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Osteoporosis After Transplantation

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Abstract Transplantation is an established therapy for end-stage diseases of kidney, lung, liver, and heart among others. Osteoporosis and fragility fractures are serious complications of organ transplantation, particularly in the first post-transplant year. Many factors contribute to the pathogenesis of osteoporosis following organ transplantation. This review addresses the mechanisms of bone loss that occurs both in the early and late post-transplant periods, including the contribution of the immunosuppressive agents as well as the specific features to bone loss after kidney, lung, liver, cardiac, and bone marrow transplantation. Prevention and treatment for osteoporosis in the transplant recipient are also discussed.

Keywords Secondary osteoporosis · Transplantation · Immunosuppressive agents · Bone loss

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Introduction

Organ transplantation nowadays is an important treatment option for several end-stage diseases. The number of successful organs transplanted has increased as well as the survival of the transplant recipients. This has resulted in increased recognition of long-term complications of transplantation itself and also due to the action of immunosuppressive drugs. In this regard, osteoporosis and fragility fractures are present in transplanted patients as an early or late complication [1, 2]. Bone loss after transplantation is related to adverse effects of immunosuppressive drugs (eg, glucocorticoids [GCs] and calcineurin inhibitors) on bone remodeling [3]. Immobilization also plays a role in this process. However, it is important to note that low bone mass and fractures may antedate transplantation, which could be related to the effects of chronic disease, other risk factors for osteoporosis, and end-stage organ failure and its therapy, on the skeleton. In this article, we review the general mechanisms of bone loss after the organ transplantation, as well as the specific features relevant to each organ such as kidney, lung, liver, heart, and bone marrow. The therapeutic measures recommended for the prevention and treatment of osteoporosis after transplantation are also addressed.

Skeletal Effects of Immunosuppressive Drugs

The natural history of post-transplantation osteoporosis suggests that there are two main phases, an early and late phase. The difference between the two phases is mainly due to the doses of immunosuppressive drugs [1].

Glucocorticoids

GCs are used in most immunosuppressive regimens after transplantation. Typically, in the early phase, which is usually in the first 6 weeks after transplantation, steroids doses are generally high (eg, 30–50 mg/day of prednisone or prednisolone) followed by lower doses. Therefore, during the first 6 months after transplantation, the rapid bone loss in cancellous bone is secondary to an effect of GCs (Fig. 1a) [4]. The pathophysiology of GC-induced bone disorder is multifactorial [5]. Bone formation is inhibited by decreased proliferation, function (by reducing levels of type I collagen, insulin-like growth factor 1, and osteocalcin), and lifespan (by induction of osteoblast apoptosis) [6]. GCs also promote osteoclastogenesis by increasing levels of the receptor activator of nuclear factor-κB ligand (RANKL) system [5]. Other indirect effects of GCs also play a role in the mechanisms of bone loss (eg, decreased intestinal calcium

