Bone Disease after Renal Transplantation

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It has been well established that a rapid decrease in bone mineral density (BMD) occurs in the first 6 to 12 mo after a successful renal transplantation and persists, albeit at a lower rate, for many years. This rapid BMD loss significantly increases the fracture risk of these patients to levels that are even higher than those of patients who have chronic kidney disease stage 5 and are on dialysis. The presence of low BMD in renal transplant patients as a predictor of risk fracture is controversial. Indeed, as has been suggested also for patients with postmenopausal osteoporosis, there is not a compelling correlation between the decline in BMD and skeletal fractures. However, bone disease after renal transplantation probably represents a unique bone disorder that must encompass underlying renal osteodystrophy. In fact, this syndrome results from multiple factors that include pretransplantation bone status, use of glucocorticoids and other immunosuppressive drugs, hypophosphatemia, and alterations of the calcium–vitamin D axis. Recent studies have demonstrated decreased osteoblast number, reduced bone formation rate, delayed mineralization, and increased osteoblast and osteocyte apoptosis. Bisphosphonates and vitamin D metabolites may be valuable in preventing or diminishing early bone loss. However, clinicians should be careful with the use of bisphosphonates and oversuppression of bone, especially in patients with low bone turnover. New prospective, controlled trials are required to confirm the real efficacy of these drugs, particularly in long-term renal transplant patients.

Changes in Bone Mineral Density

Bone mineral density (BMD) as assessed by dual x-ray absorptiometry has been used as a noninvasive method to assess bone mass loss. However, these changes in BMD clearly differ in the early and late posttransplantation periods. Several studies have documented that early bone mass loss occurs after renal transplantation. Julian et al. (1) found that after 6 mo after transplantation, there was a sharp decrease in lumbar spine BMD by almost 7%, with a further decrease, reaching up to a 9% loss, at 18 mo. Similarly, Almond et al. (2) found a 3.9% decrease in femoral neck BMD in male transplant recipients at 3 mo after transplantation. More recently, Mikuls et al. (3) in a prospective study showed within 6 mo of transplantation a loss of a mean of 2.4% BMD at the lumbar spine with no significant decline at the femoral neck in more than one third of the patients. Other studies have confirmed a significant decrease of predominant lumbar spine BMD with minimal or no change in femoral neck BMD early after transplantation.

Changes late after transplantation have been more controversial. We previously demonstrated in a group of long-term renal transplant patients that BMD progressively improved as time after transplantation increased, approaching normal values after 10 yr (4). Similar results were found by Grotz et al. (5) in Germany. Nevertheless, recent data that were obtained from patients between 6 and 20 yr after renal transplantation showed a mean annual decrease in lumbar T scores of −0.6 ± 1.9%, a value that is relatively similar to the observed decline in the general population with aging. The mean annual BMD loss was statistically indistinguishable between men and women, but low estradiol levels were associated with accelerated bone loss (6).

Changes in BMD have not been confirmed uniformly by different studies, however, and the assessment and the interpretation of BMD results were questioned recently in the context of renal osteodystrophy, suggesting that we should cate-
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Is There an Increased Fracture Risk after a Kidney Transplant?

Numerous publications have confirmed the increased fracture risk after renal transplantation as compared with patients who have CKD stage 5 and are on dialysis. Ball et al. (8) found that after 3 yr after kidney transplantation, the risk for hip fracture increased by 34% when compared with dialysis patients. Patel et al. (9) evaluated 165 transplant patients and found evidence of osteoporosis, depending on gender or measured site, in 10 to 44% of the patients. Similarly, 27 (16%) patients had either vertebral deformities or a history of a low trauma fracture after transplantation. Ramsey-Goldman et al. (10) found that the most common site of fracture was the foot, and this occurred similarly in both premenopausal and postmenopausal women after transplantation.

Fractures occur during the early and late posttransplantation periods, with a wide range of incidence depending on, among other factors, time after transplantation, severity of previous bone disease, diabetes, and immunosuppressive regimens used. In a recent review by Sprague and Josephson (11), the longer the time after transplantation, the higher the report of fracture rate. An interesting aspect to be considered is the relationship between BMD and fracture risk in transplant patients. Although a low BMD is a potent fracture risk factor, many transplant patients with low BMD do not have fractures, as shown by Grotz et al. (12). Furthermore, a study by Duriex et al. (13) showed that 44% of patients at least 5 yr after transplantation had a history of fractures. More than one third of these fractures occurred in patients with no BMD criteria of osteoporosis according to the World Health Organization, suggesting that BMD assessment does not discriminate between patients who will or will not have fractures and that other bone abnormalities may play a role in the increased fracture rate, as is discussed in the next section.

