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REVIEW

Osteoporosis after solid organ and bone marrow transplantation

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Abstract Organ transplantation has become increasingly common as a therapy for end-stage renal, liver, cardiac and pulmonary disease. The population of patients who have survived organ transplantation has grown dramatically over the last 2 decades. Although organ transplant recipients now benefit from greatly improved survival, long-term complications of organ transplantation, such as osteoporosis, adversely affect quality of life and must be addressed. In the early post-transplantation period, the effects of high dose glucocorticoids, combined with other immunosuppressive drugs such as cycosporine A and tacrolimus, cause rapid bone loss particularly at the spine and proximal femur. In this setting, fracture incidence rates as high as 25–65% have been reported. Treatment and prevention strategies must target this early post-transplant period, as well as the patient awaiting transplantation and the long-term transplant recipient. This review will discuss the clinical features of transplantation osteoporosis, the pathophysiology of post-transplantation bone loss and prevention and therapy of this unique bone disease.

Keywords Bisphosphonates · Cyclosporine · Fracture Glucocorticoids · Osteoporosis · Tacrolimus Transplantation

Introduction

Within the past 3 decades, organ transplantation has become an established therapy for end-stage diseases of the kidney, heart, liver and lung. Survival after organ transplantation is improving and increasing numbers of organ transplantation procedures are performed each year. Unfortunately, improved survival rates have highlighted new therapeutic challenges in the long-term management of these patients. The increased propensity to fracture after organ transplantation is one such long-term complication that significantly affects quality of life of transplanted patients.

The pathogenesis of transplantation osteoporosis is complex and incompletely understood. It is probably related to a combination of insults to the skeleton that occur both before and after organ transplantation. Cardiac, renal, lung and liver failure each have unique pathophysiologies that influence bone and mineral metabolism before transplantation. Additional factors such as aging, nutritional deficiencies, immobility, tobacco and alcohol may affect the skeletons of these patients before and after transplantation. In the post-transplant period, patients are then subjected to a drug regimen that usually includes high doses of glucocorticoids, the most common cause of secondary osteoporosis. Moreover, glucocorticoids are prescribed in combination with other immunosuppressive agents, such as calcineurin inhibitors (cyclosporine A or tacrolimus), rapamycin, mycophenylate mofetil, and azathioprine. Of these agents, both cyclosporine A and tacrolimus are thought to have specific adverse effects upon skeletal integrity. It is thought that the independent and interrelated skeletal effects of glucocorticoids and calcineurin inhibitors lead to a form of bone disease characterized by rapid bone loss and high rates of fractures.

In this review, we will discuss the clinical features of osteoporosis specific to different types of organ failure, the various immunosuppressive medications that contribute to the pathophysiology of post-transplantation bone disease, the clinical features of osteoporosis specific to different types of organ transplantation, and the prevention and treatment of osteoporosis in this ever-enlarging group of patients.

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Bone disease in candidates for organ transplantation

Studies evaluating bone disease both before and after transplantation have used varying definitions of osteoporosis. For the purposes of this review, we have accepted definitions of osteoporosis that describe subjects in relation to age and gender matched controls (Z-score ≤ -2 SD), as well as in relation to criteria established by the World Health Organization in postmenopausal Caucasian women (T-score ≤ -2.5 SD).

End-stage renal disease (ESRD)

Some form of renal osteodystrophy is almost universal in patients with longstanding chronic renal insufficiency. A complete discussion of renal osteodystrophy is beyond the scope of this review and the reader is referred to recent reviews of this topic [1,2,3]. Suffice it to say that patients with renal failure have the most complex form of pre-transplant bone disease. Several different pathogenetic mechanisms may be involved that may ultimately lead to one or more types of bone disease including hyperparathyroidism, osteomalacia, adynamic bone disease perhaps caused by overzealous use of active vitamin D metabolites to control hyperparathyroidism, osteosclerosis, and beta-microglobulin amyloidosis. In addition, hypogonadism, common in patients with ESRD, and certain medications (loop diuretics, heparin, glucocorticoids or cyclosporine) may also affect bone health prior to transplantation. In dialysis patients, the prevalence of low bone mineral density (BMD) is increased at the spine, hip, and distal radius [4,5,6]. Risk factors for low BMD include female gender [5], older age [5], amenorrhea [4], lower weight or body mass index (BMI) [5,7], elevated parathyroid haemone (PTH) [5,7], duration of hemodialysis [7], and previous renal transplantation [4]. The prevalence of vertebral fracture is as high as 21% [7] and the relative risk of hip fracture is increased 2- to 14-fold [8]. Increased fracture risk has correlated with older age [8,9], female gender [8,9], Caucasian race [8,9], diabetic nephropathy [10], the presence of peripheral vascular disease [9], low lumbar spine (LS) BMD [7], and lower PTH levels [7].

Congestive heart failure

Patients with severe congestive heart failure (CHF) are commonly found to have low BMD [11,12,13]. Immobility, poor nutritional status, and medications such as furosemide and heparin may all contribute to the bone loss. In patients with CHF awaiting heart transplantation, LS osteopenia (T-score ≤ -1.0) was found in 43%, and osteoporosis (T-score ≤ -2.5) in 7% of patients [13]. Vitamin D deficiency, manifested by low serum 25-hydroxyvitamin D (25-OHD) and/or serum 1,25-dihydroxyvitamin D [1,25 $(OH)_2$ D] levels, and secondary hyperparathyroidism were also common. Urinary markers of bone resorption were increased.