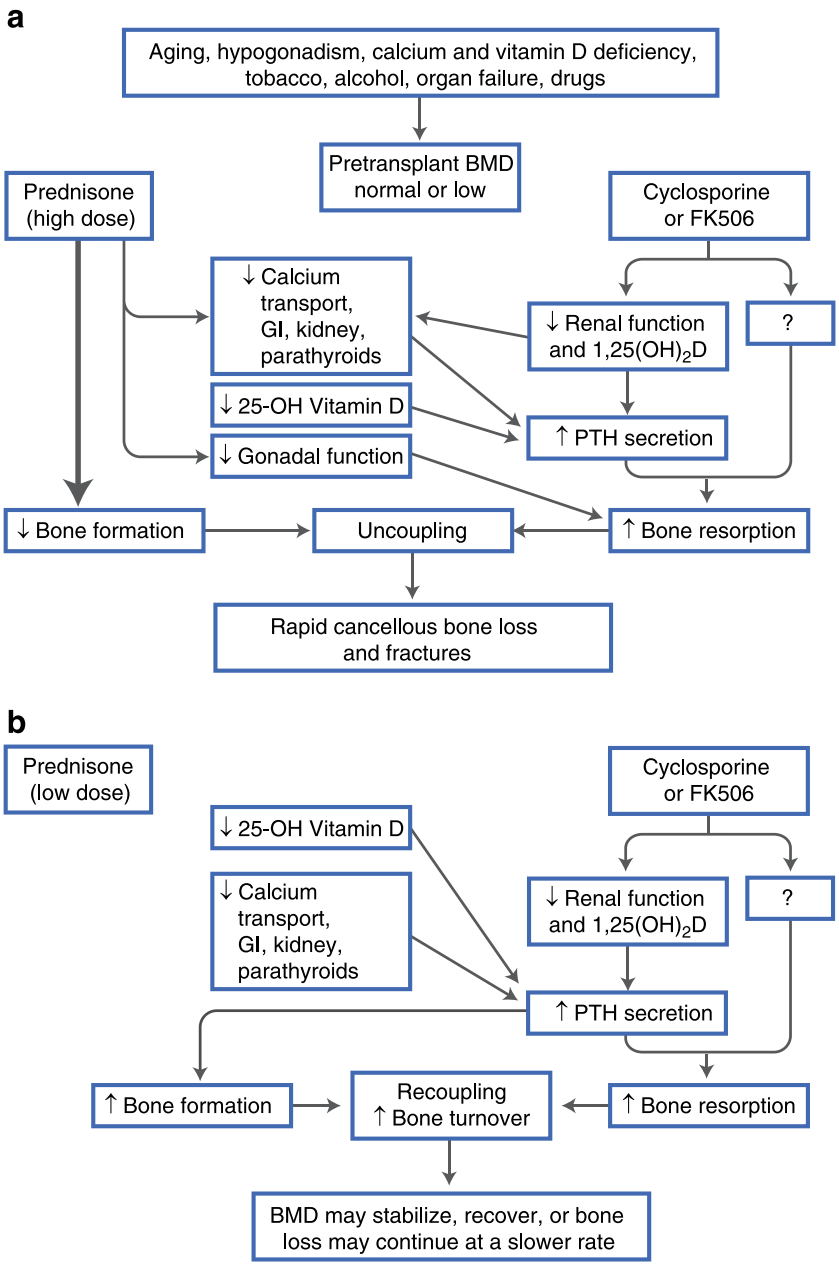

Fig. 1 **a**, Mechanisms of bone loss in the early phase of the post-transplantation period. **b**, Mechanisms of bone loss in the later phase of the post-transplantation period. *BMD* bone mineral density; *GI* gastrointestinal; *PTH* parathyroid hormone. *(*Adapted from: Kulak CAM, Shane E: Transplantation Osteoporosis: biochemical Correlates of Pathogenesis and Treatment. In *Dynamics of Bone and Cartilage Metabolism, 2nd edition*. Edited by Seibel MJ, Robins SP, Bilezikian JP. Philadelphia: Elsevier; 2006:701–716, with permission from Elsevier*)* [60]

absorption, renal calcium wasting, and impaired gonadal hormone production) [7–9]. Furthermore, GCs may induce a muscle weakness, which additionally delays post-transplant mobilization with subsequent aggravation of bone loss [9].

Calcineurin Inhibitors: Cyclosporin A and Tacrolimus

Cyclosporin A (CsA), small fungal cyclic peptide that inhibits the T-cell phosphatase calcineurin, decreases rejection episodes and is therefore very important in transplantation regimens [3]. CsA may cause bone loss through direct effects on osteoclasts or acting indirectly on T-cell function. In addition, CsA may have independent effects on bone and mineral metabolism that contribute to post-transplantation bone loss [10]. However, studies evaluating the presence of bone loss secondary to CsA have conflicting results. One study of kidney transplant recipients demonstrated that bone loss was associated with cumulative CsA dose and independent of the effects of GCs during the first 2 years after transplantation [11]. In contrast, another study evaluating patients after renal transplantation who received CsA in a GC-free regimen did not show any bone loss [12]. Tacrolimus (FK506), another calcineurin inhibitor, inhibits T-cell activation and proliferation and cytokine gene expression [3, 13]. Although studies demonstrated that FK506 leads to bone loss in rats, skeletal effects in human are not well studied. Both liver and cardiac transplant recipients have been shown to sustain rapid bone loss with tacrolimus [14]. However, it is less intense than the bone loss seen with the use of CsA, probably due to the fact that FK506 permits lower doses of GCs [13]. The isolated effects of calcineurin inhibitors to the skeleton are difficult to evaluate in human studies because they are usually used concomitantly with GCs. Therefore, population-based studies focused on fracture risk could not establish an association between the use of calcineurin inhibitors and fracture risk [15].

