Calcium Metabolism and Skeletal Problems after Transplantation

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Successful renal transplantation (RT) corrects the abnormalities of mineral metabolism that lead to renal osteodystrophy. This includes correction of uremia, normalization of serum calcium and phosphorus levels, and restoration of calcitriol production. However, the degree of renal function recovery is usually incomplete, and persistence of hyperparathyroidism is common. In addition, the immunosuppressive drugs used to prevent graft rejection exert profound effects on bone metabolism. Finally, persistent metabolic acidosis in patients with chronic impairment of graft function and the use of loop diuretics may also affect bone and mineral metabolism after RT. As a whole, detrimental factors predominate over beneficial factors, and disturbances of mineral metabolism and skeletal alterations are common causes of morbidity after RT. The major clinical problems include hypercalcemia and persistent hyperparathyroidism, hypophosphatemia, posttransplantation bone loss and fractures, osteonecrosis, and bone pain syndromes.

Persistent Hyperparathyroidism and Hypercalcemia

Serum parathyroid hormone (PTH) concentrations decrease progressively during the first 3 to 6 mo after grafting (1). However, 1 yr after transplantation, resolution of hyperparathyroidism is incomplete in 50% of recipients (2). Only 23% of long-term recipients with good renal function (serum creatinine <2 mg/dl) show PTH levels within the normal range, and 27% show a value more than twice the upper normal limit (3). Persistent hyperparathyroidism was detected in 43% of long-term renal transplant patients with a serum creatinine <1.5 mg/dl if a cutoff value for intact PTH of 90 pg/ml was taken, i.e., the mean value plus 2 SD observed in nontransplanted patients with mild chronic renal failure (4). Duration of dialysis, parathyroid gland size, and development of nodular and/or monoclonal hyperplasia of parathyroid glands are the most important factors responsible for persistent hyperparathyroidism (5). Although the reported improvement of parathyroid function observed between 3 and 6 mo after RT has been attributed to a reduction of the parathyroid functional mass (6), the process of involution may take from a few months to several years. The long lifespan of parathyroid cells (approximately 20 yr) with a cell renewal rate of approximately 5% per year (7) contributes to the very slow involution of the gland after renal transplantation. Additional factors that may contribute to maintain high PTH concentrations are incomplete normalization of renal function (3), suboptimal levels of calcitriol (2,8), and decreased intestinal calcium absorption induced by corticosteroids.

In recipients with serum creatinine <2 mg/dl and more than >1 yr after grafting, the prevailing PTH levels correlate with pretransplant PTH concentrations (3,9). Preliminary observations using receiver-operator curve analysis, have demonstrated that PTH concentrations above 230 pg/ml at the time of transplantation predict long-term persistent hyperparathyroidism (PTH >90 pg/ml) with a low sensitivity (45%) but a high specificity (85%) (4). Interestingly, this cutoff value is similar to the PTH concentration that is required to avoid significant hyperparathyroid bone lesions in dialysis patients (10,11).

Postransplantation hypercalcemia is a common problem that results from the effect of increased PTH concentrations on different target tissues. High PTH concentrations stimulate the renal production of calcitriol that, in turn, increases intestinal calcium absorption and improves the skeletal mobilization of calcium. Correction of uremia and normalization of serum phosphorus levels are additional factors contributing to the resolution of the skeletal resistance to PTH, thus facilitating the release of calcium due to osteoclastic bone resorption (12). Finally, resorption of soft tissue calcifications can also contribute to postransplantation hypercalcemia.

In a recent study, hypercalcemia (>10.5 mg/dl) developed after RT in 52% of 129 patients 3 mo after grafting (13). Subacute hypercalcemia develops within the first 3 mo, and calcium levels are in the range of 12 to 15 mg/dl; it usually causes graft dysfunction and, rarely, calciphylaxis. Typically, these patients suffer severe preexisting hyperparathyroidism with overt radiological bone erosions, and early postransplantation parathyroid surgery is required (1). Fortunately, and due to the improved management of secondary hyperparathyroidism in dialysis patients, this form of hypercalcemia is currently rare. Transient postransplantation hypercalcemia is more common, and spontaneous resolution occurs in most cases within 1
yr after grafting. However, in about 5 to 10% of recipients, hypercalcemia persists beyond the first year but resolves gradually within 2 to 5 additional years (1,14). Such persistent mild hypercalcemia is usually well tolerated and is not associated with graft dysfunction or other complications. Nevertheless, a small proportion of patients (<5% in our transplant clinic) maintain persistent hypercalcemia above 12 mg/dl. In this case, renal dysfunction, nephrocalcinosis, pancreatitis, and vascular calcifications become significant risks and elective parathyroidectomy is recommended.