Several studies have addressed the issue of bone fractures during the late posttransplantation period. In a retrospective study of 1572 kidney transplant recipients who were a mean of 6.5 yr after transplantation, one or more fractures occurred in 19.1% of the patients, with patients with diabetes doubling this fracture risk. In the same study, a history of fracture during dialysis almost doubled the risk after transplantation (14). Similarly, Grotz et al. (12) found that postmenopausal women had more fractures (21%) than premenopausal women (6%). An important issue that was raised by this study was that low BMD at the femoral neck was not associated with peripheral fractures, but patients with bone fractures had lower BMD at the lumbar spine.

Finally, Vautour et al. (15) followed 86 patients for a mean 10.6 yr per patient in a retrospective cohort study. The cumulative incidence of any fracture at 15 yr was 60% versus 20% expected. In a multivariate analysis, only age and diabetic nephropathy were independent predictors of fracture risk, whereas higher activity status was protective. Nevertheless, it is possible that the increased mobility of patients after transplantation could favor the increased fracture rate. Diabetes was the only independent predictor of lower limb fractures, whereas age and osteoporosis history predicted vertebral fractures. Cumulative corticosteroid dosage was not associated with increased fracture risk in this analysis. Finally, it has been shown that BMD at the distal radius is predictive of fracture risk and correlates with parathyroid hormone (PTH) levels in patients who have CKD 5 and are on hemodialysis (16).

In summary, the presence of low BMD as a predictor of risk fracture is controversial. Indeed, although in the general population BMD measurements are accepted as a noninvasive means for fracture risk, the value of these measurements in the evaluation of CKD and transplant patients is not well established. Serial BMD measurements are valuable in the evaluation of bone disease in kidney transplant recipients. For these reasons, the Kidney Disease Outcomes Quality Initiative clinical guidelines for posttransplantation bone disease recommended the assessment of BMD by dual-energy x-ray absorptiometry at the time of transplantation and 1 and 2 yr after transplantation (17).

Alterations of Bone Remodeling after Transplantation

Although some early reports have linked posttransplantation bone disease mainly to glucocorticoid excess, it has become clear that it rather comprises a spectrum of metabolic alterations of bone remodeling that include the status of bone metabolism during dialysis (secondary hyperparathyroidism, adynamic bone disease, osteomalacia, and mixed bone disease), as well as new factors that occur after transplantation (Table 1). Thus, posttransplantation bone disease represents a complex disarray that could encompass the variable preexisting renal

<table>
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<th>Table 1. Contributing factors of posttransplantation bone disease²</th>
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<td><strong>Pretransplantation factors</strong></td>
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<td>adynamic bone disease</td>
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²PTH, parathyroid hormone.
osteodystrophy alterations. It is interesting that these bone lesions are observed frequently in patients who have relatively normal kidney function and often are independent of serum PTH levels.

Studies by Julian et al. (1) showed that as early as 6 mo after transplantation, patients exhibited decreased mineral apposition rate and delayed mineralization. Although the authors suggested that this represented adynamic bone disease, these findings could be explained by the dramatic decrease in PTH levels in patients with relatively mild bone disease before transplantation. In addition, the high doses of glucocorticoids as used during the early months after transplantation may explain the high prevalence of low bone turnover (18).

Studies that were performed in patients with long-term renal transplantation and relatively normal GFR are discrepant. Whereas Velasquez-Forero et al. (19) showed mainly alterations that were consistent with adynamic bone disease and increased deposition of iron in the mineralization front, other studies have shown decreased bone formation and prolonged mineralization lag time in the presence of persisting bone resorption (4,20,21). Our studies in patients with normal renal function, after a mean of 7.5 yr after renal transplantation, showed mainly a mixed histologic pattern that was characterized by an increase in bone resorption, whereas bone formation rate was low and mineralization lag time prolonged (4). These lesions were more severe in patients with less time after transplantation but approached normal values in patients who were >10 yr after transplantation. Similar results were shown by Cueto-Manzano et al. (21) in the majority of patients. More recently, Monier-Faugere et al. (18) in a study of posttransplantation patients after 4 to 6 yr showed bone alterations that were characterized by low bone turnover, decreased bone formation, and prolonged mineralization, whereas increased erosion surface was observed in fewer than 25% of the patients. A striking finding of this study was the presence of generalized or focal osteomalacia in many patients.

In conclusion, there are discrepancies among the findings described in the various studies, but it seems evident from the majority of them that the main alterations in bone remodeling after renal transplantation consist of a decrease in bone formation and mineralization in the face of persistent bone resorption, producing an imbalance in remodeling and favoring resorption. Likewise, the defective bone formation may be a consequence of alterations in osteoblast function, decreased osteoblastogenesis, or increased osteoblast death rate.

