

NEPHROLOGY

Rounds™

Bone Disease in the Renal Transplant Patient

By JEAN E. MULDER, M.D., and MERYL S. LEBOFF, M.D.

Since the first renal transplant at Brigham and Women's Hospital, by Dr. Joseph Murray in 1954, survival of patients with kidney disease has increased dramatically, however, there are long-term consequences associated with renal transplantation that affect skeletal health. In comparison with other transplant recipients, renal transplant recipients (RTRs) are unique because of the impact that renal insufficiency and end-stage renal disease (ESRD) have on pre-transplant skeletal health. Pre-transplant bone disease greatly influences the course of post-transplant bone disease. An examination of renal osteodystrophy in the patient with ESRD is beyond the scope of this issue; however, the subject has been reviewed recently,¹⁻³ and several other reviews provide a comprehensive summary of post-transplant bone disease.⁴⁻⁸ Early post-transplant bone disease and fracture risk are influenced by many variables, including the underlying disease that necessitated renal transplant and the presence or absence of pre-transplant renal osteodystrophy. As a result of these variables, there is substantial individual variation in the type and natural history of post-transplant bone disease. This issue of *Nephrology Rounds* provides information about the changes in calciotropic hormones after successful renal transplantation and the well-documented effects of immunosuppressive agents on skeletal remodeling. It also reviews diagnostic modalities to measure bone density in RTRs and discusses the likelihood of fracture and ways to manage fracture risk in these patients.

Changes in calciotropic hormones post transplant

After successful transplantation, there is a decrease in the secretion of the parathyroid hormone (PTH) that occurs secondary to an increase in endogenous calcitriol production from the healthy graft. Decreases in phosphorous and alkaline phosphatase also occur. Prolonged hypophosphatemia occurs in some patients. While PTH values improve within the first 3 months post-transplant, normalization does not occur in as many as 50% of patients (Figure 1).⁹ Risk factors for failure to normalize serum PTH levels include higher PTH values pre-transplant, older age, and longer time interval on dialysis.⁹ Persistent hyperparathyroidism, therefore, is most likely related to pre-transplant parathyroid gland hyperplasia, which may or may not be reversible with time. Some patients with persistent hyperparathyroidism post-transplant develop hypercalcemia, requiring parathyroidectomy,^{9,10} suggesting that autonomy has occurred that may be irreversible. Whether or not a transplant recipient has persistent hyperparathyroidism after transplant will influence the pattern of post-transplant bone disease.

Immunosuppressive agents

Immunosuppressive agents also have a significant effect on post-transplant bone disease.¹¹ High-dose glucocorticoids are often a component of early immunosuppressive regimens. Doses are generally reduced over several weeks, but may be increased again for episodes of rejection. Glucocorticoids are associated with a reduction in bone mineral density (BMD), particularly at cancellous sites, and an increase in fractures. Glucocorticoids exert their adverse effects by suppressing bone formation through direct inhibition of osteoblast production and activity. Additional glucocorticoid effects include decreased intestinal calcium absorption, increased urinary calcium excretion,

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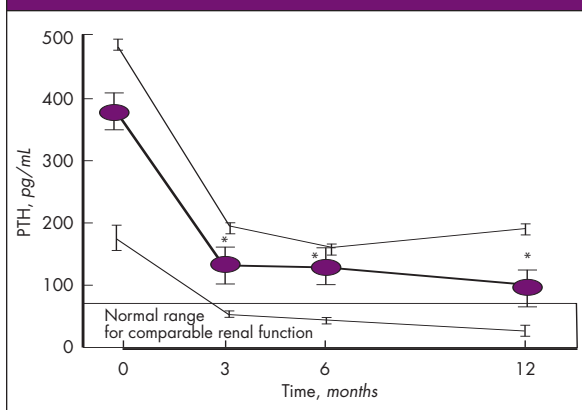
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Figure 1: Behavior of parathyroid hormone (PTH) after renal transplantation⁹



The thicker line represents the behavior in the total number of patients. The 2 thinner lines represent:
Group A (lower line), normal PTH levels by the third month
Group B (upper line), persistently elevated PTH level by the third month.
PTH levels fell rapidly during the first 3 months and, thereafter, remained substantially stable (mean \pm SE; * $P < 0.01$ vs. basal values; the differences between the 2 groups were all statistically significant by definition)

and suppressed hypothalamic-pituitary-gonadal axis, all of which may increase bone resorption.⁵

