

Post-transplantation osteoporosis

Osteoporose pós-transplante

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SUMMARY

Transplantation is an established therapy for many hematologic disorders as well as for end-stage diseases of the kidney, lung, liver, heart among others. Osteoporosis and a high incidence of fragility fractures have emerged as a complication of organ transplantation. Many factors contribute to the pathogenesis of osteoporosis following organ transplantation. In addition, most patients have some form of bone disease prior to transplantation, which is usually related to adverse effects of end-stage organ failure on the skeleton. This chapter reviews the mechanisms of bone loss that occur both in the early and late post-transplant periods including the contribution of immunosuppressive agents as well as the specific features of bone loss after kidney, lung, liver, cardiac and bone marrow transplantation. Prevention and treatment for osteoporosis in the transplant recipient will also be addressed. *Arq Bras Endocrinol Metab.* 2010;54(2):143-9

Keywords

Secondary osteoporosis; transplantation; immunosuppressive agents; bone loss

SUMÁRIO

Transplante de órgãos ou medula óssea é uma terapia conhecida para muitas doenças hematológicas e para estágios finais de doenças renais, pulmonares, hepáticas, cardíacas, entre outras. A osteoporose e o aumento da prevalência de fraturas por fragilidade óssea têm se mostrado como uma complicação do transplante. Muitos fatores contribuem para a patogênese da osteoporose relacionada ao transplante. Além disso, a maioria dos pacientes apresenta doença óssea antes do transplante, a qual é secundária à doença grave de base. Este artigo revisa os mecanismos da perda óssea que ocorrem tanto na fase precoce quanto na fase tardia após o transplante, incluindo o uso das drogas imunossupressoras, como também os fatores específicos envolvidos na perda óssea relacionados ao transplante renal, pulmonar, hepático, cardíaco e de medula óssea. A prevenção e o tratamento da osteoporose após transplante também são abordados nesta revisão. *Arq Bras Endocrinol Metab.* 2010;54(2):143-9

Descritores

Osteoporose secundária; transplante; drogas imunossupressoras; perda óssea

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INTRODUCTION

Within the past two decades organ transplantation has become established as an important treatment option for several end-stage diseases of the kidney, heart, lung, liver and for many hematological disorders. The number of organs transplanted has increased along with the survival of transplant recipients. This has resulted in increase of recognition of long-term complications of transplantation such as osteoporosis and fractures (1-3). Low bone mass and fractures may antedate transplantation, related to traditional risk factors for osteoporosis,

effects of chronic illness, and end-stage organ failure and its therapy on the skeleton (Table 1). Bone loss after transplantation is related to adverse effects of immunosuppressive drugs (glucocorticoids and calcineurin inhibitors) on bone remodeling (Figure 1). In this chapter, we will review the general mechanisms of bone loss after organ transplantation as well as the specific features relevant to each organ such as kidney, lung, liver, heart and bone marrow. In addition, we will address the therapeutic measures recommended for the prevention and treatment of osteoporosis after transplantation.

Table 1. Specific factors that contribute to bone fragility before transplantation

End-stage renal disease
Renal osteodystrophy:
Secondary hyperparathyroidism
Adynamic bone disease
Osteomalacia
Mixed uremic disease
Metabolic acidosis
Hypogonadism
Long-term hemodialysis
Vitamin D deficiency
End-stage lung disease
Smoking
Glucocorticoid
Hypercapnia
Hypoxia
Hypogonadism and pancreatic insufficiency (cystic fibrosis)
End-stage liver disease
Alcohol abuse
Low body weight
Vitamin D deficiency and secondary hyperparathyroidism
Cholestasis
Hypogonadism
Heart failure
Exposure to loop diuretics
Exposure to heparin
Vitamin D deficiency and secondary hyperparathyroidism
Mild renal insufficiency
Bone marrow transplant recipients
Glucocorticoids
Chemotherapy
Hypogonadism

SKELETAL EFFECTS OF IMMUNOSUPPRESSIVE DRUGS

The natural history of post-transplantation osteoporosis suggests that there are two main phases, an early and a late phase; the difference between the two phases is mainly due to the doses of immunosuppressive drugs (2)

GLUCOCORTICOIDS

Glucocorticoids (GCs) are used in most immunosuppressive regimens after transplantation. Typically, in the early phase, which generally encompasses the first 6 weeks after transplantation, steroid doses are generally high (e.g., 30-50 mg/day of prednisone or prednisolone at transplantation followed by rapid tapering to 5-10 mg by 6 months). This causes marked suppression of osteoblast-mediated bone formation and inhibition