**Hypophosphatemia**

The clinical significance of hypophosphatemia differs according to whether it occurs early or late after transplantation. During the first 4 mo, many transplanted patients, up to 93% in a recent study, develop moderate hypophosphatemia with serum phosphate concentrations between 0.9 and 2.25 mg/dl (15). Increased urinary loss due to primary tubular dysfunction of the allograft (16) and persistent hyperparathyroidism is the main cause, compounded by the effects of immunosuppressive and diuretic drugs. By $^{31}$P nuclear magnetic resonance, muscle phosphate concentration was estimated to be decreased by 25% during the early posttransplantation period (15). The correlation between serum phosphate concentration and muscle phosphate content was poor. When the plasma phosphate concentration is below 1.4 mg/dl, patients often present with muscle weakness and possibly osteomalacia. Severe phosphate depletion, with serum phosphate concentrations below 0.9 mg/dl is rare. It may lead to hemolytic anemia, rhabdomyolysis, decreased myocardial contractility, and respiratory failure.

Oral phosphate supplements have been shown to normalize serum phosphate concentration and muscle phosphate content after transplantation (15). Furthermore, the prolonged phosphaturia caused by the administration of neutral phosphate increases renal net acid excretion leading to faster recovery from the latent metabolic acidosis observed during the early posttransplantation period.

When the allograft functions well, the decrease in PTH concentration and improvements in tubular function lead to normalization of the serum phosphate concentrations within months after transplantation in most patients. Late after transplantation, mild hypophosphatemia is common in patients with persistent hyperparathyroidism. Phosphate is known to increase PTH synthesis and secretion and to decrease calcitriol concentrations; therefore, phosphate supplements convey the potential risk of worsening hyperparathyroidism. Early after transplantation, oral phosphate supplements do not seem to affect calcium and PTH metabolism (15), but a significant increase in PTH levels has been detected in patients with well-functioning renal allografts who received oral phosphorus supplements in the late posttransplantation period (mean transplantation time, 41 mo) (17).

**Posttransplantation Bone Loss**

*Natural History of Posttransplantation Bone Loss*

Prospective studies have demonstrated a rapid rate of bone loss during the first 6 mo after grafting, mainly affecting the trabecular bone compartment. Bone mass stabilizes or even tends to recover at 12 mo (18-21). The study by Horber et al. (20) in predominantly cadaveric renal transplant recipients demonstrated a rate of bone loss of 1.6%/mo at the lumbar spine during the first 5 mo after RT. In two studies, men experienced a substantial 3.6% bone loss at the proximal femur over 3 mo, whereas in women, there was only a tendency to decrease (19,20). The magnitude of such early bone loss can be best appreciated if compared with the average 1.7% annual loss demonstrated in postmenopausal women at the lumbar spine (22). These findings underscore the importance of starting prophylaxis immediately after kidney grafting.

Longitudinal studies in stable long-term recipients have demonstrated a slower but significant rate of bone loss of 1.7%/yr at the lumbar spine (23). However, Grotz et al. (24) demonstrated no change, or even a slight increase, in bone mineral density in a similar study. This apparent discrepancy between the two reports can be explained by differences in the mean daily dose of corticosteroids.