In a recent study, we examined the possible role of an early increase in osteoblast apoptosis and alterations in osteoblastogenesis, as well as the influence of preexisting bone disease, in the bone histomorphometric alterations after transplantation (22). The study was performed shortly after renal transplantation, a period in which patients receive high doses of glucocorticoids, and some of the preexisting alterations of bone metabolism still may be present. Patients were subjected to a bone biopsy on the day of transplantation and within 21 to 120 d after transplantation. The main alterations in bone histology were a decrease in osteoid and osteoblast surfaces and adjusted bone formation rate, whereas the mineralization lag time was prolonged. Resorption and osteoclast surfaces remained above the normal range. In addition, almost half of the patients showed early osteoblast apoptosis and a decrease in the osteoblast surface and number. Osteoblast apoptosis was observed more frequently in patients with adynamic bone disease, osteomalacia, and mixed bone disease than in patients with high bone turnover, suggesting a pathogenic role of the preexisting bone disease and glucocorticoid excess, as is discussed later (Figure 1). Because apoptosis is a short-lasting phenomenon, that it was observed in some posttransplantation biopsies but not in pretransplantation biopsies suggests that there is an increase in the proportion of cells that undergo apoptosis. Another finding was a change in osteoblast morphology, demonstrating a marked shift toward quiescence or inactive form from the cuboidal morphology of active osteoblasts (Figure 2), even in the presence of elevated osteoid thickness in many patients, suggesting defective mineralization.

Pathogenesis of Posttransplantation Bone Disease

It is evident that posttransplantation bone disease is a complex problem that ranges from low to high turnover (1,4,18–23), indicating that the pathogenesis of posttransplantation bone disease is multifactorial and could include the following contributing factors (Table 1).

Pretransplantation Renal Osteodystrophy. In the past several years, the spectrum of renal osteodystrophy in dialysis patients has changed considerably. The incidence and the prevalence of low bone turnover, particularly adynamic bone disease, has increased steadily, becoming the main type of bone alteration in many centers. Therefore, it seems reasonable to consider low pretransplantation bone turnover as a risk factor for development or aggravation of the characteristics of adynamic bone lesions in the early posttransplantation period favored by the use of relatively high doses of glucocorticoids.

PTH. There seems to be no doubt that pretransplantation renal osteodystrophy plays an important role in the maintenance or development of posttransplantation alterations of bone remodeling. Indeed, most transplant patients have various forms of preexisting bone disease that may persist after transplantation. The prevalence of hyperparathyroidism among transplant patients is approximately 30 to 50% (23–26).

In patients with nonsuppressible nodular parathyroid hyperplasia, the persistently elevated PTH levels after restoration of normal renal function may play a primary role in maintaining a high bone turnover. Likewise, in patients with less severe secondary hyperparathyroidism, restoration of normal serum PTH levels may take several years. In addition, not infrequently, patients may develop de novo secondary hyperparathyroidism that results from progressive functional alterations of the transplanted kidney (1,15,17). Therefore, at least some of the skeletal and mineral abnormalities can be attributed to persistently elevated PTH levels. However, in many studies, the bone histopathologic findings are heterogeneous, without apparent correlation with posttransplantation serum PTH levels (4,5,8–10), suggesting that other factors that start operating after transplantation could play a central role in the development of these bone alterations.
Finally, we found a positive correlation between osteoblast surface and the serum levels of pre- and posttransplantation PTH, suggesting an important role of the hormone in preserving osteoblast number and activity after transplantation (22).

Indeed, previous studies by Jilka et al. (27) indicated that in mice, PTH increases the lifespan of mature osteoblasts by preventing apoptosis. These findings are in agreement with the fact that posttransplantation apoptosis was rare in patients with pretransplantation secondary hyperparathyroidism (22).

There is no evidence in the literature as to the optimal PTH values to be reached after renal transplantation, and it is not clear at whether these changes in bone cell morphology relate to the drop in PTH level or its absolute value. The high prevalence of persistent or de novo hyperparathyroidism after transplantation limits the feasibility of establishing these values. However, we could speculate that the PTH levels after transplantation, in patients with relatively normal renal function, should approach normal values to reestablish normal bone turnover, counteracting the effects of glucocorticoids and other immunosuppressant agents.

**Immunosuppressive Therapy.** Several studies suggest that posttransplantation immunosuppressive therapy constitutes a major factor in the pathogenesis of posttransplantation bone disease (28–31). The possible role of the calcineurin inhibitor cyclosporine remains controversial. Studies in animals and humans have shown that cyclosporine causes high bone turnover (28–30). In the rat, cyclosporine causes bone loss that is associated with increased bone resorption and formation (28); however, other studies have failed to demonstrate an effect of the drug on mineral and bone metabolism in renal transplant recipients (4,21,22). It should be considered, however, that the role of cyclosporine in transplant patients has been difficult to evaluate because its effects on bone turnover may be masked by glucocorticoids. Indeed, some reports indicated that, in the

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**Figure 1.** Representative microphotograph of bone biopsies showing cell apoptosis by the method of terminal deoxynucleotidyl transferase–mediated diUTP nick-end labeling (TUNEL). (A) Direct immunofluorescence staining of a biopsy of a patient with mixed bone disease showing TUNEL-positive osteoblasts (arrows). (B) Direct immunofluorescence staining of a biopsy from a patient with osteomalacia showing apoptotic bodies in the proximity of osteoid seams. (C) Direct immunofluorescence staining showing apoptotic osteocytes (arrows). Adapted from reference (22), with permission.