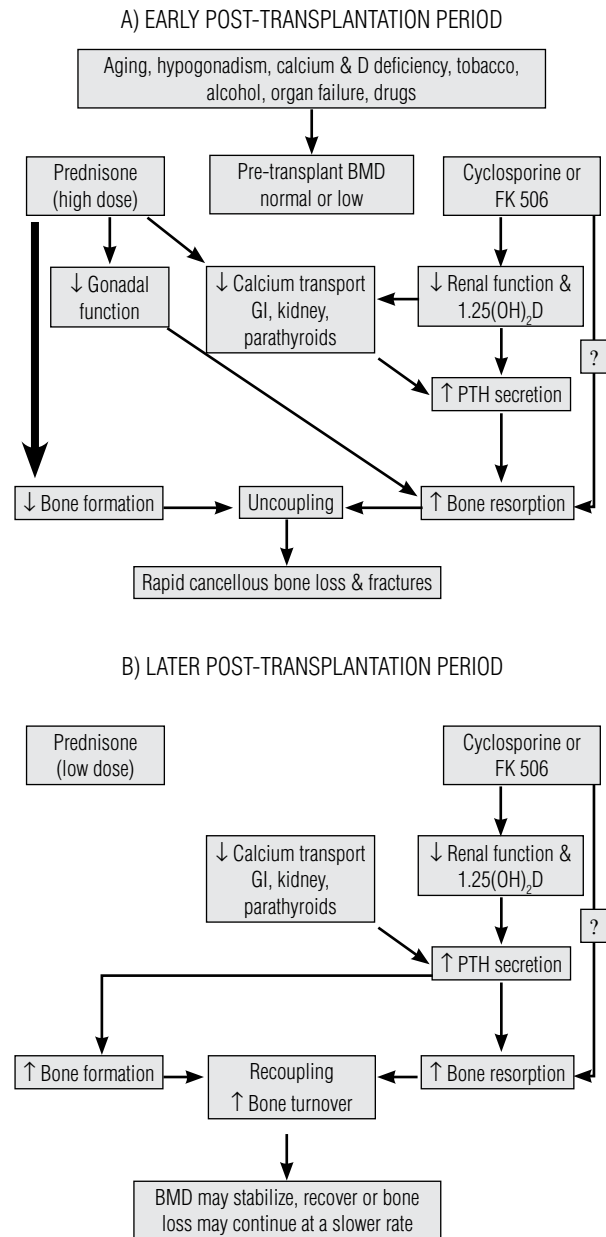


Figure 1. (A) Mechanisms of bone loss in the early phase of post-transplantation period. (B) Mechanisms of bone loss in the later phase of post-transplantation period.

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of osteoblast synthetic function (4). In comparison, direct effects of GCs on bone resorption are less prominent. However, GCs may increase resorption indirectly through reduction of intestinal and renal calcium absorption leading to a secondary hyperparathyroidism as well as inhibition of gonadal steroid synthesis. In addition, glucocorticoids stimulate osteoclastogenesis throughout the osteoprotegerin-RANK-L system (5).

CALCINEURIN INHIBITORS: CYCLOSPORINE A AND TACROLIMUS

Cyclosporine A (CsA), small fungal cyclic peptide that inhibits the T-cell phosphatase calcineurin, decreases rejection episodes and therefore is very important in transplantation regimens (6). 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 (7). However, studies evaluating the presence of bone loss secondary to CsA have conflicting results. One study on the kidney transplant recipient demonstrated that bone loss was associated with cumulative CsA dose and independent of the effects of GCs during the first two years after transplantation (8). In contrast, another study evaluating patients after renal transplantation who received CsA in a GC-free regimen did not show any bone loss (9). Tacrolimus (FK506), another calcineurin inhibitor, inhibits T-cell activation and proliferation and cytokine gene expression (6,10). Although studies have demonstrated that FK506 leads to bone loss in rats, the skeletal effects in humans have not been thoroughly studied. Both liver and cardiac transplant recipients have been shown to sustain rapid bone loss with tacrolimus (11). 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 (10).

Later during the post-transplant period, when the GCs doses are tapered to below 5 mg per day, there is recovery of osteoblast function and consequently an increase in bone formation and recoupling of the bone remodeling activity. However, both the direct and the indirect effects of cyclosporine and FK506 continue to influence the skeleton, resulting in secondary hyperparathyroidism and increased bone resorption. During this later phase, rates of bone loss slow down and there may even be some recovery, particularly at sites comprised predominantly of cancellous bone (2).