**Pathogenesis of Posttransplantation Bone Loss**

**Role of Immunosuppressive Drugs.** The major cause of posttransplantation bone loss is corticosteroid treatment. This has been clearly shown in several reports comparing the evolution of bone mineral density (BMD) in patients on cyclosporine A (CsA) monotherapy versus those receiving CsA plus prednisone with or without azathioprine (25,26). Twelve to 18 mo after grafting, BMD remained unchanged or even increased both at the lumbar spine (25,26) and femoral neck (25) in the group without corticosteroids and significantly decreased in the corticosteroid-treated group. Furthermore, Julian et al. (18) observed that at the ilium, the mean wall thickness, a measure of the amount of bone replaced during a remodeling cycle, significantly decreased 6 mo after transplantation. Bone formation and mineralization lag times were prolonged; this association points to the presence of an osteoblastic dysfunction (18). In contrast, bone resorptive indices were normal, suggesting that progressive bone loss was due to an imbalance between bone formation and resorption (18). This picture fits with the known histologic effects of corticosteroids, suggesting that they are the predominant factor causing posttransplantation bone loss.

The pathogenesis of corticosteroid-induced bone loss is multifactorial and has been reviewed extensively (27). The main deleterious effect of corticosteroids is a direct and profound inhibition of bone formation. They inhibit osteoblast differentiation and induce apoptosis in mature osteoblasts as well as osteocytes (28). They also decrease gastrointestinal calcium absorption, resulting in a negative calcium balance and secondary hyperparathyroidism. In addition, corticosteroids directly suppress gonadotropins and may cause hypogonadism.

*In vivo* rat studies have shown that CsA induces high turnover osteoporosis with a transient rise in serum osteocalcin, which is exaggerated in the presence of estrogen deficiency (29). Interaction between the immune system and bone turnover seems to be important, as the effects of CsA seem to be dependent upon the presence of T lymphocytes (29). It has
been suggested that CsA increases bone turnover by inhibiting the production of antiresorptive cytokine(s) by T cells (30). However, the clinical data in RT do not support an adverse effect of CsA on bone mass, because CsA monotherapy does not reduce BMD 12 to 18 mo after grafting (25,26). Furthermore, normocalcemic nondiabetic transplant patients on low-dose prednisone (10 mg/d) and CsA exhibited an increase in the lumbar spine BMD Z score (assessed by quantitative computed tomography) beyond 3 mo after transplantation (31). This increase in Z score was associated with lower prednisone and higher CsA dosages, and both higher plasma concentrations of bone formation and resorption markers at 6 mo. The increase in bone markers correlated with CsA concentrations, therefore, it has been suggested that CsA may counterbalance the depressive effect of low-dose prednisone on bone formation and BMD by stimulating bone remodeling (31). At an earlier posttransplantation period, when higher doses of corticosteroids are used, osteoblast dysfunction may be so severe that rapid bone loss ensues. However, these findings contrast with the reported bone histomorphometry data in long-term renal transplant patients on CsA monotherapy (32). Histomorphometry in 16 patients who were receiving CsA monotherapy was similar than in patients under CsA + prednisone or azathioprine + prednisone. Increased osteoclast activation, suppression of osteoblast function, and retardation of bone formation were noted, and these findings were independent of PTH levels (32). Obviously, additional studies are required to clarify the role of CsA in the genesis of posttransplantation bone disease.

In terms of producing osteopenia in the rat, the calcineurin inhibitor FK-506 seems to be as deleterious as CsA (29). FK-506 does differ from CsA in that the serum osteocalcin concentration does not increase significantly after FK-506 injection (29). Another study showed that FK-506 reduced femoral bone mineral density in normal rats, although the reduction was much less severe than with CsA (33). Clinical data in renal transplant recipients are needed to confirm this finding obtained in experimental animals.

Unpublished study results suggest that mycophenolate mofetil does not affect bone. Rapamycin has also not been shown to cause bone loss but may increase bone remodeling and decrease longitudinal growth (34).