Later during the post-transplant period, when the GC doses are tapered to below 5 mg/day, there is recovery of osteoblast function and, consequently, an increase in bone formation and recoupling of bone remodeling activity (Fig. 1b). However, both the direct and the indirect effects of cyclosporine and FK506 continue to influence the skeleton with bone resorption. During this later phase, rates of bone loss slow and there may even be some recovery, particularly at sites comprised predominantly of cancellous bone [1].

Kidney Transplantation

Although successful transplantation is capable of reversing many complications of end-stage organ failure, disturbances of bone and mineral metabolism may persist contributing to substantial long-term morbidity of the recipients. Three major components contribute to bone metabolism disturbances in patients after renal transplantation: pre-existing renal osteodystrophy, effects of immunosuppressive drugs on bone, and effects of reduced renal function after renal transplantation. Regarding renal osteodystrophy, there are several types, based on histomorphometric features, in which many patients present more than one defined disorder [15]. Osteitis fibrosa is a high-turnover bone disease due a secondary hyperparathyroidism, whereas osteomalacia and adynamic bone disease are low-turnover diseases showing mineralization defect and decreased remodeling activity, respectively. The diagnosis of bone turnover abnormalities is important because the therapeutic approaches to the different abnormalities are distinctly different and misdiagnosis can lead to serious adverse clinical outcomes.

Tertiary Hyperparathyroidism or Persistent Hyperparathyroidism

Tertiary hyperparathyroidism or persistent hyperparathyroidism is usually defined as elevated parathyroid hormone (PTH) levels and hypercalcemia after successful kidney transplantation. PTH levels usually decline rapidly (>50%) during the 3–6 months after renal transplantation because of the reduction in functional parathyroid gland mass. Persistently elevated levels of serum PTH despite normalization of renal function have been reported in 25% of patients 1 year after transplantation [16] and may cause serious problems such as soft tissue calcification, hypophosphatemia, and hypercalciuria [17]. Additional factors that may contribute to elevated PTH levels are an incomplete normalization of kidney function, relative hypovitaminosis D, and decreased intestinal and renal calcium reabsorption caused by GCs [18].

After renal transplantation, $1,25(OH)_2$ vitamin D levels are low during the first months. The reason is an action of GCs reducing the 1α-hydroxylase activity and increasing its catabolic enzymes synthesis. However, in this case it is recommended to give cholecalciferol to replace the substrate to calcitriol and then minimize the 1α-hydroxylase deficiency.

Bone Mineral Density and Fractures

Particularly during the early post renal transplantation period, patients experience a rapid loss of bone mass. Besides the immunosuppressive drugs, the decreasing of bone mineral density (BMD) seen in post-transplant patients also correlates to time of hospitalization and malnutrition after engraftment [19]. The risk for fragility fractures is clearly increased in this population. According to estimates,

approximately 7–10% of all renal transplant recipients will suffer one or more fractures over their lifetime, which commonly involve appendicular sites such as hip, ankle, and feet [20]. The overall fracture risk of these patients is 30% higher during the first 3 years after transplantation than in patients on dialysis [21]. The fracture risk seems to remain unchanged during the first 10 years after renal transplantation, decreasing after this time, to about twice higher than healthy individuals.

Indications for Bone Biopsy

1. Symptoms of bone pain, muscular weakness without correlations to laboratory findings
2. Fragility fractures
3. Diagnosis of osteomalacia
4. Severe osteoporosis with indication for antiresorptive therapy, however with low normal PTH, being difficult to rule out adynamic bone disease.

It is important to point out that a low bone turnover disease is a contraindication with use of bisphosphonate (BP), because it worsens remodeling and mineralization leading to a skeleton fragility. Bone biopsy is the gold standard method for diagnosing low bone turnover disease. Low PTH and alkaline phosphatase might give a suspicion of the low turnover status.