The calcineurin inhibitors – cyclosporin (CsA) and tacrolimus – also have direct adverse effects on bone remodeling. In animal studies, both CsA and tacrolimus increase bone resorption and cancellous bone loss.¹¹ Despite these adverse effects, immunosuppressive regimens that reduce glucocorticoid exposure are beneficial for bone health.^{12,13} In one study,¹² subjects who received CsA alone, without steroids, had an increase in their lumbar spine (LS) Z-score 18 months after renal transplantation, whereas those treated with CsA plus a steroid or CsA plus steroids and azathioprine (Aza) had a decrease in their LS Z-score. However, in another study in long-term transplant recipients (55-229 months post-transplant)¹⁴ BMD Z-scores of the distal radius, femoral neck, and LS were normal and did not differ between groups receiving CsA monotherapy or Aza plus prednisone. T-scores were below -1.0 at the distal radius in both groups. The T-score was also below -1.0 in the femoral neck (FN) of the CsA group. None of the BMD measurements were significantly different between treatment groups, although there was a trend toward a better LS BMD in the CsA group compared with the prednisone group.¹⁴ These findings suggest that the beneficial effects of steroid avoidance may occur only in the early post-transplant period.

Newer immunosuppressive agents, such as mycophenolate mofetil, do not appear to decrease bone mass in rat models, although osteocalcin levels are suppressed.¹⁵ Thus, further studies are necessary to determine the skeletal effects of mycophenolate mofetil in humans.

Assessment of post-transplant bone disease – histomorphometry

There are a limited number of ways to assess bone disease in RTRs, including histomorphometry, BMD, PTH levels, and biochemical indices of bone turnover, such as osteocalcin, and pyridinoline crosslinks. Given the broad spectrum of skeletal abnormalities comprising renal osteodystrophy, histomorphometric analysis provides the most accurate information;¹⁶ however, due to the invasive nature of bone biopsies, there are relatively few histomorphometric studies. A small study in the early post-transplant period revealed decreased rates of bone formation with a prolonged formation period, and a net decrease in bone formation during each remodeling cycle.¹⁷ A more recent study in 20 patients who had bone biopsies before, and 6 months after, transplant revealed improvement in bone turnover in half of the subjects who had adynamic bone disease pre-transplant (12 subjects), likely related to improvement in calciotropic hormones.¹⁸ In addition, subjects with high-turnover bone disease at baseline had improvements post-transplant, but several (5 of 8) developed low-turnover bone disease. The presence or emergence of decreased bone turnover and a net decrease in bone formation in the early post-transplant period have generally been attributed to the use of higher dose corticosteroids for immunosuppression.¹⁷

Histomorphometric abnormalities suggestive of decreased bone formation, however, persist in the late-transplant period.^{14,19,20} For example, Monier-Faugere et al evaluated 57 subjects a mean of 5.6 years after transplant.²⁰ Immunosuppressive regimens varied and included prednisone, Aza, and CsA; 63% of patients had a high creatinine, indicative of moderate renal failure. Not surprisingly, a similar majority of patients had hyperparathyroidism, although only 21% were hypercalcemic. Histomorphometric analysis revealed decreased cancellous bone volume and low bone turnover indices in 56% and 46% of patients, respectively. Bone formation indices were reduced in 59.7%. On the other hand, very few subjects had high bone turnover indices (increased erosion surface 21.1%, increased activation frequency 26.3%). Stepwise regression analysis revealed that prednisone was the main factor contributing to low bone volume and low bone turnover, without an association with cumulative exposure to CsA and Aza or PTH levels.

The majority of patients in the above study²⁰ had moderate renal failure. Cueto-Manzano et al¹⁴ studied 25 transplant recipients, all with good renal function at least 5 years post-transplant. Thirteen subjects received CsA monotherapy, and 12 received Aza + prednisolone. Histomorphometric analyses revealed mixed renal osteodystrophy in 10, adynamic bone in 7, predominant hyperparathyroid disease in 4, and normal bone in 3. The histomorphometric findings revealed slight osteo-

clast stimulation and osteoblast suppression with retardation of mineral apposition and bone formation rates. The findings did not differ between immunosuppressive groups.¹⁴ These data suggest that bone abnormalities are variable and persist years after transplantation, despite good renal function and despite steroid-sparing immunosuppressive regimens.