Preexisting Hyperparathyroidism. A direct correlation between the magnitude of early posttransplantation bone loss at the lumbar spine and pretransplantation PTH concentrations has been observed in two separate studies (19,21). Patients with a pretransplantation PTH level >250 pg/ml experienced a higher rate of bone loss after 3 mo of grafting than those with PTH values <250 pg/ml (21). In addition, the resolution of persistent hyperparathyroidism by parathyroidectomy has been associated with recovery of bone mineral density ranging between 1 and 8% at different sites (35). Higher cancellous bone volume is a known feature of patients with renal hyperparathyroidism. Consequently, early posttransplantation reduction in vertebral mineral density may in part be attributable to resolution of secondary hyperparathyroidism resulting from the loss of trophic effects of PTH on cancellous bone. The higher corticosteroid doses used early after transplantation adversely affect the osteoblast function and aggravate the imbalance between formation and resorption. However, cross-sectional studies in long-term graft recipients have not demonstrated a correlation between the prevailing PTH levels and BMD or different bone histomorphometry parameters (32,36,37).

Genetics and Posttransplantation Bone Loss. Even among recipients with identical immunosuppressive treatments, a wide variation in the rate of bone loss can be observed. Thus, posttransplantation bone loss reflects variable individual susceptibility, resembling the polygenic determination of BMD in general (38). Family studies have shown that 60 to 80% of the variation in BMD observed in the general population is genetically determined (39). As in other complex diseases, elucidating the specific genes involved has been hampered by the limitations of linkage analysis in situations in which highly variable environmental factors are major determinants of the phenotype.

A few association studies have addressed the role of vitamin D receptor (VDR) polymorphism on BMD changes after transplantation. The VDR polymorphism has been shown to influence the rate of bone loss during the first year (21). Preliminary data, derived from 71 patients who received a renal transplant, confirm that this polymorphism is significantly associated with the rate of bone loss during the first year after transplantation, with patients carrying the 'bb' genotype losing approximately half of the amount of BMD compared with non 'bb' individuals (40). Interestingly, similar findings have been reported during the first trimester after liver transplantation (41). Corticosteroids decrease intestinal calcium absorption and could provide an environmental setting in which the influence of VDR polymorphism becomes more evident.

The controversy on the relative role of the genetic polymorphisms reported to date on variability of BMD could be clarified in the near future, when the complete sequence of the human genome can be used to investigate other genetic variants that could be in linkage disequilibrium with the commonly tested polymorphisms. Alternative strategies for the study of genetic predisposition to complex diseases, such as family-based studies, should provide linkage information that is useful for the assessment of the relevance of findings in association studies. In addition, the contribution of the projects to tally the ethnic diversity of the human genome and to catalogue a large number of single-nucleotide polymorphisms will provide a better understanding of the genetic predisposition to BMD.

Bone Fractures after Renal Transplantation

The increased rate of bone loss places the renal transplant patient at increased risk of pathologic fractures. In fact, the yearly rate of fractures is much higher in this population than in age-matched control subjects. A similar estimate of 3 to 4% per year has been observed in two different studies (42,43). In terms of prevalence, fractures have been reported in approximately 7 to 21% of recipients, generally late in the posttransplantation period (42–44). Despite the preferential cancellous bone loss, most of the fractures involve the appendicular skeleton, particularly the feet and ankles (42–44). The patient with...
type 1 diabetes is at increased risk of fractures, and in a recent cross-sectional study, the 40% fracture prevalence in patients with diabetes contrasted with the 11% in the nondiabetic group (44). In addition, the fracture rate in simultaneous kidney/pancreas transplant patients may be as high as 12%/yr (43). Finally, postmenopausal women are also at increased risk of fractures after RT (42,43).

The genesis of fractures in type 1 diabetes after transplantation is probably multifactorial. Impaired vision and neuropathy may interfere with gait and postural stability. In addition, early onset of diabetes may decrease peak bone mass (44).

Some questions remain to be answered with respect to the value of BMD measurements with dual-energy x-ray absorptiometry (DEXA) in assessing the risk of fractures after renal transplantation. First, the peripheral distribution of fractures contrasts with the preferential cancellous bone loss demonstrated with densitometry. Furthermore, in one cross-sectional study, patients with fractures after minor trauma showed significantly lower BMD at the lumbar spine than those without fractures, although the broad overlap of BMD values limited the value of DEXA measurements to assess the fracture risk (42). It is important to note that no significant difference was observed at the femoral neck between patients with or without fractures. These findings suggest that BMD measurements may not have the same predictive power in the setting of RT as in postmenopausal osteoporosis. Thus, it is clear that additional information is needed regarding the utility of serial BMD measurements to assess the risk of fractures in transplant recipients. Finally, the pathogenetic role of other factors affecting bone architecture must be also investigated.