**Figure 2.** Representative microphotograph of bone biopsies from a patient before and 21 d after a kidney transplant. In the pretransplantation biopsy, the osteoid surface is covered by numerous cuboidal osteoblasts (arrows). In the biopsy that was obtained 21 d after transplantation, a change in osteoblast morphology is observed, shifting from the cuboidal morphology of active osteoblasts toward a flat and quiescent appearance (arrows). This phenomenon occurs even in the presence of an increased osteoid thickness.
absence of glucocorticoids, cyclosporine does not seem to induce bone loss (11). Tacrolimus, another calcineurin inhibitor, also causes trabecular bone loss in the experimental animal (29), but the information on the skeletal effect of this drug in humans is limited. In liver transplant recipients, tacrolimus has been associated with a significant higher femoral neck BMD 2 yr after transplantation as compared with patients who were treated with cyclosporine (32).

Limited information is available regarding rates of bone mass loss and fractures with newer immunosuppressive agents such as mycophenolate mofetil, sirolimus, basiliximab, or daclizumab. However, with these new regimens that also reduced glucocorticoid requirements, the risk of bone alterations may be reduced.

Many studies in kidney transplant patients have shown a correlation between glucocorticoid cumulative dose and BMD. In some biopsy studies, glucocorticoids also seem to be the sole determinant of bone volume and turnover (1,18). Thus, the cumulative and mean prednisone doses correlated negatively with bone turnover, whereas there was no correlation with cyclosporine cumulative dose or serum PTH (18). Because neither immunosuppressive therapy nor biochemical and hormonal parameters, including PTH, calcitriol, and serum phosphorus, correlated with delayed mineralization, they concluded that posttransplantation bone disease is mainly a consequence of glucocorticoid therapy (18).

The mechanisms whereby glucocorticoids may affect bone metabolism are multifactorial. These drugs increase osteoclastic resorption and decrease osteoblastic activity (33). Similarly, they also may affect indirectly bone metabolism by decreasing intestinal calcium absorption, leading to increased PTH secretion.

There is evidence suggesting that under normal conditions, an important number of osteoblasts undergo apoptosis (34). Moreover, studies in mice indicate that glucocorticoids promote osteoblast and osteocyte apoptosis and inhibit osteoblastogenesis, resulting in the defective bone formation that is observed in glucocorticoid-induced osteoporosis (35). Therefore, it seems possible that continuous use of glucocorticoids represents an important pathogenic factor in the development and maintenance of posttransplantation bone disease. It is interesting that we found early after transplantation a negative correlation between cumulative dose of glucocorticoids and posttransplantation osteoblastic surface (22). Because the study was performed during a period of maximal glucocorticoid use, it seems possible that glucocorticoids may have played a role in the increased osteoblast apoptosis. However, we could not demonstrate a correlation between glucocorticoids and the number of osteoblast apoptosis.

Localized osteonecrosis is another important long-term bone alteration that is associated with glucocorticoid use and represents the most debilitating of the musculoskeletal complications after renal transplantation. It is usually multifocal, with 50 to 70% of affected patients having more than one joint involved. It usually begins at the weight-bearing surface of the femoral head with collapse of surface bone and cartilage. Previous studies suggested an incidence of approximately 15% within 3 yr of transplantation; however, the risk decreased after the introduction of cyclosporine (with consequent decreases in glucocorticoid dosage) (36). A prospective study of 48 patients without evidence of femoral osteonecrosis before renal transplantation noted an incidence of 4% when examined by magnetic resonance imaging 6 mo after the procedure (37). Although many factors, such as vascular thrombosis, localized vasculitis, and fatty embolism, have been linked to the pathophysiology of this entity, chronic glucocorticoid administration remains the main risk factor for this complication.

**Role of the Hypophosphatemia.** Hypophosphatemia is observed frequently after renal transplantation (38–42). Decreased phosphate reabsorption in the proximal tubule seems to be the main factor responsible for posttransplantation hypophosphatemia. In our study, patients who showed increased osteoblastic apoptosis had significantly lower serum phosphorus levels compared with those without evident apoptosis (22). Furthermore, posttransplantation serum phosphorus correlated negatively with the number of apoptotic osteoblasts and positively with the number of active osteoblasts, suggesting a role of hypophosphatemia in the mechanisms that lead to posttransplantation bone disease. Indeed, hypophosphatemia has been associated with severe alterations in bone turnover that include a decrease in osteoblast activity that leads to rickets and osteomalacia (38,43). Nevertheless, further studies are required to prove a direct association between hypophosphatemia and osteoblast apoptosis. Persistently elevated PTH levels may be advocated as the cause of decreased phosphate reabsorption by the proximal tubule, but glucocorticoids and relatively low levels of 1,25(OH)₂ vitamin D₃ also may play a role.

