turnover bone process. There is no clear-cut pattern even when accounting for time posttransplantation. Cueto-Manzano et al obtained baseline bone biopsy examinations at a mean of 133 months posttransplant and repeated them 12 months later. Without specific treatment directed at bone disease, 71% of patients undergoing biopsy examinations had different histologic findings on the second biopsy examination compared with the first.

Julian et al found that declines in PTH levels correlated with decreases in bone turnover indices in patients undergoing bone biopsy examinations at baseline and again at 6 months. In contrast to these findings several other studies have not found that PTH and alkaline phosphatase levels are predictive of biopsy findings. Cueto-Manzano et al found no significant association between transformation to adynamic bone and PTH reduction. Despite the finding by Cruz et al that patients with biomarkers indicative of a high turnover state lose bone, no single biomarker or combination of markers has been shown to unequivocally distinguish between histologic findings.

**SKELETAL EFFECTS OF IMMUNOSUPPRESSIVE DRUGS**

**Glucocorticoids**

Glucocorticoids in high doses (eg, ≥50 mg/d of prednisone or prednisolone) commonly are prescribed immediately after transplantation, with subsequent dose reduction over several weeks and transient increases during rejection episodes. Exposure varies with the organ(s) transplanted, the number and management of rejection episodes, and with the practice of transplantation programs. The introduction of cyclosporine A (CsA), tacrolimus, and, more recently, rapamycin and daclizumab have reduced glucocorticoid requirements. However, there is still sufficient exposure, particularly during the first few months after transplantation, to cause substantial bone loss.

Glucocorticoids reduce BMD predominantly at trabecular sites and even small doses are associated with markedly increased fracture risk. Glucocorticoids cause direct and profound reductions in bone formation by decreasing osteoblast replication, differentiation and lifespan, and by inhibiting genes for type I collagen, osteocalcin, insulin-like growth factors, bone morphogenetic proteins and other bone matrix proteins, transforming growth factor β and the receptor activator for nuclear factor κ B ligand (RANK-L). Direct effects of glucocorticoids on bone resorption are minor relative to effects on formation. However, steroids may increase bone resorption indirectly by inhibiting synthesis of gonadal steroids and inducing hyperparathyroidism secondary to reduced intestinal and renal calcium absorption, although hyperparathyroidism is thought to be of minor importance in the pathogenesis of steroid-induced bone loss.

**Calcineurin Inhibitors: CsA and Tacrolimus**

The introduction of CsA to transplantation regimens was associated with a marked reduction in rejection episodes and an improvement in survival. CsA inhibits calcineurin, a T-cell phosphatase, and reduces T-cell function via suppression of regulatory genes expressing products such as interleukin 2, interleukin receptors, and the proto-oncogene, H-ras, and c-myc. Although in vitro studies showed that CsA inhibits bone resorption in cultured bone, in vivo rodent studies suggest that CsA has independent adverse effects on bone and mineral metabolism that could contribute to bone loss after organ transplantation. In the rat, CsA administration caused severe bone loss, particularly in trabecular bone, that was associated with marked increases in both bone resorption and formation, with increased levels of osteocalcin and 1,25-(OH)2D3. The CsA-mediated bone loss was associated with testosterone deficiency and independent of renal function and attenuated by parathyroidectomy. Antiresorptive agents such as estrogen, raloxifene, calcitonin, and alendronate prevented CsA-induced bone loss. CsA may cause bone loss by direct effects on calcineurin genes expressed in osteoclasts or indirectly via alterations in T-cell function. These animal studies suggest that CsA could be responsible for the high-turnover aspects of posttransplantation bone disease. However, the effects of CsA on the human skeleton are still unclear, particularly in view of reports that kidney transplant patients receiving CsA in a steroid-free regimen do not appear to lose bone.
Tacrolimus (FK506), another calcineurin inhibitor that inhibits cytokine gene expression, T-cell activation, and T-cell proliferation, also causes trabecular bone loss in the rat.\textsuperscript{84} Fewer studies have evaluated the skeletal effects of FK506 in humans. However, liver transplant recipients taking FK506 had significantly higher femoral neck BMD 2 years after transplantation than those receiving CsA.\textsuperscript{93} The patients on FK506 received less prednisone, thus FK506-based regimens may benefit the skeleton by allowing for the use of even lower glucocorticoid doses.