End-stage liver disease

Chronic liver diseases (cholestatic liver diseases [14,15,16], alcoholic cirrhosis [17,18,19], viral hepatitis [20], hemochromatosis [21], and glucocorticoid-treated chronic active hepatitis [22,23]) are frequently associated with low BMD, fractures and abnormalities of mineral metabolism [24,25]. Osteoporosis at the spine or hip (T-score ≤ -2.5 or Z-score ≤ -2) has been documented in 26–52% of patients awaiting liver transplantation [25,26,27]. In a recent study of 243 patients evaluated for liver transplantation [27], low BMD was correlated with increased age, lower body weight, and the presence of cholestatic liver disease. Pre-transplantation laboratory evaluation has documented decreased serum concentrations of 25-OHD, PTH, osteocalcin and testosterone in these patients when compared to healthy controls [28].

Chronic respiratory failure

Severe osteoporosis may be most common in patients awaiting lung transplantation. Hypoxia, respiratory acidosis, tobacco, and glucocorticoids may all contribute. Cystic fibrosis (CF) is associated with additional risk factors for bone disease (pancreatic insufficiency, vitamin D deficiency, calcium malabsorption, hypogonadism, inactivity) [29]. Densitometric osteoporosis has been reported in 29–61% of patients with end-stage pulmonary disease [30,31,32,33,34,35,36]. In a cross-sectional evaluation of 15 patients with chronic obstructive pulmonary disease awaiting transplantation, 45% had osteoporosis (Z-score ≤ -2) at the spine or hip [30]. In patients with CF, a retrospective cohort study of 70 patients found osteoporosis (T-score ≤ -2.5) in 57% [37]. Cross-sectional studies have found osteoporosis (Z-score ≤ -2) in 13–34% [38,39], and have shown an inverse correlation between BMD and disease severity. A recent study of 74 candidates for lung transplantation found that chronic glucocorticoid use, BMI, and pulmonary functional parameters (FEV_1 percent of predicted) correlated significantly with BMD at the spine and hip [36]. Histomorphometric analysis suggests low bone turnover and reduced bone formation [40]. In patients with CF, vertebral and rib fractures were 10- to 100-fold more common than expected among the general population [37]. Prevalent vertebral fractures have also been documented in 29% of patients with emphysema [32].

Candidates for bone marrow transplantation

Patients receiving allogeneic bone marrow transplantation (BMT) for various hematological conditions are exposed to many factors that may influence bone mass and bone metabolism. Induction and consolidation regimens (which may involve chemotherapeutic agents, glucocorticoids, and/or total body irradiation), hypogonadism, and immobility may all contribute. In patients studied prior to transplantation (after chemotherapy), normal bone density at the LS and femoral neck (FN) has been documented in 72%, osteopenia in 24% and osteoporosis in only 4% [41].

Skeletal effects of immunosuppressive drugs

Glucocorticoids

Glucocorticoids are included in most post-transplant immunosuppressive regimens. High doses (e.g. $\leq$ 50 mg/day of prednisone or prednisolone) are commonly prescribed immediately after transplantation with subsequent dose reduction over several weeks and transient increases during rejection episodes. Doses vary with the organ transplanted, the number and management of rejection episodes, and with the practice of individual transplantation programs. The introduction of cyclosporine A and tacrolimus, and more recently, rapamycin and daclizumab have permitted more rapid lowering of glucocorticoid doses. However, there is still sufficient exposure to glucocorticoids, particularly in the early period after transplantation, to cause substantial bone loss.

Glucocorticoids reduce BMD predominantly at trabecular sites, and even small doses (equivalent to 2.5–7.5 mg/day prednisone) are associated with markedly increased fracture risk [42,43,44]. Glucocorticoid-induced osteoporosis is characterized by direct and profound reductions in bone formation [45,46]. Glucocorticoids lower osteoblast numbers by decreasing replication and differentiation and shorten osteoblast lifespan by causing apoptosis of osteoblasts and osteocytes. Glucocorticoids also reduce osteoblast function by inhibiting expression of genes for type I collagen, osteocalcin and other bone matrix proteins, transforming growth factor β (TGFβ) and receptor activator for NFκB-ligand (RANK-L). Early in the course of their administration, glucocorticoids may increase bone resorption. However, effects on resorption are minor in comparison to the profound effects on formation. With chronic, long-term use, it is now accepted that glucocorticoid administration is associated with decreased bone resorption. Since administration of glucocorticoids alone is not usually associated with increased bone resorption, it is thought that the increased resorption observed in the early and late phases of the post-transplantation setting results from other mechanisms (calcineurin inhibitors, other medications, renal insuffiency, secondary hyperparathyroidism, immobility, nutritional factors).