**Posttransplantation Bone Disease:**

**Histologic Abnormalities**

To develop adequate prophylactic and therapeutic strategies for posttransplantation bone abnormalities, it is essential to understand the underlying histologic bone abnormalities and their evolution over time. Results from different publications are summarized in Table 1 (18,21,32,36,37,45–48). The predominant lesion in adult recipients is a decrease in bone turnover associated with normal/high bone resorption, i.e., uncoupling of bone resorption and formation. In two studies, the cumulative dose of corticosteroids was the main factor that influenced bone turnover (36,48). Therefore, the continuous use of corticosteroids late after transplantation is an important pathogenetic factor in the genesis of bone alterations after transplantation.

**Prevention and Management of Posttransplantation Bone Loss**

Information regarding the effects of different therapies to prevent posttransplantation bone loss is scarce.

**Prevention of Early Bone Loss**

In the study of Fan et al. (49), 26 recipients who had immunosuppressive therapy comprising CsA, prednisone, and azathioprine, were randomized to receive placebo or the bisphosphonate pamidronate (0.5 mg/kg intravenously), at the time of grafting and 1 mo later. In the placebo group at 1 yr, the BMD had decreased by 6.4% and 9% at the lumbar spine and the femoral neck, respectively. In contrast, patients who received pamidronate experienced nonsignificant reduction of BMD at either site. The regimen of two intravenous doses of pamidronate was well tolerated, and apart from transient hypocalcemia in two patients, no discernible side effects were observed. Bisphosphonates improve bone density in corticosteroid-treated patients, and recent reports point to a reduction in the risk of vertebral fracture (50). However, in transplant patients fractures more typically involve the appendicular skeleton, and little information exists about the ability of bisphosphonates to reduce the fracture risk at this site in corticosteroid-treated patients. Thus, despite the beneficial effect on BMD, additional trials are needed to confirm that treatment with bisphosphonates reduces the number of fractures as well.

In a preliminary report, 85 patients were randomized to receive oral intermittent calcitriol (0.5 μg/48 h, at night) or placebo, during the first 3 mo after grafting; all patients received calcium supplementation. Calcitriol induced a more pronounced decrease in PTH levels after transplantation and a better preservation of the BMD at the proximal femur as compared with placebo (0.1 ± 0.6% versus −1.9 ± 0.7%, respectively; P < 0.05) (51). However, in another preliminary report, 62 patients were randomized to receive both calcium and calcitriol or double placebo, and at 12 mo, only a small therapeutic effect of calcium and calcitriol was observed at the lumbar spine (52).

**Prevention of Late Bone Loss**

In one study, 30 long-term renal transplant patients were randomized to receive placebo or calcitriol (0.25 μg/d) plus calcium (0.5 g/d). They were studied at baseline and 1 yr later by bone biopsy and densitometry (53). Osteoclast suppression and a trend to maintain trabecular bone volume and wall thickness were observed in the calcitriol group. It is possible that studies with longer follow-up are required to elucidate whether this therapy has a significant impact on bone status of long-term renal transplant recipients.

Grotz et al. (54) randomized 46 osteopenic recipients on average 57 mo after transplantation to supplemental calcium alone or in combination with cyclical clodronate or calcitonin during 12 mo. BMD at the lumbar spine increased by 4.6% in the clodronate group, by 3.2% in the calcitonin group, and by 1.8% in the calcium alone group. Although both clodronate and calcitonin treatments caused a statistically significant increase of BMD over baseline, no differences between the groups were found. BMD at the femoral neck did not change significantly in any of the groups.