A recent controlled study suggested that rapamycin-based immunosuppression prolonged the phosphate leak of the allograft kidney, leading to low serum phosphate levels during the first weeks after transplantation (44). Several recent studies strongly indicate that posttransplantation hypophosphatemia frequently is independent of PTH, suggesting the presence of a circulating humoral factor (phosphatonin) that induces phosphaturia in CKD and early transplantation (41,42). This factor increases the fractional excretion of phosphate by inactivation of the Na/Pi co-transporter, leading to inhibition of phosphate transport from the cell membrane to the cytosol (42). The persistence of this factor after transplantation would induce phosphaturia and hypophosphatemia.

**Role of the Phosphatonins.** Recent evidence from diseases that are characterized by phosphaturia and hypophosphatemia, such as X-linked hypophosphatemic rickets, autosomal hypophosphatemic rickets, and oncogenic osteomalacia, has identified fibroblast growth factor 23 (FGF23) as one of the possible candidates that fulfills the criteria for phosphatonin (45,46). It induces phosphaturia and hypophosphatemia. FGF23 has been cloned and characterized as a causative factor of oncogenic osteomalacia (45,46). Thus, the implantation of Chinese hamster ovary that expresses FGF23 into nude mice induces phosphaturia and osteomalacia (47).

Several studies have shown increased FGF23 levels in CKD (48–50). In these patients, FGF23 has shown a highly significant correlation with serum phosphorus levels. Given the relatively
high prevalence of hypophosphatemia in kidney transplant patients, it seems very provocative to examine a possible role of FGF23 in this observable fact and the posttransplantation bone alterations. Indeed, patients with osteoblast posttransplantation apoptosis had lower serum phosphorus levels compared with those without apoptosis (22). However, a cause–effect relationship requires further studies.

**Role of Deteriorating Renal Function.** The level of renal function that is achieved as a result of transplantation is a critical determinant of whether secondary hyperparathyroidism will be present. Patients who do not achieve a GFR >70 ml/min per 1.73 m² are at greater risk for progression of renal bone disease (51). In addition, as mentioned previously, some patients may develop de novo secondary hyperparathyroidism that results from progressive functional alterations of the transplanted kidney (52,53).

**Role of Hypogonadism.** In addition to the physiologic decrease in gonadal steroids that is associated with aging and menopause, endocrine dysfunction that leads to premature hypogonadism or impaired gonadal function is a common feature of CKD. Therefore, the role of hypogonadism and postmenopausal osteoporosis should not be overlooked when evaluating skeletal health in CKD and transplant patients (54–56).

In conclusion, although the alterations of bone remodeling after transplantation are heterogeneous, most studies reflect a decreased bone formation in the face of persistently elevated bone resorption. This imbalance in bone remodeling that favors resorption leads to a progressive loss of bone mass and increased fracture risk. As summarized in Figure 3, the mechanisms that are involved in these alterations include preexisting conditions such as the predominant state of bone turnover before transplantation, but posttransplantation events such as the effects of glucocorticoids, the occurrence of hypophosphatemia, and perhaps other biochemical factors seem to be fundamental for the alterations of bone remodeling.

**Treatment of Bone Disease in Renal Transplantation**

The management of bone disease after renal transplantation should take into account at least three different issues: The optimal treatment of renal osteodystrophy before renal transplantation and the prevention of bone disease during the first year, when the bone loss has been demonstrated to be most important; the treatment of decreased bone mass in the long-term renal transplant patient; and, perhaps more important, that posttransplantation bone disease, as shown in Table 2, is a complex disorder that extends beyond simple osteoporosis and includes systemic and local derangements of the bone and mineral metabolism that should be detected and treated accordingly.

Published studies that have addressed these issues often have significant limitations that include lack of randomization, inadequate number of patients, and that many patients are being treated with different immunosuppressive agents or treated with drugs that potentially affect bone and mineral metabolism (57). Similarly, most published studies have not proved that the variations in BMD have significantly changed after the proposed therapy, and, finally, very few clinical trials have addressed the crucial issue of bone fractures after transplantation.

**Treatment of Renal Osteodystrophy before Transplantation**

As discussed previously, several alterations of bone metabolism, including high-turnover bone disease (osteitis fibrosa cystica resulting from secondary hyperparathyroidism) and low-turnover bone disease (osteomalacia and adynamic bone disease), as well as hypogonadism, metabolic acidosis, and β2-microglobulin amyloidosis, may play different roles in the complex disorder of bone structure before transplantation. Therefore, optimal treatment of these abnormalities has a pivotal role in prevention and treatment of posttransplantation bone disease. Extensive reviews on the management of renal osteodystrophy before transplantation have been described elsewhere (58–60).