Cyclosporine

The introduction of cyclosporine (CsA) to post-transplantation immunosuppressive regimens in the early 1980s was associated with a marked reduction in the number of rejection episodes and an improvement in graft survival [47]. CsA inhibits calcineurin, a T cell phosphatase, and reduces T cell function via suppression of regulatory genes expressing products such as IL-2, interleukin receptors, and the protooncogenes H-ras and c-myc [47,48,49]. Early in vitro studies demonstrated that CsA inhibits bone resorption in isolated osteoclasts [49,50] and inhibits osteoclast formation in marrow cultures [51]. However, in vivo studies in rodent models strongly suggest that CsA has independent adverse effects on bone and mineral metabolism that could contribute to bone loss after organ transplantation [49]. Studies in the rat showed that CsA administration resulted in severe bone loss that was dose- and duration-dependant and preferentially affected trabecular bone [49,52,53,54]. In contrast to in vitro studies, CsA in vivo was associated with marked increases in both bone resorption and formation, and with increased levels of osteocalcin and $1,25(OH)_2D$ [49,53]. The CsA-mediated bone loss was associated with testosterone deficiency [55], independent of renal function [49] and was attenuated by parathyroidectomy [56]. In the rat model, antiresorptive agents such as estrogen [57], raloxifene [58], calcitonin [59] and alendronate [60], have been shown to alleviate the CsA-induced bone loss. The mechanism of CsA-induced bone loss remains unclear. It is possible that increased bone turnover is caused by direct effects of CsA on calcineurin genes expressed in osteoclasts [61]. However, T lymphocytes are essential mediators of its effects in vivo [62], suggesting that CsA may act on bone cells indirectly via changes in cytokine production due to alterations in T cell function. These studies in animal models suggest that CsA may, in part, mediate the high-turnover aspects of post-transplantation bone disease. In contrast, other researchers have reported a lack of bone loss in renal transplant patients receiving CsA in a glucocorticoid-free regimen [63,64,65]. Thus, the isolated clinical effects of CsA on the human skeleton are still unclear.

Tacrolimus

Tacrolimus (FK506), a fungal macrolide, is another calcineurin inhibitor that inhibits cytokine gene expression, T cell activation, and T cell proliferation [49]. Histomorphometric studies in the rat also showed severe trabecular bone loss with FK506 [50]. However, a more recent rat study found that FK506 was associated with lower deoxypyridinoline excretion and less trabecular

bone loss than CsA [66]. The mechanism of bone loss associated with FK506 and CsA are thought to be similar (vide supra).

Few studies have evaluated the skeletal effects of FK506 in humans. Both cardiac [67] and liver [68] transplant recipients have sustained rapid bone loss with FK506-based immunosuppression. However, other researchers have noted decreased bone loss with FK506 [69,70]. A recent study of liver transplant recipients found that those receiving FK506 had significantly higher FN BMD 2 years after transplantation than those receiving CsA [70]. Cumulative glucocorticoid dose was significantly lower in the FK506-treated group, suggesting that FK506-based regimens may benefit the skeleton by permitting use of lower glucocorticoid doses.

Other agents

Limited information is available regarding the effects of other immunosuppressive drugs on BMD and bone metabolism. Azathioprine, sirolimus (rapamycin), and mycophenelate mofetil do not cause bone loss in the rat model [71,72,73]. The skeletal effects of newer agents, such as daclizumab, have not been studied.

Clinical features of transplantation osteoporosis

The clinical features of osteoporosis after transplantation are summarized in Table 1, and will be discussed in this section by organ type.

Renal transplantation

In general, renal osteodystrophy improves after transplantation. PTH levels decline [74,75] and aluminum bone disease resolves [74] during the first post-transplant year. Bone resorption remains elevated in a substantial proportion of renal transplant recipients, as evidenced by biochemical [76] and histomorphometric [77] studies. However, histomorphometric studies also demonstrate osteoblast dysfunction and decreased mineral apposition rate, consistent with glucocorticoid effect [74,77,78,79].

Cross-sectional studies of patients evaluated several years after renal transplantation have reported low BMD. Osteoporosis (defined as a BMD Z-score ≤ -2 or a T-score ≤ -2.5) has been found in 17–49% at the LS, 11–56% at the FN [76,80,81,82,83,84,85,86] and 22–52% at the radius [76,85,86]. Several studies have shown a correlation between cumulative dose of glucocorticoids and osteoporosis [84,85,87].

Longitudinal studies show that the majority of bone loss occurs in the first 6–18 months after transplantation [74,75,88,89,90,91,92]. The amount of bone loss ranges from 4 to 9% at the LS and 5 to 8% at the FN. Some studies report gender differences in the site of bone loss, with men losing more bone at the hip [90,91]. A small study of 47 renal transplant patients documented a significantly lower rate of LS bone loss over the first year in those patients receiving an alternate day prednisone regimen [93]. Bone loss has not been consistently related to gender, patient age, cumulative glucocorticoid dose, rejection episodes, activity level, or PTH levels.

Longitudinal studies have also evaluated bone loss several years after renal transplantation. In a recent study [94], changes in BMD over 1 year were evaluated in 62 patients at a mean of 6.5 years after renal transplantation. A subset of 43 patients with elevated markers of bone turnover (urinary pyridinoline, urinary deoxypyridinoline, or serum osteocalcin) lost significantly more bone mass at the spine and the hip compared to the group without high bone turnover [94]. In renal transplant patients studied a mean of 9.5 ± 3.4 years after transplantation, glucocorticoid withdrawal was associated with a significant increase in LS and FN BMD at 1 year compared to those who remained on low dose glucocorticoids [95]. Glucocorticoid withdrawal has been associated with a significant increase in markers of bone formation and little change in markers of bone resorption [95].