Lung Transplantation

Osteoporosis is very common in patients referred for lung transplantation, especially among chronic obstructive pulmonary disease (COPD) candidates. Steroid consumption is the mean risk factor [22]. However, we recently demonstrated that low bone mass and microarchitecture deterioration happen in COPD patients without GC use [1, 23, 24••]. Pretransplantation lower BMD and longer prior GC therapy were correlated to the incidence of fractures. Spira et al. [25] evaluated BMD in 28 patients prior to and 6–12 months post lung transplantation. There was a 5% reduction in BMD of both lumbar spine and femur neck, which was associated with cumulative steroid dose after transplantation. In addition, 18% sustained osteoporotic fractures, despite vitamin D and calcium supplementation. Prospective studies have also demonstrated changes in bone mass and fracture incidence in patients who have received a lung transplant [25–27]. Rates of bone loss at the lumbar spine and femoral neck range from 2% to 5% in the first year after lung transplantation [2, 26]. In addition, fracture rates also are high, ranging from 18% to 37% during the first year, even in those patients who received antiresorptive therapy. Osteoporosis screening prior to lung transplantation should be performed to identify high-risk subjects for fracture and allow for intervention.

Cardiac Transplantation

The most rapid rate of bone loss after cardiac transplantation also occurs during the first year. The hallmark of osteoporosis after cardiac transplantation is the high rate of bone loss. BMD decreases 3–10% at the lumbar spine and 6–11% at the femoral neck, then seems to stabilize during the second year and may even increase after the third year [2, 28•]. However, BMD has been shown not to be efficient to identify bone fragility after heart transplantation. In a study with 157 patients evaluated after an average of 10 years after the cardiac transplantation with BMD and spine radiographs, the authors observed vertebral fractures in 40% of subjects, whereas osteoporosis was only in 13% of spine and in 25% of hip scans, suggesting that BMD or at least the standard densitometric criteria is unreliable to identify bone fragility after cardiac transplantation [29••].

Vertebral fractures have been reported to occur from 14% to 36% during the first post transplantation year and 22–35% of long-term cardiac transplant recipients [30]. Bone resorption markers are increased in the initial period after transplantation whereas bone formation markers (osteocalcin) are reduced [2]. The increase of resorption may be associated with CsA-induced renal insufficiency and resultant secondary hyperparathyroidism. In general, bone formation markers return to normal by 6–12 months after cardiac transplantation. Serum osteoprotegerin declines during immunosuppressive therapy and accounted for 67% of the variance of lumbar spine bone density changes during the first 6 months post transplantation [28•]. A new concern exists regarding the interference of bone loss at bone acquisition in kids after heart transplantation [31].

Bone Marrow Transplantation

Bone marrow transplant (BMT) recipients have many known risk factors for developing low BMD after transplantation. The pathogenesis of bone disease following BMT differs from other forms of post-transplantation osteoporosis: recipients are usually younger, and the impact of the primary disease or their treatment in bone mass prior to transplantation is relevant and can interfere with bone accrual growth in children or induce bone loss in the adult population [32•].

The rate of bone loss increases during the first year following BMT, from 2% to 9% at the lumbar spine and 6–11% at the femoral neck. In a study of long-term follow-up of bone loss after BMT, Schulte et al. [33] observed that

lumbar spine BMD begins to recover after 12 months, returning to baseline at 48 months. High levels of bone marrow interleukin-6 during the immediate post-BMT period were related to the bone loss. Chronic graft versus host disease (GVHD) affects 30–60% of patients after BMT and is treated with high doses of GCs, which contributes to bone loss in BMT recipients [34]. In addition, low BMD was associated with insulin resistance [35•]. A marked decline in the serum levels of 1,25-dihydroxyvitamin D_3 and 25-hydroxyvitamin D_3 in the course of allogeneic BMT was observed [36]. It may be explained by the fact that after BMT, patients have low sun exposures to prevent GVHD. Further, a study evaluating children and adolescents after BMT reported they have low ingestion of calcium and vitamin D [1]. Recently, McClune et al. [32•] reported a review of clinical trials using different drugs for prevention and treatment of bone loss after transplantation. In this report, variable results regarding BMD after treatment were shown.