**Prevention of Early Bone Loss after Renal Transplantation**

Most of the studies regarding prevention of bone loss after transplantation have examined either different vitamin D metabolites or bisphosphonates. Table 3 summarizes the results of randomized, controlled studies that have evaluated preventive therapy in the early stages after renal transplantation. The majority of them used BMD as a surrogate of bone mass.
This same group in a recent report randomly assigned 60 adult plus intermittent calcitriol (0.5 μg/d) for 3 mo, prevented bone loss at the proximal femur and decreased PTH levels more rapidly than calcium supplementation alone. Josephson et al. (69) performed a prospective, randomized, double-blind study to determine whether calcium and calcitriol prevent posttransplantation bone loss. Sixty-four patients who did not have previous steroid exposure and were undergoing their first kidney or kidney-pancreas transplant were randomly assigned to calcium, calcium plus calcitriol, or placebo. At 1 yr, patients who were treated with placebo experienced a 2% decline in BMD at the lumbar spine and distal radius and a 1.3% increase at the femoral neck. In contrast, patients who were treated with calcium and calcitriol had a 0.1% decline at the spine and 2.9 and 4.8% increases at the radius and femur, respectively. In conclusion, vitamin D metabolites may have a potential role in the prevention of bone mass loss after transplantation, particularly by mitigating the bone-wasting effect of glucocorticoids by enhancing calcium absorption and reducing PTH secretion.

**Bisphosphonates in the Prevention of Bone Loss after Renal Transplantation**

In two studies that used multiple doses of pamidronate during the initial months after renal transplantation, prevention of bone loss occurred, even after the treatment was discontinued. In the study of Fan et al. (70) in 26 randomly assigned patients, intravenous pamidronate (0.5 mg/kg) at the time of transplantation and again 1 mo later prevented the 1-yr bone loss that was observed in the placebo group at the lumbar spine (6.4%) and at the femoral neck (9%). In the study by Coco et al. (71), 76 patients were randomly assigned to receive 60 mg of intravenous pamidronate within 48 h after transplantation, followed by 30 mg at months 1, 2, 3, and 6, plus oral calcitriol and calcium or calcitriol plus calcium alone in the placebo group. This study demonstrated that pamidronate preserved bone mass at 6 and 12 mo as assessed by bone densitometry and histomorphometry. Control subjects had decreased vertebral BMD at 6 and 12 mo by 4.8 and 6.1%, respectively. Surprising, bone histology revealed low-turnover bone disease in 50% of the patients at baseline. At 6 mo, all of the pamidronate-treated patients showed evidence of adynamic bone histology, on the basis of static parameters of cellularity, woven osteoid, and fibrosis, whereas 50% of the control subjects continued to have or developed decreased bone turnover. Therefore, pamidronate treatment was associated with development of adynamic bone histology. No fracture data were available in these two studies.

### Table 2. Changes in bone metabolism after renal transplantation

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<tr>
<th>Beneficial Effects</th>
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<td>Decreased phosphorus levels</td>
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<tr>
<td>Decreased serum PTH</td>
<td>Hypercalcemia</td>
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<td>Increased 1,25(OH)₂D₃ levels</td>
<td>Persistent or de novo hyperparathyroidism</td>
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<td>Decreased aluminum deposits</td>
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<td>Decreased soft tissue calcifications</td>
<td>Decreased BMD</td>
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<td>Increased fracture risk</td>
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*BMD, bone mineral density.*
and the question of the improvement of BMD with adynamic bone histology requires further study to assess the long-term bone health in renal transplant recipients.

Intravenous ibandronate, another potent bisphosphonate, was used by Grotz et al. (72) in 80 randomly assigned transplant recipients at a dose of 1 mg immediately before the transplant and 2 mg at 3, 6, and 9 mo after transplantation. The study demonstrated prevention of bone loss, spinal deformation, and loss of body height during the first year after kidney transplantation in the treated group.

Zoledronate was evaluated by Haas et al. (73) in a 6-mo, randomized, placebo-controlled study in 20 kidney transplant recipients who received either 4 mg of zoledronic acid or placebo twice within 3 mo after engraftment. Lumbar spine BMD was increased in the zoledronic acid group without change in the placebo group. Similarly, femoral neck BMD showed no change in the zoledronic acid group but decreased in the placebo group. Bone histomorphometric analysis evidenced that high-turnover bone disease resolved similarly in both groups, with a significant reduction in the eroded bone surface and the osteoclastic and osteoblastic surface. Serologic markers of bone formation and resorption were significantly lower in the zoledronic acid–treated patients throughout the study. The same group of investigators evaluated whether this early short-term intervention exhibited a sustained bone-sparing effect later in time, demonstrating that zoledronate therapy confers

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<th>Table 3. Randomized, controlled studies that evaluated preventive therapy immediately after renal transplantation</th>
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| (67)     | 60          | 12 mo    | 1. α-Calcidiol 0.5 μg  
2. Alendronate 5 mg/d  
3. Calcitonin 200 IU every other day + 500 mg calcium (all groups) | Lumbar spine and femoral neck in all groups | ND |
| (69)     | 64          | 12 mo    | 1. Calcium  
2. Calcitriol + calcium | Lumbar spine and femoral neck in both groups | ND |

*ND, not determined.*
Control of Mineral Metabolism Alterations after Renal Transplantation

As shown in the Kidney Disease Outcomes Quality Initiative clinical practice guidelines for bone metabolism and disease in CKD, serum levels of calcium, phosphorus, total CO₂, and plasma intact PTH should be monitored after kidney transplantation (17). During the first week after kidney transplantation, serum levels of phosphorus should be measured daily. Kidney transplant recipients who develop persistently low levels of serum phosphate should be considered for treatment with phosphate supplementation. However, phosphate administration is not without risk, and caution should be exerted because it may exacerbate a possibly already existing secondary hyperparathyroidism. Therefore, every attempt should be made to prescribe the strict minimum doses.