Table 1 Osteoporosis after solid organ and bone marrow transplantation

Type of transplant	Prevalence after transplantation		Bone loss: first post-transplant year	Fracture incidence
	Osteoporosis[a]	Fractures		
Kidney[b]	11–56%	Vertebral: 3–29% Peripheral: 11–22%	Spine: 4–9% Hip: 8%	Vertebral: 3–10% Peripheral: 10–50%
Heart	25–50%	Vertebral: 22–35%	Spine: 3–8% Hip: 6–11%	10–36%
Liver	30–46%	Vertebral: 29–47%	Spine: 0–24% Hip: 2–4%	Vertebral: 24–65%
Lung	57–73%	42%	Spine: 1–5% Hip: 2–5%	18–37%
Bone marrow	4–15%	5%	Spine: 2–9% Hip: 6–11%	1–16%

[a]Accepted definitions included BMD of spine and/or hip (by dual X-ray absorptiometry) ≥2 SD below age- and sex- matched control or ≥2.5 SD below young normal controls

[b]Definition of osteoporosis also included BMD of predominantly cortical sites such as the femoral shaft or proximal radius that are adversely affected by excessive PTH secretion

In renal transplant patients, fractures affect appendicular sites (hips, long bones, ankles, feet) more commonly than axial sites (spine and ribs) [96,97,98]. Women [97,98,99] and patients transplanted for diabetic nephropathy [98,99,100,101] have a particularly increased risk of fractures. The majority of fractures occur within the first 3 years after transplantation [98,100]. A recent cohort study of 101,039 patients with ESRD found that renal transplantation was associated with a 34% greater risk of hip fracture compared to patients continuing dialysis [10]. This increased relative risk of hip fracture in the transplant recipients disappeared after the first 1–3 years following transplantation.

Kidney-pancreas transplantation

Particularly severe bone loss and fractures have also been documented in this small population of transplant recipients with type 1 diabetes and ESRD. In a cross-sectional study of 31 patients, a mean of 40 ± 23 months after transplantation, 23% had osteoporosis (T-score < -2.5) at the LS and 58% had osteoporosis at the FN [102]. Although elevated osteocalcin was found in 45%, none had elevated hydroxyproline excretion. Vertebral or non-vertebral fractures were documented in 45%, and fractures were more prevalent in patients with osteoporosis at the LS ($P = 0.05$) [102]. Retrospective studies by other groups have documented a fracture prevalence of 26–49% when patients are evaluated several years after kidney-pancreas transplants [2,103].

Cardiac transplantation

Low BMD is also common after cardiac transplantation. Approximately 2 years after transplantation, LS and FN Z-scores ≤ -2 were found in 28% and 20%, respectively, of 40 heart transplant recipients [104]. The most rapid rate of decline in BMD occurs in the first year. LS BMD declines by 6–10% during the first 6 months [105,106,107,108,109], with no decrease thereafter [105,108]. FN BMD falls by 6–11% in the first year [105,108,109,110,111]. BMD stabilizes at the hip, but continues to decline at the wrist over the second and third years post-transplant, perhaps reflecting post-transplant secondary hyperparathyroidism. In some studies, there has been partial recovery of LS BMD in later years [105,112]. Vitamin D deficiency and testosterone deficiency (in men) are associated with more severe bone loss during the first year [105]. Some studies [105], but not others [106,108,112], have found correlations between glucocorticoid dose and bone loss.

Cross-sectional studies of cardiac transplant recipients have found vertebral fracture prevalence rates of 22–35% [11,104,113]. One longitudinal study demonstrated a vertebral fracture incidence of 36% during the first year following cardiac transplantation [114]. The majority of fractures involved the spine, and 85% of patients who sustained fractures did so within the first 6 months. Similar results were found in a European study of 105 patients [115] in which approximately one-third of the patients had sustained a vertebral fracture by the end of the third post-transplant year. An LS T-score below –1.0 conferred a greater risk (hazard ratio 3.1) of vertebral fracture [115].

With respect to the biochemical correlates of the bone loss, there are transient increases in markers of bone resorption and decreases in markers of bone formation (osteocalcin) soon after transplantation [105,116]. Both return to the upper end of the normal range by 6–12 months after transplantation [105]. Other studies have observed sustained high bone turnover [11,104,108,113,117,118] that differs from the low-turnover state and decreased osteocalcin levels found in patients on glucocorticoids alone [44,46]. Secondary hyperparathyroidism, perhaps related to CsA-induced renal insufficiency [113], has been documented in some [113,117,118] but not other studies [11,105].