Liver Transplantation

Bone loss and increased risk for fracture are common complications after liver transplantation [37]. The progression of bone loss is similar to that following lung and cardiac transplantation, being more severe in the first 6 months. In earlier studies, bone loss after liver transplantation was characterized by a marked decrease in lumbar spine BMD by 3.5–24%, primarily during the first 3–6 months. However, in more recent studies, rates of bone loss have been as low as 2.3% at the femoral neck, or even absent [38]. Fracture incidence is also highest in the 6–12 months following the transplantation, with rates ranging from 24% to 65%; the ribs and vertebrae are the most common sites [2]. In prospective studies, the risk of post-transplantation bone loss and fractures were related to age, pretransplantation BMD, and previous vertebral fracture as well as menopause status [39, 40•]. Bone turnover has been reported to be low in many patients with liver failure; however, there is conversion to a high-turnover state after liver transplantation that persists afterward. The increase in turnover may result from resolution of cholestasis or hypogonadism, increased PTH secretion, or CsA or FK506 administration. Significant increase in osteoprotegerin and RANKL levels during the first 2 weeks after liver transplantation provide further evidence of high bone turnover disease [41]. Bone histomorphometry study showed that bone loss stops around 6 months, followed by a gain of bone mass, mainly at the cancellous bone, in the first 2 years after the liver transplantation [39]. The increase in BMD was significant higher among premenopausal than perimenopausal and postmenopausal women, probably due the protective estrogen effect to the skeleton [40•].

Prevention and Management of Transplantation Osteoporosis

Pretransplantation Measures

All transplant candidates should be evaluated and treated before transplantation, as bone disease is common in patients awaiting organ transplantation. An evaluation of BMD and some parameters of bone and mineral metabolism should be performed prior to the organ transplantation. This pretransplant evaluation could be helpful to select patients who would benefit from immediate therapy. For patients with end-stage renal disease, evaluation and treatment for renal osteodystrophy according to accepted guidelines is highly recommended. Furthermore, patients must be encouraged to modify lifestyle factors with adverse effects on the skeleton, such as immobilization, smoking and alcohol abuse. Factors such as hypogonadism, vitamin D deficiency, and secondary hyperparathyroidism should be corrected. In addition, a diet rich in calcium is recommended.

Prevention of Early and Late Post-Transplantation Bone Loss

As discussed above, the rate of bone loss is highest immediately following transplantation leading to increased fracture risk. Therefore, preventive and therapeutic measures should be instituted at the time of transplantation, minimizing the dose of GCs to the best extent possible.

Vitamin D Deficiency

The vitamin D insufficiency (<30 ng/mL) and deficiency (<15 ng/mL) are extremely common among patients with end-stage organ failure and have been well documented in organ transplant patients with heart failure, end-stage pulmonary disease, liver failure, and chronic kidney disease [28•]. Severe vitamin D deficiency affects 59–91% of transplanted patients and may persist during years after transplantation [42]. Several factors place patients with end-stage organ failure at particular risk for vitamin D deficiency. These include limited sunlight exposure because of risk of skin cancer, low dietary intake of vitamin D–containing foods, hepatic dysfunction, and use of GCs, which may increases catabolism of 25(OH) vitamin D [43, 44]. In addition, administration of calcitriol or its analogues is often recommended to prevent or treat osteoporosis after transplantation throughout different actions. They reverse GC-induced decreases in intestinal calcium absorption, limit the resultant secondary hyperparathyroidism, promote differentiation of osteoblast precursors into mature cells, and may potentiate the immunosuppressive activity of CsA [45].

Calcidiol (25[OH]D) and calcitriol also prevent bone loss in heart [28•] and renal transplant recipients [46].

Gonadal Hormone Replacement Few studies have approached the replacement of hormone replacement therapy (HRT) for transplant recipients, although a recent study showed a protective effect on the skeleton [47]. It is appropriate to delay HRT initiation until the patient has successfully engrafted, is medically stable, and off of most other medications (typically 3–6 months post transplant). Options for HRT include oral and transdermal standard menopausal HRT with the inclusion of either cyclic or continuous progesterone or oral combined contraceptive pills (OCCPs). OCCPs provide supraphysiologic levels of estrogen that are not required for amelioration of symptoms, but may be the most emotionally acceptable and simplest formulation for these patients. OCCPs also offer contraceptive doses of hormones for young women without ovarian failure and at risk for pregnancy. If a patient chooses a cyclic OCCP for both HRT and contraception, she should be counseled on the importance of compliance and the likelihood that vasomotor symptoms may return during the pill-free period [48].

Standard HRT options include transdermal and oral estrogen preparations. Typical formulations of estrogen include transdermal 17β-E2 of 50–100 μg, or oral conjugated estrogens 0.625–1.25 mg/day or oral 17β-E2 1–2 mg/day. Patients with a uterus should be given endometrial protection through continuous or cyclical progesterone therapy, 14 days every 30–60 days. Special attention should be given to liver post-transplantation patients, where transdermal therapy should be preferred.