KIDNEY TRANSPLANTATION

Kidney transplantation is the treatment of choice for end-stage renal disease (ESRD). Restoration of renal function after kidney transplantation rectifies many of the disturbances that lead to renal osteodystrophy. There is resolution of hyperphosphatemia, an increase in serum $1,25(\text{OH})_2\text{D}$ levels and a rapid decline in the elevated levels of parathyroid hormone (PTH), al-

though they may never completely normalize. In the first few months after kidney transplantation, PTH-dependent hypercalcemia and hypophosphatemia may develop. In addition, post-transplant hypophosphatemia may also be related to a primary defect in renal phosphate handling due to increased serum concentrations of circulating factors (12).

Bone loss rates are greatest in the first 6-18 months after kidney transplantation and range from 5% to 8% at the hip and 4% to 9% at the lumbar spine (13). Although low estradiol and testosterone levels have been associated with accelerated bone loss (14), bone loss has not been consistently related to gender, patient age, cumulative GC dose, rejection episodes, activity level, or PTH levels.

Fracture prevalence varies from 7% to 11% in non-diabetic renal transplant recipients, but is considerably higher in patients transplanted because of diabetic nephropathy and in those who receive kidney-pancreas transplants (15). Fractures occur relatively late in the post-transplant period, usually within the first three years after transplantation, and more commonly involve appendicular sites (hips, long bones, ankles, feet) than the axial sites (spine and ribs) (16). A large study of ESRD patients demonstrated that kidney transplantation was associated with a 34% greater risk of hip fracture than continued dialysis (17).

LUNG TRANSPLANTATION

Prospective studies have also demonstrated changes in bone mass and fracture incidence in patients who have received lung transplant (18-20). Bone loss rates at the lumbar spine and femoral neck range from 2% to 5% in the first year after lung transplantation (13,18). In addition, fracture rates are also high, ranging from 18% to 37% during the first year, even in those patients who received antireabsorptive therapy. Pre-transplantation lower bone mineral density (BMD) and longer prior glucocorticoid therapy were correlated to the incidence of fractures. Spira and cols. (19) evaluated BMD in 28 patients prior and 6 to 12 months post lung transplantation (19). All patients received calcium (1 g per day) and vitamin D (400 UI per day) after the transplantation. There was a 5% reduction in BMD of both lumbar spine and femur neck, which was associated with the cumulative steroid dose after transplantation. In addition, 18% sustained osteoporotic fractures, despite vitamin D and calcium supplementation.

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% to 10% at the lumbar spine and 6% to 11% at the femoral neck and then seems to stabilize during the second year and may even increase after the third year. (1,3).

Vertebral fractures have been reported to occur from 14% to 36% during the first post transplantation year and 22% to 35% of long-term cardiac transplant recipients (21). Bone resorption markers are increased in the initial period after transplantation whereas bone formation marker (osteocalcin) is reduced (3). 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 to 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 (22).

BONE MARROW TRANSPLANTATION

Bone marrow transplant (BMT) recipients have many known risk factors for developing low BMD after transplantation (23). The pathogenesis of bone disease following BMT differs from other forms of post-transplantation osteoporosis; recipients are usually younger; the time from primary diagnosis to the BMT usually does not exceed 2 years; history of prolonged bed rest is uncommon.

The rate of bone loss increases during the first year following BMT from 2% to 9% at the lumbar spine and 6% to 11% at the femoral neck. In a study of long term follow up of bone loss after BMT, Schulte and Beelen observed that lumbar spine BMD begins to recover after 12 months, returning to baseline at 48 months (24). 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 GC, which contributes to bone loss in BMT recipients (25). In addition, low BMD was associated with insulin resistance (26). A marked decline in serum levels of 1,25-dihydroxyvitamin D₃ and 25-hydroxyvitamin D₃ in the course of allogeneic BMT was observed (27). This may be explained by the fact that after BMT patients

have low sun exposure to prevent GVHD. Further, a study evaluating children and adolescents after BMT reported low ingestion of calcium and vitamin D (28).

LIVER TRANSPLANTATION

Bone loss and increased risk for fracture are common complications after liver transplantation (29). The progression of bone loss is similar to that following lung and cardiac transplantation, being more severe in the first 6-12 months. In earlier studies, bone loss after liver transplantation was characterized by a marked decrease in lumbar spine BMD of 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 femoral neck, or even absent (30). Fracture incidence is also at its highest in the 6-12 months following the transplantation, with rates ranging from 24%-65%; ribs and vertebrae are the most common sites (13). In recent prospective studies, the risk of post-transplantation fractures was related to older age and pre-transplantation BMD at the LS and FN (31). In addition, pre-transplantation vertebral fractures also have been shown to predict post transplantation vertebral fractures. 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 elevations in osteoprotegerin and RANK-L levels during the first 2 weeks after liver transplantation (32) provide further evidence of high bone turnover.