Other Immunosuppressive Agents

Limited information is available regarding the effects of other immunosuppressive drugs on BMD and bone metabolism. Azathioprine, sirolimus (rapamycin), and mycophenolate mofetil do not cause bone loss in the rat model. The skeletal effects of newer agents such as dycluzimab and basilizimab have not been studied. However, by reducing glucocorticoid requirements, they may be relatively beneficial to the skeleton.

EVALUATION FOR POSTTRANSPLANT BONE DISEASE

Given that transplant recipients lose bone and are at ongoing increased risk for fracture, long-term monitoring of their bone risk is warranted. Specific evaluation protocols have not been tested and various approaches are likely useful. In Table 2, we provide one potential approach for long-term monitoring.

Table 2. Recommendations for Evaluation of the Transplant Recipient

| 1. Monitor BMD by DEXA at the lumbar spine and femoral neck within one month pre-or post-transplantation |
| 2. Obtain a dietary calcium, vitamin D intake (the type and the amount), menses pattern, oophrectomy, hormone use, steroid use, Dilantin intake, Coumadin intake, prolonged history of immobilization, alcohol usage, exercise and smoking habits history |
| 3. Obtain a history about what happened during dialysis. Ask about parathyroidectomy, calciphylaxis, symptoms of calciphylaxis, a frequent history of high phosphorous and pruritis, hypercalcemia, and what modes of dialysis they used and for how long. |
| 4. Obtain a baseline PTH |
| 5. Follow serum calcium, albumin, and phosphorous concentrations. |
| 6. Within 6-12 months post-transplant repeat the BMD |
| 7. If the BMD shows a decline (>5% decrease or half of a standard deviation), recheck the PTH, vitamin D level and intake and evaluate gonadal status (LH, FSH, estradiol, total testosterone, and prolactin in the setting of impotence, amenorrhea, oligomenorrhea, or complete cessation of menses). |
| 8. If the bone mineral density is decreasing as described in 7 above, recheck a BMD yearly |
| 9. If the bone mineral density is stable (less than 5% decline yearly) recheck every 2 years |
| 10. If the PTH was initially elevated, monitor yearly |
| 11. Bone biopsy if bone loss continues as measured by BMD and the etiology of the bone disease is not clear. |
| 12. If the PTH is persistently elevated (>500-600 by intact assay), hypercalcemia and hypophosphatemia persist and are not responsive or worsened by oral Vitamin D analogues or oral calcitriol, parathyroidectomy should be considered. |

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Virtually all studies have shown that bone loss is most rapid immediately after transplantation. Fractures may occur very early and affect patients with both low and normal BMD. Therefore, we believe that most patients (even those with normal BMD) should have preventive therapy instituted immediately after transplantation. In addition, there is an ever-enlarging population of patients who have been transplanted months or years previously, yet have never been evaluated or treated for bone disease.

There are a limited number of therapeutic studies in patients undergoing kidney transplantation whereas the majority of the therapeutic trials are in patients undergoing other solid organ transplantation. These studies have focused on the use of vitamin D metabolites and antiresorptive drugs, particularly the bisphosphonates.

Vitamin D metabolites may reduce posttransplantation bone loss by reversing glucocorticoid-induced decreases in intestinal calcium absorption and by mitigating secondary hyperparathyroidism.\textsuperscript{94} Theoretically, they could reduce glucocorticoid exposure by virtue of their immunomodulatory effects.\textsuperscript{94}
To our knowledge, there have been no studies evaluating the use of the parent form of vitamin D and only one prospective study using calcidiol (25-hydroxyvitamin D₃) in the prevention or treatment of post–kidney transplant bone disease. The use of 500 mg calcium and 50 μg calcidiol did not increase either proximal femur or lumbar BMD in 6 patients treated for 1 year posttransplantation. However, calcidiol has been shown to both prevent bone loss and increase lumbar spine BMD after cardiac transplantation. There are also very few studies with calcitriol (1, 25-dihydroxyvitamin D₃) for the prevention or treatment of bone disease post-kidney transplantation. The results of these studies are not conclusive. Cueto-Manzano et al were unable to show protection from posttransplant bone loss with calcitriol and calcium when started in patients a mean of 119 months after transplantation. However, in a preliminary report, we were able to show an increase in BMD of the femoral neck, lumbar spine, and radius after 12 months of calcitriol and calcium treatment compared with double placebo, when used to prevent early posttransplantation bone loss.