Bisphosphonates Studies using both intravenous and oral BPs have shown they are effective to prevent bone loss after transplantation [49–52]. Alendronate has been studied in both immediate [53] and long-term [52] transplant recipients. A randomized trial comparing alendronate (10 mg/d) and calcitriol (0.25 μg twice daily) for 1 year in patients directly after cardiac transplantation found that both regimens prevented bone loss at the lumbar spine and hip when compared with reference subjects who received only calcium and vitamin D [53]. In the second year after cardiac transplantation, BMD remained stable, although alendronate and calcitriol were discontinued [28•]. Similarly, studies demonstrated the efficacy of intravenous ibandronate, zoledronic acid, and pamidronate in the prevention of bone loss after renal, heart, lung, liver, and BMT recipients, independently of the time following the transplantation [49–51, 54, 55].

A recent systematic review of 24 trials evaluated the benefits and risks of treatments used to reduce bone disease following kidney transplantation [56]. Meta-analysis of all available such trials combined, however, shows that any intervention for bone disease in kidney transplant recipients does reduce the risk of fractures. These agents also provide a significant improvement in BMD when given after transplantation, although the clinical significance of this is uncertain due to the lack of validation of bone densitometry (duel-energy x-ray absorptiometry; DXA) in chronic kidney disease. Because extra osseous calcifications are frequent complications in uremic patients and after renal transplant, the use of improved BMD as an end point is potentially problematic, as DXA cannot differentiate between calcium accumulation in the bone and that surrounding soft tissue.

Maybe a safe therapeutic approach for renal transplant recipients with fractures, unexplained hypercalcemia, or bone pain is the performance of a bone biopsy because of the high risk of low bone turnover after transplantation. In patients with low bone volume and in those with increased bone resorption to formation ratio, it is indicated that the use of antiresorptive agents adjusted the glomerular filtration rate. Patients with mineralization defects as determined by histology are treated with both 25(OH) vitamin D and active vitamin D analogues. Calcium supplementation can also be given carefully, if they do not show vascular calcification. In patients with low bone turnover and severely suppressed rates of bone remodeling, BPs are contraindicated [57].

Teriparatide One double-blind randomized trial treated 26 kidney transplant recipients treated with teriparatide (PTH 1–34) or placebo and demonstrated that teriparatide does not improve BMD early after kidney transplantation [58]. In addition, neither histologic analysis nor bone markers provide evidence of improved bone turnover or mineralization.

Recently, a meta-analysis evaluated 11 studies (2003–2010) to determine whether treatment with BPs or active vitamin D analogues during the first year after transplantation reduces fracture risk and prevents bone loss [59••]. Based on the results of 780 transplant recipient patients, it was concluded that both BP and vitamin D reduced the number of patients with fractures (odds ratio [OR], 0.50 [0.29–0.83]) and increased BMD at the lumbar spine (2.98%) and femoral neck (3.05%). When BP trials were examined separately, the reduction in all fracture rates was maintained; however, there was no significant decrease in vertebral fractures (OR, 0.34 [0.09–1.24]). These results suggest that in the first year after organ transplantation, both BP and vitamin D analogues are effective in the prevention of fractures and bone loss.

Conclusions

Patients with end-stage organ failure and candidates for all types of transplantation have significant risk factors for osteoporosis and abnormal mineral metabolism before the organ transplantation. The exposure to high doses of GCs and calcineurin inhibitors is associated with rapid bone

loss immediately after transplantation and high fracture incidence. Effective therapies should incorporate pre-transplant measures to treat pre-existing bone diseases and also aggressive prevention of bone loss during the first 6–12 months after transplantation. The optimal dose, timing, and frequency of administration of these therapies remain to be determined.

Of the presently available treatment modalities, BPs are the most consistently effective for both prevention and treatment of osteoporosis in transplant recipients. Use of agents such as strontium ranelate, RANKL antagonists, and cathepsin K inhibitors in the management of osteoporosis after transplantation are lacking. Because the greatest amount of bone loss occurs during the first few months after transplantation, primary prevention therapy should commence immediately after surgery. However, the follow-up of bone and mineral status of these patients should be maintained.

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- •• Of major importance

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