It has been shown that the administration of dipyridamole increases renal phosphate reabsorption in experimental animals and humans (79); nevertheless, its use in renal transplant patients has not been performed. Metabolic acidosis after kidney transplantation may be present, and correction of the acidosis may assist in the general resolution of the electrolyte abnormalities that are associated with posttransplantation osteoporosis. Hypercalcemia after kidney transplantation is common and usually is due to hyperparathyroidism that persists from the preceding period of CKD. Increased serum calcium concentration has been described to persist for years after transplantation. Parathyroid gland hypertrophy and autonomy hardly resolve after establishment of sufficient renal function except in mild cases or when secondary to vitamin D deficiency. In 1 to 5% of transplant recipients, abnormal PTH secretion persists, causing hypercalcemia that may require parathyroidectomy (17).

Role of Calcimimetics

Treatment of persistent hyperparathyroidism in renal transplant patients who are resistant to calcium and vitamin D sterols is limited and on many occasions requires parathyroidectomy. Calcimimetics inhibit PTH secretion by modulating the calcium-sensing receptor in the parathyroid gland and could represent an alternative approach in these patients. In a recent study, 30 mg/d cinacalcet for 3 mo normalized the serum calcium in all but two patients, whereas serum PTH and phosphate levels did not change significantly (80). Similarly, Serra et al. (81) showed in a short study of 10 wk duration that cinacalcet was effective in correcting the hypercalcemia and reducing PTH values in patients who received a transplant and had persistent hyperparathyroidism. Finally, a recent retrospective study showed that cinacalcet was able to lower the serum calcium and increase serum phosphorus, with no significant changes in the PTH values (82). Nevertheless, Boulanger et al. (83) showed a therapeutic failure of cinacalcet in a single case report. New prospective studies are required to reach a firmer conclusion about the possible beneficial effect of this drug.

Treatment of Bone Loss in the Long-Term Renal Transplant Recipient

As we have shown here, bone loss prevention is feasible in the renal transplant patient. We now turn to the treatment of the patient with osteoporosis/osteopenia during the later post-transplantation period, as well as those with established post-transplantation bone disease. Several studies have examined the effects of different drugs or combination of them on BMD. Table 4 summarizes the results of the randomized, controlled studies that have evaluated various schemes of treatment for long-term posttransplantation bone disease. As discussed previously, no studies in this group evaluated fracture reduction rate after treatment, and only one of them examined bone histomorphometry (84).
<table>
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<th>Reference</th>
<th>Sample Size</th>
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| (85)      | 45          | 12 mo    | 36 mo                           | 1. Calcitriol 0.5 μg  
2. Calcitonin 200 IU/d intranasal for 2 wk every 3 mo + calcium in all groups | Lumbar spine in both groups  
No change in femoral neck | ND |
| (84)      | 45          | 12 mo    | 119 mo                          | Calcitriol 0.25 μg + calcium 500 mg | NS | Bone histomorphometry: significant osteoclast suppression and a trend to maintain trabecular bone volume |
| (88)      | 35          | 12 mo    | 49 mo                           | 1. Alendronate 10 mg/d  
2. Calcitriol 0.5 μg + 1000 mg in both groups | Lumbar spine in both groups.  
No change in femoral neck in both groups | ND |
| (90)      | 117         | 12 mo    | 7.1 yr (alendronate), 9.6 yr (calcitriol) | 1. Alendronate 10 mg/d  
2. Calcitriol 0.25 μg + 500 mg in both groups | Lumbar spine and femoral neck in both groups | ND |
| (86)      | 30          | 12 mo    | 48 mo                           | α-Calcidiol 0.25 μg | Lumbar spine | ND |
| (87)      | 46          | 12 mo    | 50 mo                           | 1. Daily oral clodronate (800 mg)  
2. Calcitonin 200 IU/d intranasal for 2 wk every 3 mo + 500 mg in both groups | Lumbar spine and femoral neck in both groups | ND |
| (89)      | 40          | 12 mo    | 61 mo                           | 1. Alendronate 10 mg/d + calcitriol 0.5 μg  
2. Calcitriol 0.5 μg + calcium (500 mg) in both groups | Lumbar spine and femoral neck in alendronate + calcitriol group  
No change in calcitriol group | ND |
**Vitamin D Metabolites**

Calcitriol has been studied either alone or in combination with other drugs. In a randomized trial by Cueto-Manzano et al. (84), the effect of calcitriol plus calcium carbonate on the bone loss that was associated with long-term renal transplantation was investigated in 30 patients who were an average of 10 yr after transplantation. This treatment did not significantly improve bone loss in the distal radius, lumbar spine, or femoral neck. However, significant osteoclast suppression and a trend to maintain trabecular bone volume and wall thickness were observed in the calcitriol treatment group.