Several studies suggest that bisphosphonates may be useful in either preventing or treating bone loss after renal transplantation. Administration of intravenous pamidronate at time of transplantation and repeated 1 month later was shown to prevent lumbar spine and proximal femoral bone loss at 1 year. The use of the more potent bisphosphonate, ibandronate, administered at time of transplantation, and 3, 6, and 9 months after transplantation also resulted in a significant protective effect on BMD in the lumbar spine and proximal femur at 1 year. A small study (n = 20) compared the use of oral alendronate with calcitriol. A regimen that included alendronate (10 mg/d), calcium carbonate (2 g/d), and calcitriol (0.25 μg/d) was associated with a 6.3% increase in lumbar spine BMD in the first 6 months after transplantation, compared with a decrease of 5.8% with calcium and calcitriol alone. In another trial comparing therapy for 1 year with either alendronate, calcitriol and calcium, or calcitriol and calcium treatment alone in 40 kidney transplant recipients in whom therapy was begun an average of 5 years after transplantation reported an increase of 5% at the lumbar spine and 4.5% at the femoral neck in the alendronate-treated group. BMD remained stable in the patients treated with calcitriol and calcium. Finally, Haas et al evaluated bone biopsy specimens in 6 patients given placebo and 7 patients who received zoledronic acid and found similar resolution of the high turnover lesions in both groups, however, those receiving zoledronic acid had significant improvement in trabecular calcification. Thus, bisphosphonates may be promising for the management of posttransplant bone loss. This may be especially true immediately after transplantation and in those patients with high turnover bone lesions. However, controversies remain regarding the optimal administration of bisphosphonates, whether continuous or intermittent therapy should be used, the duration of therapy, the level of renal impairment at which bisphosphonates should be avoided, whether they are safe in kidney transplant recipients with low turnover bone disease, and their use after pediatric transplantation. Finally, one must be cautious in the use of bisphosphonates because there are reports of the development of sclerosing focal segmental glomerulonephritis after the use of pamidronate.

There essentially are no data on the use of calcitriol or hormone replacement therapy after transplantation. Hypogonadism is a common sequela in patients with chronic kidney disease and may persist after transplantation, thus an evaluation of gonadal status would be appropriate. The potential benefits of either estrogen replacement or testosterone therapy have to be weighed against the potential risks in the individual patient.

SUMMARY AND CONCLUSIONS

Pretransplantation bone disease and posttransplantation immunosuppressive regimens combining high doses of glucocorticoids and calcineurin inhibitors interact to produce a variety of bone and mineral disorders, which result in rapid bone loss and increased fracture rates. Bone biopsy information reveals that transplant bone disease is not a single entity, with studies showing uncoupling of bone turnover with many biopsy examinations exhibiting features of increased bone resorption and decreased bone formation. Unfortunately, bone biomarkers have not been shown to be useful probes to distinguish the underlying process. Although BMD is used as a surrogate for bone disease, we do not know if BMD can predict fractures in the renal transplant population. Management of these patients should combine assessment and treatment of
pretransplantation bone disease with preventive therapy in the immediate posttransplantation period because most bone loss occurs in the first months after successful grafting. In addition, bone mass measurement and therapy of bone loss in the long-term organ transplant recipient should be addressed. There are no pretransplantation variables that reliably predict posttransplantation bone loss and fracture risk in the individual patient. Therefore, all transplant recipients should be considered at risk for posttransplantation bone loss and fractures. Although recent observations suggest that rates of bone loss and fracture may be lower in patients treated with the newer immunosuppressive regimens, morbidity from transplantation bone loss remains unacceptably high. Therapeutic trials have shown promise to decrease bone loss, however, no trial has shown an effect on preventing fractures. Furthermore, these trials have not been applied based on the underlying disease process. Given the variety of findings on histology, the uncertainty of BMD to accurately predict fractures, it is time to test therapies based on underlying bone biopsy findings. We need to determine if patients with specific underlying bone dynamics are at differing risks for fracture, will respond better to specific therapies, or if tailoring the therapy to the process is necessary at all.

REFERENCES