Liver transplantation

The progression of osteoporosis after liver transplantation resembles that following cardiac transplantation [28,115,119,120,121,122,123,124,125]. Bone loss and fracture rates are highest in the first 6–12 months. Spine BMD declines by 2–24% during the first year in most earlier studies [28,120,122,123]. In contrast to these, a more recent study documented bone loss of only 2.3% at the FN, with preservation of spinal BMD during the first year after liver transplantation [126], and another documented increases in BMD at 1 year [26]. Recovery of BMD at the spine and hip has been documented during the second and third years following transplantation in patients receiving no treatment for bone disease [26,28,122,127,128]. Fracture rates range from 24 to 65% [28,115,121,122,129,130] and, as with cardiac transplantation, ribs and vertebrae are the most common sites [28,115,122,129]. Although women with primary biliary cirrhosis have been reported to have particularly high fracture rates [122,123], other studies have suggested that type of liver disease, glucocorticoid exposure, and markers of bone turnover do not reliably predict bone loss or fracture risk [28,115,129]. Other variables such as older age and pre-transplant BMD at the LS and FN predicted post-transplantation fractures in one recent prospective study [28] and pre-transplant vertebral fractures predicted post-transplant vertebral fractures in two recent prospective studies [115,130].

The high-turnover state documented after liver transplantation [28,131,132,133,134] contrasts with decreased bone formation and low-turnover seen before transplantation [134]. This change from low to high bone turnover may be due to resolution of cholestasis or hypogonadism, increased PTH, CsA or FK506, or a combination of factors. Although PTH is generally

normal after liver transplantation [131,135], significant increases in PTH have been observed during the first 3–6 months [26,28,136]. As in cardiac transplant patients, it is possible that a decline in renal function due to renal effects of CsA or FK506 may lead to the development of secondary hyperparathyroidism in the post-transplantation period.

Lung transplantation

Lung transplant recipients are probably the most severely affected patients with transplantation osteoporosis. In one cross-sectional study, 73% had osteoporosis (Z-score ≤ -2) [30]. During the first year after lung transplantation, rates of bone loss at the LS and FN range from 2 to 5% [34,137,138]. Fracture rates are also high during the first year, ranging from 18 to 37% [137,138], even in patients who received antiresorptive therapy to prevent bone loss. Some [34,137], but not all [138] studies have found that bone loss correlates with glucocorticoid dose. Bone turnover markers are consistent with increased resorption and formation [138,139]. Histomorphometric data from transplanted and non-transplanted CF patients shows evidence of increased osteoclastic and decreased osteoblastic activity [140].

Bone marrow transplantation

Bone marrow transplantation protocols expose recipients to induction and consolidation regimens (which may involve chemotherapeutic agents, glucocorticoids, and/or total body irradiation) as well as post-transplantation immunosuppressive regimens that often utilize CsA and glucocorticoids. Over the first year after BMT, studies have found rates of bone loss of 2–9% at the LS and 6–11% at the FN [41,141,142,143,144,145]. Recovery of LS BMD after the first 6–12 months has also been documented [41,144]. An uncoupling of bone turnover, with increased markers of resorption and decreased markers of formation has been shown in the weeks just prior to and after transplantation [142,143,144,145,146]. Studies of bone marrow stromal cells suggest that osteoblastic differentiation may be affected by the BMT medication regimen, resulting in decreased bone formation [145,147]. Bone loss has also been correlated to glucocorticoid exposure [142,145] and amenorrhea (in the female patients) [142] in prospective studies. Vertebral and nonvertebral fracture incidence has ranged from 1 to 16% [41,141,142,144].

Mechanisms of post-transplantation bone loss

In the previous sections, we have summarized the now considerable body of research published over the past decade into the natural history and pathogenesis of bone loss and fracture after organ transplantation. This accumulating knowledge base has yielded fairly consistent data that now enables us to develop a unifying hypothesis of the mechanisms of post-transplantation bone loss. It seems very clear that the mechanisms differ according to the amount of time that has elapsed since transplantation. There appear to be two main phases of bone loss (Fig. 1). These phases can best be differentiated from each other by the presence (Fig. 1A) or absence (Fig. 1B) of high dose glucocorticoids in the immunosuppressive regimen.

During the first 6 months after transplantation, glucocorticoid doses are generally high enough to profoundly suppress bone formation by virtue of their effects to reduce osteoblast numbers, increase osteoblast apoptosis and inhibit osteoblast synthetic function. Virtually every published study has found serum markers of bone formation, particularly serum osteocalcin, to be suppressed during this period. During this same period, there has also been consistency in reports of increased urinary markers of bone resorption. The pathogenesis of the increase in resorption markers is probably in part related to suppressive effects of