Assessment of post-transplant bone disease – bone mineral densitometry

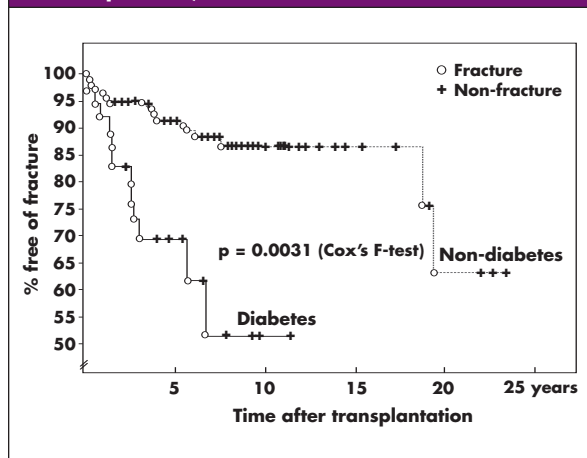
As described above, bone biopsy with histomorphometric analysis is the best way to characterize the presence and type of renal bone disease in RTRs. In place of invasive assessments, biochemical parameters (eg, PTH) and markers of bone remodeling, and BMD are often substituted. In one study, there was a correlation between changes in volumetric vertebral mineral density, as measured by quantitative computed tomography (QCT), and changes detected in trabecular bone volume by bone biopsy.²¹ However, the majority of studies measure BMD using dual x-ray absorptiometry (DXA) and histomorphometric correlations with DXA are lacking. Therefore, BMD (with DXA) interpretations in patients with underlying renal osteodystrophy are not analogous to BMD interpretations in otherwise healthy postmenopausal women and older men. Low BMD measurements in patients with ESRD or post-transplantation may reflect osteoporosis and/or renal osteodystrophy.

Densitometry by itself cannot distinguish the type of renal bone disease. Furthermore, the World Health Organization (WHO) criteria defining osteopenia and osteoporosis were developed for a postmenopausal Caucasian population and the cutpoints may not necessarily reflect fracture risk in the population with ESRD.⁷ The predictive relationship between BMD and fracture in healthy postmenopausal women, therefore, may not be the same in the RTR population. Fracture risk is a function of decreased bone density, bone quality, and bone turnover. Bone densitometry measurements are not reflective of bone quality or turnover. Despite these limitations, BMD measurements are still used to guide skeletal therapy in RTRs because DXA is readily available, noninvasive, and carries very little risk.

There are many studies demonstrating a decline in BMD after renal transplantation.^{17,21-23} Vertebral BMD decreases 7%-14% within the first 3-6 months post-transplant,^{17,21-23} whereas BMD of the radius may improve¹⁷ and BMD of the femur has been reported to decrease in males, but not in females.²³ The decline in BMD can exceed 10% in the first year after transplant.^{4,22,23} Factors associated with early bone loss after transplantation include high pre-transplant PTH levels^{21,22} and glucocorticoid use.¹⁷

Although the rate of bone loss decreases after the initial transplant period, reduced BMD persists in long-term RTRs.²⁴⁻²⁶ Osteoporosis, according to the

Figure 2: Free of fracture Kaplan-Meier survival curves for insulin-dependent diabetes mellitus (IDDM) and non-DM patients in relation to number of years after transplantation (dated from the first transplantation, when retransplanted)³⁰



WHO definition, has been reported in 26%-53% of RTRs a mean of 8-9 years after transplant. Osteopenia occurs in 40%-78% of subjects.^{25,26} Factors that correlate with low BMD include female gender, low glomerular filtration rate (GFR), low body mass index (BMI), cumulative steroid dose, and pretransplantation diabetes.^{25,26} Longitudinal studies suggest that BMD remains stable in some and decreases in others.^{24,27} One study,²⁴ but not another,²⁷ noted that ongoing bone loss is greater in RTRs who have elevated markers of bone turnover (pyridinoline crosslinks, osteocalcin).