It is important to point out that many of these studies are older and were conducted in an era of higher GC doses than those which are used today and that more recent studies suggest lower rates of bone loss and fracture rates than those that were reported in the mid-1990s and early 2000s.

PREVENTION AND MANAGEMENT OF TRANSPLANTATION OSTEOPOROSIS

Pre-transplantation 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 pre-transplant 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 (33). 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, the dose of glucocorticoids should be minimized to the extent possible and the recommended daily allowance for calcium (1,000-1,500 mg/day) and vitamin D (400-800 IU/day) followed.

Prevention of early and late post-transplantation bone loss

It is well known that the rates of bone loss and fracture incidence are highest immediately following transplantation. Therefore, preventive and therapeutic measures should be instituted at that time and without delay.

Active vitamin D metabolites

Vitamin D metabolites influence post transplantation bone loss through several mechanisms: they reverse GC-induced decreases in intestinal calcium absorption, limit the resultant secondary hyperparathyroidism (SHPT), promote differentiation of osteoblast precursors into mature cells, and may potentiate the immunosuppressive activity of CsA (34). Calcidiol (25-OHD) and alfacalcidol, protect against bone loss in heart transplantation patients (35) and renal transplant recipients (36). Calcitriol (1,25(OH)₂D) has been studied in recipients of heart, lung, and liver transplants, with somewhat conflicting results. Beneficial effects have been seen with the use of 0.5 µg/d or more. A randomized study of heart or lung transplant recipients who received placebo or calcitriol (0.5-0.75 µg/d) for either 12 or 24 months after transplantation found that LS bone loss did not differ between groups (37). Furthermore, in a study of long-term heart transplant recipients found no protective effect of the calcitriol on the skeleton (38). In addition, hypercalcemia and hypercalciuria, common side effects of vitamin D metabolites, may develop at any point during treatment. Frequent monitoring of urine and serum is required. In our opinion, active vitamin D metabolites should

not be selected as first-line treatment because of their limited effectiveness and narrow therapeutic window.

Gonadal hormone replacement

Few studies have approached the proposal of hormone replacement therapy (HRT) for transplant recipients, although a recent study showed a protective effect on the skeleton (39). The use of HRT in premenopausal women who develop amenorrhea after transplant should be administered provided there are no contraindications.

Bisphosphonates

Studies using both intravenous and oral bisphosphonates have shown they are effective to prevent bone loss after transplantation (23,40-42). Alendronate has been studied in both immediate (43) and long-term (42) 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 LS and hip when compared with reference subjects who received only calcium and vitamin D (43). In the second year after cardiac transplantation, BMD remained stable, although alendronate and calcitriol were discontinued (44). Similarly, studies demonstrated the efficacy of intravenous ibandronate, zoledronic acid and of pamidronate in the prevention of bone loss after renal, heart, lung, liver and bone marrow transplant recipients, independent of the time following transplantation (23,40,41,45,46).

A recent systematic review of 24 trials evaluated the benefits and risks of treatments used to reduce bone disease following kidney transplantation (47). Meta-analysis of all available such trials combined, however, shows that any intervention (bisphosphonate, vitamin D sterol, or calcitonin) for bone disease in kidney transplant recipients does reduce the risk of fractures. These agents also provide a significant improvement in bone mineral density when given after transplantation, although the clinical significance of this is uncertain due to the lack of validation of bone densitometry in chronic kidney disease. Regarding renal safety issues, the dose schedule is different for iv bisphosphonates. Infusion rate should be reduced to half the recommended rate in patients with glomerular filtration rate below 30 mL/min or baseline creatinine below 2 mg/dL (48).

Teriparatide

One double-blind, randomized trial, treated 26 kidney transplant recipients with administration of teriparatide (PTH 1-34) or placebo, and demonstrated that teriparatide does not improve BMD early after kidney transplantation (49). In addition, neither histological analysis nor bone markers provide evidence of improved bone turnover or mineralization.

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 organ transplantation. Exposure to high doses of GCs and calcineurin inhibitors is associated with rapid bone loss and high fracture incidence immediately after transplantation. Effective therapies should incorporate pre-transplant measures to treat pre-existing bone diseases and also aggressive prevention of bone loss during the first 6 to 12 months after transplantation. The optimal dose, timing and frequency of administration of these therapies remains to be determined.

Of the presently available treatment modalities, bisphosphonates are the most consistently effective for both prevention and treatment of osteoporosis in transplant recipients. Use of new agents such as RANK-L antagonists and cathepsin K inhibitors in the management of osteoporosis after transplantation is 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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