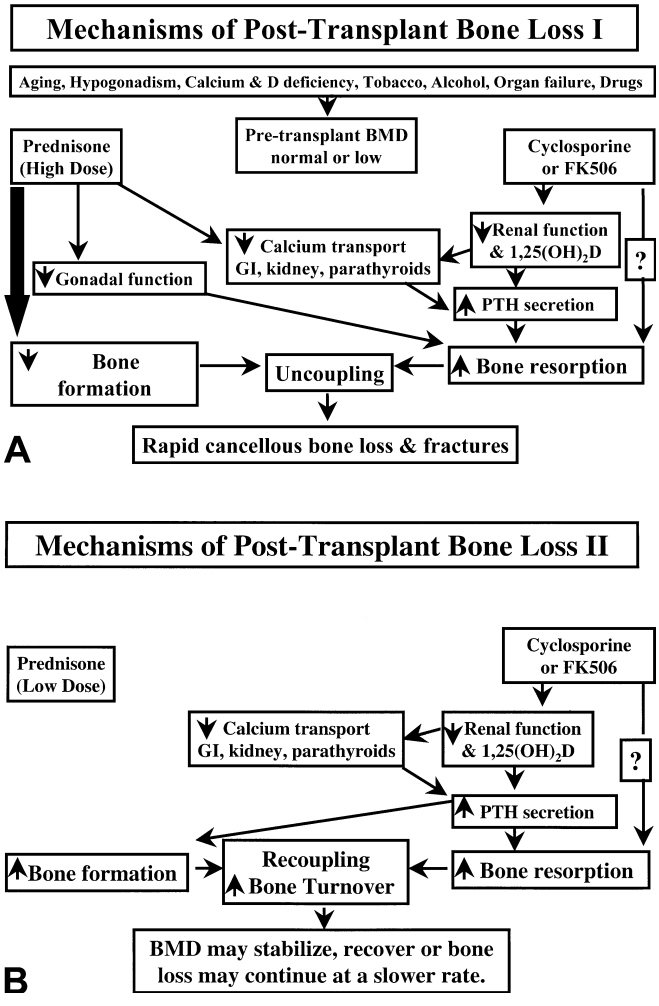

Fig. 1a,b Mechanisms of transplant bone loss

glucocorticoids on osteoblast synthesis of OPG, on the hypothalamic-pituitary-gonadal axis and on calcium transport across the intestinal, renal tubular and parathyroid cell membranes. In addition, the well-known nephrotoxic effects of CsA and FK506 administration result in measurable declines in renal function and decreased synthesis of $1,25(OH)_2D$ that also inhibits calcium transport in the gut. Thus, both calcineurin inhibitors and glucocorticoids have the potential to cause secondary increases in PTH secretion, which in turn increases osteoclast-mediated bone resorption. In addition, there may be direct effects of both CsA and FK506 to increase bone resorption. The concomitant administration of high dose glucocorticoids and CsA (or FK506) is therefore associated with profound uncoupling of resorption and formation. During this phase of the post-transplant period, rapid bone loss and high fracture rates are evident.

As glucocorticoid doses are tapered to below 5 mg per day, osteoblast function recovers and the suppressive effects on bone formation are reversed. However, adverse effects of CsA and FK506 remain—both the direct effects on the skeleton and those indirect effects mediated by renal toxicity of these drugs that result in secondary hyperparathyroidism. Thus, resorption remains elevated. With the tapering of glucocorticoids, bone formation increases also, resulting in "recoupling" of bone turnover. Rates of bone loss slow and there may even be some recovery, particularly at the spine. Each time glucocorticoid doses are increased for treatment of rejection or stress, the pathophysiologic picture again resembles the first phase.

Prevention and management of osteoporosis

Before transplantation

Because of the high prevalence of osteoporosis, osteopenia and abnormal bone and mineral metabolism in patients awaiting transplantation and the morbidity caused by osteoporosis after transplantation, it is our position that all candidates for organ transplantation would benefit from an evaluation of bone health. BMD of the hip and spine should be measured before transplantation, and whenever possible, at the time of acceptance to the waiting list. Spine radiographs should be performed to detect prevalent fractures. If BMD is low, an evaluation for secondary causes of osteoporosis should be undertaken and secondary causes of osteoporosis should be treated specifically. All patients should receive the recommended daily allowance for calcium and vitamin D (1000–1500 mg/day of calcium and 400–800 IU/day of vitamin D). Patients with renal failure should be evaluated and treated for renal osteodystrophy according to currently accepted standards of care [1,2].

Whether therapy for osteoporosis before transplantation reduces fracture risk after transplantation is presently unclear. Bisphosphonates, in particular, provide suppression of bone resorption for up to 12 months after discontinuation of therapy. For the patient who is transplanted with bisphosphonates already "on board", prevention of the increase in resorption that develops immediately after transplantation could theoretically mitigate the bone loss that develops after transplantation. Moreover, antiresorptive therapy clearly increases BMD and reduces fracture rates in other populations [148,149]. Therefore, individuals awaiting lung, liver and heart transplantation with osteoporosis or osteopenia should be evaluated and treated similarly to others with these conditions. The pre-transplant waiting period is often long enough (1–2 years) to achieve significant improvements in BMD. The situation is clearly different and more complex in patients awaiting kidney transplantation. Since there are few published data on the use of antiresorptive drugs in patients with end-stage renal disease, it is not possible to make general recommendations for these individuals.

After organ transplantation

Studies in various transplant populations have shown that bone loss is most rapid immediately after transplantation. Fractures may occur very early and affect patients with both low and normal pre-transplantation BMD. Therefore, we believe that most patients (even those with normal BMD) should have preventive therapy instituted immediately after transplantation. In addition, there is an ever-increasing population of patients who have been transplanted months or years before, yet have never been evaluated or treated for osteoporosis. General recommendations for treatment should include adequate vitamin D and calcium supplementation (1000–1500 mg/day of calcium and 400–800 IU/day of vitamin D). In addition, transplant physicians should be encouraged to use the lowest possible doses of immunosuppressive agents.