In a study by Ugur et al. (85), in patients with BMD <1 SD of normal and an average of 3 yr after transplantation, calcitriol (0.5 µg/d) or intranasal calcitonin plus calcium stopped the bone loss that was observed in the calcium-treated control group. In children, El-Husseini et al. (86) ascertained the value of α-calcidiol in the treatment of bone loss in young renal transplant recipients who were a mean duration after transplantation of 48 ± 34 mo.

Some of these studies have reported hypercalcemia and hypercalciuria in some patients while on calcitriol therapy. Nevertheless, these adverse effects wane quickly after the drug is stopped.

**Bisphosphonates**

Bisphosphonates have been shown to have beneficial effects in the treatment of postmenopausal osteoporosis, increasing the BMD at trabecular and cortical sites and dramatically reducing the number of bone fractures in these patients. They act by inhibiting osteoclast-mediated bone resorption. Second- and third-generation bisphosphonates are very effective in preventing bone loss after transplantation. Grotz et al. (87) randomly assigned 46 patients with osteopenia or osteoporosis to daily oral clodronate (800 mg) or daily intranasal calcitonin (200 IU) for 2 wk every 3 mo. These two groups were compared with a control group. Every patient was supplemented with 500 mg/d calcium. BMD at the lumbar spine was increased by 4.6% in the clodronate group, by 3.2% in the calcitonin group, and by 1.8% in the control group. However, the differences in BMD changes among the groups were not statistically significant.

Different studies have compared calcitriol with alendronate in long-term renal transplant patients. Koc et al. (88) found similar improvement in lumbar spine BMD in 35 patients who were treated with calcium and either alendronate (10 mg/d) or calcitriol (0.5 µg/d). In another study, Giannini et al. (89) enrolled 40 patients who had received a renal allograft at least 6 mo before. The patients were randomly assigned into a group of 10 mg/d alendronate, 0.5 µg/d calcitriol, and 500 mg/d calcium carbonate and a group of 0.5 µg/d calcitriol and 500 mg/d calcium carbonate. Lumbar spine BMD increased significantly after 1 yr only in the alendronate-treated patients. Finally, in a larger study (n = 117) of long-term renal transplant patients, treatment during 1 yr with calcium and either alendronate or calcitriol was associated with significant and similar increases in lumbar spine and femoral neck BMD (90).

Most of these studies showed that bisphosphonates generally are well tolerated after transplantation with few adverse effects. Therefore, the use of bisphosphonates in long-term studies has not been associated with higher incidence of renal dysfunction or increased mortality (91). Nevertheless, as pointed out in the section Prevention of Early Bone Loss after Renal Transplantation, the amount of bone loss after transplantation does not necessarily predicts fracture risk, an issue that was not evaluated in these trials. Therefore, more studies that evaluate the role of bisphosphonates in posttransplantation patients and address fracture reduction rate are required.

**Conclusions**

The evidence that is provided by the various studies suggests that preventive therapy could provide certain benefit in many patients, because there is a rapid bone loss during the first year after transplantation. Although more studies are needed, therapy should be considered in patients who are at risk, such as those with significantly low BMD, history of fractures, or biopsy-proven posttransplantation bone disease.

All patients should get the recommended daily allowance of calcium (1000 mg/d for men and 1500 mg for postmenopausal women) and vitamin D. In addition, special care should be taken to prevent or correct hypophosphatemia, particularly in the early stages of transplantation.

As pointed out previously, calcitriol and bisphosphonates act by different mechanisms to prevent posttransplantation bone loss, and both types of drugs have shown beneficial effects. Nevertheless, we think that bisphosphonates could have a certain role as the initial therapy for the prevention of bone loss during the first year after transplantation, provided that treatment is based on a critical clinical assessment and individualized to the specific patient. Calcitriol and other vitamin D metabolites could be used alone or in conjunction with bisphosphonates in selected patients. Care should be taken with the use of bisphosphonates because of potential oversuppression of bone turnover, particularly in patients with initial low bone turnover or in those with impaired renal function, in whom the drug may accumulate. Thus, a transiliac crest bone biopsy with double tetracycline labeling and histomorphometric analysis often should be necessary to categorize the type of bone disease before renal transplantation. However, this approach is limited because only a few centers around the world have the ability or expertise to perform and interpret histomorphometric analysis of bone biopsies. Given the heterogeneity of posttransplantation bone disease, the generalization of therapeutic strategies is very difficult, and individualization of treatment should be encouraged. Finally, more studies that are powered to evaluate the fracture risk reduction rate should be initiated.

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