**Recommendations for Management**

Before RT, intact PTH levels should be maintained in the range of 100 to 250 pg/ml to avoid low turnover or hyperparathyroid bone disease (Table 2) (10,11). In those recipients receiving corticosteroids in their immunosuppressive regimen, it is important to monitor BMD by DEXA at the lumbar spine.
and the hip in the first few days after grafting and 3 or 6 mo later. An effort should me made to use the lowest prednisone dose compatible with graft survival. With the new immunosuppressive regimens combining anticalcineurin agents with mycophenolate mofetil or rapamycin, the prednisone dose can be safely reduced to 10 mg/d by the first month in most recipients. Because significant osteopenia may be observed with doses as low as 7.5 mg/d of prednisone, the maintenance dose at long-term should not be above this value. In nonhypercalcemic patients, calcium supplementation to ensure a total daily calcium intake above 1.2 g/d is important because corticosteroids decrease intestinal calcium absorption. In addition, a daily intake of 400 IU of vitamin D should be recommended, in order to maintain 25OHD$_3$ levels above the 50th percentile of the normal concentration. In one study, recipients with low 25OHD$_3$ concentrations had significantly higher PTH concentrations compared with recipients with higher 25OHD$_3$ concentrations irrespective of graft function (13). Lifestyle factors such as alcohol intake, smoking, and regular exercise have to be considered. Finally, recipients who show a rapid bone loss during the first 3 to 6 mo after grafting should be treated with an antiresorptive agent, such as a bisphosphonate. If not contraindicated, hormone replacement therapy can be an alternative in postmenopausal and premenopausal amenorrheic women.

### Osteonecrosis

Avascular or ischemic necrosis is the most debilitating musculoskeletal complication after renal transplantation. It results from necrosis of marrow cells, trabeculae and osteocytes un-
Table 2. Recommendations for prevention and treatment of posttransplant bone loss

1. Maintain optimum intact PTH levels (100 to 250 pg/ml) during chronic dialysis treatment.
2. Monitor BMD by DEXA at the lumbar spine and at the hip in the first few days after grafting and then 3 to 6 mo later.
3. Use the lower prednisone dose compatible with graft survival.
4. In nonhypercalcemic patients, use calcium supplementation to ensure a total daily calcium intake of 1.2 g; a daily intake of 400 IU of vitamin D is also recommended to maintain 25(OH)D3 in the upper half of the normal levels.
5. Control of lifestyle factors: alcohol consumption, smoking, and regular exercise.
6. Use an antiresorptive agent in the case of rapid bone loss during the first 3 to 6 mo after grafting: bisphosphonate, or hormone replacement therapy in postmenopausal women if not contraindicated.

Bone Pain

Osteoporotic fracture and avascular bone necrosis (see above) are major causes of bone pain. In addition, some specific osteoarticular pain syndromes have been described in patients who have received a transplant.

Intraosseous vasoconstriction and hypertension have been proposed as the mechanism underlying a form of bone pain present in CsA-treated patients, usually during periods of high CsA levels (57). This form of bone pain characteristically responds to calcium channel blockers. In another CsA-related entity, sympathetic reflex dystrophy syndrome (58), bone pain appears together with a typical skin rash, and responds to a reduction in CsA levels or, eventually, calcitomin administration.

A severe osteoarticular pain syndrome, unrelated to CsA, has also been described in up to 10% of patients who have received a renal transplant. Detailed imaging analysis (59) suggests that bone impaction induces an inflammatory reaction in the epiphyseal medulla, with vasodilation and subsequent osteoblastic hyperactivity. Knees and ankles are mainly involved, often bilaterally, during the first 6 months after transplantation. The symptoms tend to be transient, and no modification of the immunosuppressive therapy is required (59).

References


related to bacterial infection. The femoral head is most commonly affected, followed by other weight-bearing long bones. Corticosteroids play a central role in its genesis, and the use of steroid-sparing anticalcineurin agents has dramatically reduced the incidence of osteonecrosis from 15% in the pre cyclosporin era to no more than 5% (55). An x-ray evaluation may be normal at an early stage. Magnetic resonance imaging is the most useful tool for early diagnosis. Thus, magnetic resonance imaging should be performed for any recipient with persistent hip, knee, or shoulder pain. Therapy of osteonecrosis is probably dependent on the stage of the process. Recent data suggest that core decompression is a safe and effective procedure for the treatment of stage I or IIA sclerotic disease (56). The most commonly performed procedure for advanced osteonecrosis of the femoral head is prosthetic arthroplasty.


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