The majority of therapeutic trials have focused on the use of vitamin D metabolites and antiresorptive agents, particularly bisphosphonates. However, the data on effective treatment for bone loss in the post-transplant period are limited by studies that include small numbers of patients and are not randomized. In addition, studies often lack adequate control data, and may include patients receiving varying immunosuppressive regimens who are evaluated at varying ages and times after transplantation. In the discussions to follow, we will summarize studies of various therapeutic agents, focusing predominantly upon randomized, controlled clinical trials. Where possible, we will distinguish between studies that focus upon the early post-transplant period (prevention trials) and those that include mainly patients with established bone loss who are more than 6–12 months distant from transplantation and have thus passed the phase of most rapid demineralization (treatment trials).

Vitamin D and analogues

Vitamin D metabolites may reduce post-transplantation bone loss by reversing glucocorticoid-induced decreases in intestinal calcium absorption and by mitigating secondary hyperparathyroidism [150]. Theoretically, they could reduce glucocorticoid exposure by virtue of their immunomodulatory effects [150,151,152].

It is clear that parent vitamin D, in doses of 400–1000 IU/day, does not prevent significant post-transplantation bone loss [34,105]. However, 25-OHD or calcidiol therapy has been associated with significant increases in vertebral BMD during the 18 months after cardiac transplantation, while calcitonin or etidronate therapy resulted in minor decreases in BMD [153,154]. Calcidiol has also been shown to prevent ongoing bone loss in long-term cardiac transplant recipients [153]. Calcitriol has been studied in heart, lung, liver and kidney transplant recipients [155,156,157,158,159,160]. The results of these trials have been contradictory.

With respect to prevention of bone loss during the immediate post-transplant period, Sambrook and colleagues [155,157] have published two studies of calcitriol. The first was a 2-year double-blind study of 65 heart or lung transplant recipients randomly assigned to receive either placebo or calcitriol (0.5–0.75 μg/day) for either 12 or 24 months after transplantation [155]. All received 600 mg of calcium daily. Spinal bone loss at 2 years did not differ between groups, averaging 3.0% for those treated with calcium alone, 2.9% for those treated with calcitriol for 2 years and 5.6% for those treated with calcitriol for the first year followed by calcium alone for the second year. At the FN, patients randomized to receive calcitriol for 24 months sustained less bone loss than those randomized to calcium alone. Bone loss at 24 months averaged 8.3% for those treated with calcium alone, 5.0% for those treated with calcitriol for 2 years and 7.4% for those treated with calcitriol for the first year followed by calcium alone for the second year. Although fracture rates were lower in the calcitriol-treated subjects, this study lacked sufficient statistical power to be certain. The second study from this group compared rates of bone loss in 41 patients randomized to receive either calcitriol (0.5 μg/day) or two cycles of etidronate during the first 6 months after heart or lung transplantation and then followed for an additional 12 months [157]. The two treatment groups were compared to a reference group of patients transplanted approximately 5 years earlier. Despite therapy, significant and comparable bone loss (3–8%) occurred at the LS and FN in both study groups. Although LS bone loss was less pronounced than in the reference group, the lack of a concurrently transplanted population, though unavoidable, limited the ability to ascribe this possible benefit to the drug intervention.

Of note, both studies suggest that rapid bone loss resumes in heart and lung transplant recipients after cessation of calcitriol therapy [155,157]. Moreover, their results are in agreement with those of Van Cleemput and colleagues, who observed that cardiac transplant recipients randomized to either alphacalcidol or cyclic etidronate sustained considerable bone loss at the LS (alphacalcidol, 7.0%; etidronate, 10.3%) and FN (alphacalcidol, 5.6%; etidronate, 8.9%) during the first year after transplantation [154,161]. A study in which subjects followed without preventive therapy for 6 months after liver transplantation were then assigned to receive one of two doses of calcitriol (0.25 or 0.5 μg/day), with or without calcium supplementation (1000 mg/day) for the next 18 months, demonstrated BMD increases for all treatment groups at the LS (5.6–10%) and FN (3.9–5.6%) [156]. Other studies of calcitriol in long-term renal [162] and heart transplant recipients [163], have found no benefit of calcitriol. In these studies, neither calcitriol nor the relatively weak, first-generation bisphosphonate, etidronate, provided optimal protection from early post-transplant bone loss.

Hypercalcemia and hypercalciuria are common side effects of vitamin D, and may develop at any point during the course of treatment. Frequent monitoring of urine and serum is required. In our opinion, active metabolites of vitamin D should not be selected as first-line treatment for transplantation osteoporosis because of their narrow therapeutic window.