Fracture

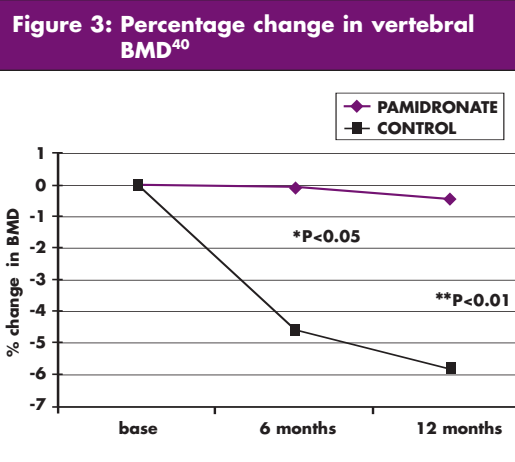
A high incidence of fractures has been reported after renal transplantation, with 2 studies demonstrating an almost 5-fold increase in fracture risk.^{28,29} Fracture risk is often greatest within the first 3-5 years post-transplant, but continues long-term following transplantation.²⁹ The incidence of fractures in the first 1.5-3 years post-transplant ranges from 8% to 17%.^{30,31} Although cancellous bone appears to be affected to a greater degree than cortical bone, vertebral fracture is reported relatively less frequently than appendicular fractures in some studies,³⁰⁻³² but not in others.²⁹ In the latter study, the cumulative incidence of vertebral fractures was 20% among 15-year survivors, compared to an expected rate of 1%.²⁹ Subjects with a history of diabetes mellitus are more likely to fracture and have multiple fractures than patients transplanted for other diseases (Figure 2).^{29,30,33} Lower limb fractures occur more commonly in patients with diabetes.^{29,30} In addition to diabetes, female gender is a risk factor for fracture post-transplant,^{30,31} as is combined kidney-pancreas transplant.³¹ Surprisingly, corticosteroid use has not been associated with fracture risk in some studies,^{29,30} nor has high-dose tacrolimus.²⁹

Ball et al³³ recently reported a higher incidence of hip fracture in RTRs (1-3 years post-transplant) than in patients receiving dialysis.

Management

The marked decrease in BMD and increase in fracture risk after transplantation is of great concern. Management issues, however, are complex and challenging because of the marked variability in the types of renal osteodystrophy and changes in calciotropic hormones after transplantation. The majority of patients should receive 1000-1500 mg of elemental calcium and 800 IU of vitamin D daily. Many may require low-dose phosphorous supplementation to correct post-transplant hypophosphatemia, although phosphorous therapy may increase PTH levels further. The importance of 1,25 dihydroxyvitamin D replacement is dependent on graft function and endogenous production after transplant, as well as post-transplant PTH values. There are several studies reporting a small beneficial effect of calcium and vitamin D analogs (alfacalcidol, calcitriol) on early post-transplant bone loss, as assessed by DXA.³⁴⁻³⁷ Therefore, most patients should receive calcitriol, in addition to calcium and vitamin D, with careful monitoring of serum and urinary calcium levels. To optimize skeletal health, steady state 25-hydroxyvitamin D levels should be maintained at a sufficient level of ≥ 32 ng/mL to prevent a compensatory rise in PTH levels.³⁸

Early post-transplant bone loss is attributed most often to glucocorticoid use. Because bisphosphonates have been shown to improve bone density in glucocorticoid-induced osteoporosis³⁹ and after cardiac and lung transplantation,⁶ they have also been evaluated in the prevention and treatment of post-kidney transplant bone disease. There are several studies demonstrating preservation of BMD, as measured by DXA, in RTRs treated with bisphosphonates (eg, pamidronate, ibandronate, alendronate, and zoledronic acid).^{26,40-43} Fan et al⁴¹ prospectively studied 26 male RTRs randomized to either placebo or intravenous pamidronate (0.5 mg/kg) at the time of transplant and 1 month later. All patients were receiving immunosuppressive therapy with prednisolone, CsA, and Aza. BMD (DXA) decreased 6.4% at the LS and 9% at the FN in the placebo group 12 months after transplant; however, LS and FN BMD were unchanged in the treatment group. The same group of investigators recently reported 4-year data from 17 of the original 26 patients who were receiving the same immunosuppressive therapy. Despite only 2 initial doses of pamidronate, BMD at the LS and FN remained stable 4 years later. There was a significant 12.3%



decrease in FN BMD in the placebo group at 4 years and a non-significant 4.64% decrease at the LS.⁴⁴