Bisphosphonates

Several studies [111,164,165,166,167,168,169,170] suggest that bisphosphonates prevent bone loss and fractures after transplantation. In an open-label study, a single intravenous dose of pamidronate (60 mg), followed by cyclic etidronate (400 mg for two weeks every three months) and daily oral calcitriol (0.25 μg/day), prevented LS and FN bone loss and reduced fracture rates in heart transplant recipients compared to historical controls [168]. Repeated doses of intravenous pamidronate in heart [165,171], renal [166], and lung transplant recipients [33,164] have been shown to prevent LS and FN bone loss. Bianda et al. reported LS and FN bone loss at 12 months after cardiac transplantation of only 1.9% and 1.4%, respectively, in patients who received a small dose of pamidronate (0.5 mg/kg every 3 months), while in patients randomized to nasal calcitonin (200 IU/day) plus calcitriol (0.25–0.5 μg/day), LS BMD fell by 7.4% and FN BMD by 6.3% [165]. Some have reported fracture reduction [172], while others [164] have not. Recent randomized trials of the more potent intravenous bisphosphonate, ibandronate, in liver [169] and renal [75] transplant recipients have also found a significant protective effect on bone mineral density at 1 year. However, in a recent trial in which patients were randomized to receive either a single dose of intravenous pamidronate administered 1–3 months prior to liver transplantation or no treatment, LS BMD did not decline significantly in either the treated or the

untreated group during the first post-transplant year, while FN BMD fell comparably in both and the incidence of new fractures was the same [126].

Several studies evaluating early prophylaxis with oral bisphosphonates utilized cyclic etidronate [161,173] in heart and liver transplant recipients, and found no benefit in terms of bone loss or fracture risk. However, one early study documented improvement in BMD in osteoporotic patients treated with cyclic etidronate after liver transplantation [131], and a more recent study found a protective prophylactic effect of etidronate in lung and heart recipients when compared to historical, untreated controls (although significant bone loss occurred in both groups) [157].

Bisphosphonate therapy has also been compared to calcitriol therapy. In a small study ($n = 20$) of renal transplant recipients, a regimen of alendronate 10 mg daily, calcium carbonate 2 g daily and calcitriol 0.25 μg daily was associated with a 6.3% increase in LS BMD in the first 6 months after transplantation, compared to a decrease in LS BMD of 5.8% with calcium and calcitriol alone [167]. A 1-year trial comparing alendronate, calcitriol and calcium treatment to calcitriol and calcium treatment alone in 40 renal transplant recipients in whom therapy was begun an average of 5 years after transplantation also documented a gain in BMD at the spine (5.0%) and the femoral neck (4.5%) in the alendronate treated group [174]. In contrast to the prior study in patients treated immediately post-transplant [167], BMD remained stable in the patients treated with calcitriol alone. In a 1-year trial, in which patients were randomized immediately after cardiac transplantation to receive either alendronate (10 mg/day) or calcitriol (0.25 μg twice daily), bone loss at the LS and hip was prevented by both regimens in comparison to control subjects who received only calcium and vitamin D [111]. As with other studies of vitamin D metabolites, hypercalciuria and hypercalcemia occurred with significantly greater frequency in those receiving calcitriol.

In our opinion, bisphosphonates are the most promising approach for the management of transplantation osteoporosis. However, controversies remain regarding optimal administration of bisphosphonates. These include whether continuous or intermittent therapy should be used, duration of therapy, the level of renal impairment at which bisphosphonates should be avoided, whether they are safe in renal transplant recipients with adynamic bone disease, and their utility after pediatric transplantation.

Calcitonin

Calcitonin increases BMD in patients with high-turnover osteoporosis [175,176]. In the rat, calcitonin prevents CsA-induced bone loss [59]. However, calcitonin is relatively ineffective in preventing bone loss after transplantation [96,144,154,177,178].

Gonadal hormone replacement

Hormone replacement therapy has been shown to protect the skeleton in women treated with glucocorticoids [44], as well as in women receiving liver [179], lung [33] and bone marrow [180] transplantation. However, in light of recent data suggesting increased rates of coronary events and stroke in postmenopausal women treated with estrogen and progesterone [181], the risks of this therapy would probably outweigh the benefits in most organ transplant recipients.

In cardiac transplant recipients, testosterone has been shown to fall immediately after transplantation, and normalize after 6–12 months [105,116]. In a recent study evaluating male cardiac transplant recipients treated with intravenous ibandronate, hypogonadal men who received testosterone supplementation showed an improved BMD response at 1 year compared to hypogonadal men who did not receive testosterone [182]. In general, testosterone replacement should be reserved for men with true hypogonadism. Potential risks of testosterone therapy, such as prostatic hypertrophy, hyperlipidemia, and abnormal liver enzymes, may have particular relevance for the transplant population.

Summary and conclusions

Pre-transplantation bone disease and post-transplantation immunosuppressive regimens combining high doses of glucocorticoids (e.g. prednisone at >10 mg/day) and CsA or FK506, interact to produce a particularly severe form of osteoporosis characterized by rapid bone loss and increased fracture rates in the early post-transplant period. Early rapid bone loss occurs in the setting of uncoupled bone turnover with many studies documenting increased bone resorption and decreased bone formation. Management of these patients should combine assessment and treatment of pre-transplantation bone disease with preventive therapy in the immediate post-transplantation period, since most bone loss occurs in the first months after grafting. In addition, bone mass measurement and therapy of osteoporosis in the long-term organ transplant recipient should be addressed. There are no pre-transplantation variables that reliably predict post-transplantation bone loss and fracture in the individual patient. Therefore all organ transplant recipients should be considered at risk for post-transplantation bone loss and fractures. Although newer studies suggest that rates of bone loss and fracture may be lower in more recently transplanted patients, morbidity from transplantation osteoporosis remains unacceptably high. Data from clinical trials suggests that bisphosphonates are the safest and most promising agents for the prevention and treatment of post-transplantation osteoporosis.

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