Coco et al⁴⁰ also prospectively evaluated pamidronate for the prevention of post-transplant bone loss. Pamidronate similarly preserved bone mass at both the LS and hip, whereas BMD decreased in the control group (Figure 3). It is noteworthy that a subset of patients had histomorphometric analysis of iliac crest bone biopsy samples before and 6 months after randomization. Although there was loss of cancellous bone volume and decreased trabecular thickness in the control group, there was none in the pamidronate group. However, all 6 pamidronate-treated subjects showed a decrease in activation frequency, consistent with adynamic bone disease. In contrast, histomorphometric analysis after treatment with zoledronic acid for the prevention of post-transplant bone loss was not suggestive of adynamic bone disease; however, this study was limited by the absence of tetracycline labeling in the initial biopsy specimens.⁴³ This issue is of particular concern because it is still unclear if BMD, as measured by DXA, is as predictive of fracture in RTRs as it is in otherwise healthy postmenopausal women. Increases in BMD after bisphosphonates may not confer fracture protection if the underlying histology is consistent with adynamic bone. Although Grotz et al⁴² demonstrated fewer vertebral deformities in RTRs treated with ibandronate, there are no prospective randomized studies demonstrating fracture prevention in RTRs treated with bisphosphonates.³²

Because of the absence of fracture prevention data and the concern that bisphosphonates may increase adynamic bone disease, their routine use after renal transplantation is controversial. Some groups advocate bisphosphonate therapy post-transplantation only in patients at highest risk for

bone loss and fracture, including those with a history of prior fracture, biochemical, or histomorphometry indices of high-turnover, postmenopausal women, diabetics, and patients undergoing combined kidney-pancreas transplant.^{7,32} Others believe the benefit of preventing rapid early bone loss outweighs the risk of adynamic bone disease and recommend short-term judicious use of a bisphosphonate with a shorter duration of action, such as pamidronate.⁶ Alternative therapies include calcium and vitamin D analogs as mentioned previously. There are no studies investigating the use of subcutaneous PTH therapy in RTRs. On the one hand, PTH therapy appears to be inappropriate in patients who have recently suffered the adverse skeletal consequences of hyperparathyroidism. On the other, low-turnover bone disease after transplantation may respond better to an anabolic agent, such as PTH, than to an antiresorptive agent, such as a bisphosphonate.⁷ Calcimimetic agents, such as cinacalcet, may play a role in post-transplant bone disease if PTH values remain elevated, although future studies are required with skeletal endpoints.

Summary

Bone disease post-renal transplantation is complex and related to the underlying disease that necessitated the transplant, the type of renal osteodystrophy, the degree of hyperparathyroidism pre-transplant, beneficial changes in calcitriol, PTH, and calcium post-transplant, and choice of immunosuppressive agents. Bone loss, based on densitometric studies, occurs predominantly in cancellous bone and most rapidly in the first 6 months post-transplant. There is an increased risk of fracture, especially in the first 5 years, but increased fracture risk persists even after 15 years. Appendicular fractures occur more commonly in RTRs with diabetes. Histomorphometric studies are variable, with the majority revealing suppression of bone formation, likely mediated by glucocorticoid immunosuppressive therapy. However, excessive osteoclast-mediated bone resorption has also been noted. Immunosuppressive therapies that minimize glucocorticoid exposure are beneficial for skeletal health in some studies. Treatment options to prevent fracture include supplementation with calcium, multivitamins, 1,25 vitamin D, and bisphosphonates. Bisphosphonates have been demonstrated to stabilize or improve BMD; however, improvement in BMD may not predict the same decrease in fracture risk in RTRs as that noted in healthy postmenopausal women. Large randomized prospective studies of bisphosphonates in RTRs are required, with fracture as the endpoint. Further studies are also required to determine if there are potential bene-

fits of calcimimetic agents and subcutaneous PTH in the post-transplantation period.

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