**POST-TRANSPLANT OSTEOPOROSIS**

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**ABSTRACT**

Organ transplantation has become an established treatment for end-stage diseases, and in recent decades, survival rates have significantly improved. This progress has made diagnosing osteoporosis and other complications essential for prevention, treatment, and enhancing the quality of life for transplant patients. Patients who undergo solid organ transplantation often have risk factors for bone loss and fractures, and these risks can increase after transplantation. Post-transplant fractures have been identified as an independent risk factor for overall mortality in these patients. Preoperative low bone mass increases the likelihood of these complications. Osteoporosis is a significant concern that can develop, worsened by glucocorticoids and immunosuppressive therapy, used after transplantation to prevent organ rejection. A major consequence of this is an elevated risk of fractures in bones with reduced strength and quality, leading to increased morbidity and mortality. Additionally, there are notable differences in bone loss and fracture rates among patients with different types of transplanted organs. Initially, reports indicated that in the first year following transplantation, there was a rapid loss of bone mass and an increased rate of fractures. Unfortunately, bone mass achieved after transplantation remains lower long-term compared to that of healthy individuals. Protocols involving less aggressive use of glucocorticoids and immunosuppressants have been introduced to reduce these complications, along with advancements in infection prevention and treatment, to improve the tolerability of treatments and long-term outcomes. Another strategy has been to optimize bone mass in transplant candidates, administering calcium, vitamin D, and bisphosphonates before surgery. Therefore, the prevention and management of bone loss in both transplant candidates and post-transplant patients should be prioritized to reduce the risk of fractures.

**INTRODUCTION**

Organ transplantation is a well-accepted procedure for treating end-stage diseases such as kidney disease, chronic liver failure, end-stage pulmonary disease, and heart failure. Over the past decade, advancements in this technique have significantly improved patient survival and quality of life. The number of transplants has steadily increased, rising from 106,879 in 2010 to 157,500 in 2020 (1). However, bone loss is a common complication affecting long-term survival and quality of life during patient follow-up.

After transplantation, rapid and significant bone loss can occur within the first 3-6 months, along with a substantial increase in fracture risk (2,3). The rapid rate of bone loss is likely due to corticosteroids. Greater bone loss has been reported at vertebral and hip sites, along with high rates of fragility fractures. Over half of transplanted patients develop osteoporosis and one-third experience vertebral fractures (4). However, recent studies show a lower rate of bone loss and fractures following transplants, likely due to reduced glucocorticoid doses and modifications in immunosuppression regimens (5,6).

Several risk factors contribute to bone loss in patients including pretransplant disease, aging, hypogonadism, vitamin D deficiency, malabsorption, low body weight, physical inactivity, excessive tobacco or alcohol use, and immunosuppressive therapy (7) (Table 1). Improved management of pretransplant risk factors has led to better bone mineral density (BMD) levels before transplantation.

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| **Table 1. Risk Factors for Bone Disease in Patients with Organ Transplantation** |
| **Organ**  |  **Potential Risk Factor** |
| **Pre-Transplant Factors Affecting All Transplant Patients** | -Pre-existing low bone disease-Lower bone mineral density-History of Fractures |
| **Factors Specific to Kidney Transplant Recipients.** | -Female gender-Older age-β-microglobulin amyloidosis-Glucocorticoids-Secondary hyperparathyroidism-adynamic bone disease-Chronic metabolic acidosis-Hypogonadism -Vitamin D deficiency-Long-term hemodialysis-Diabetes |
| **Factors Specific to Liver** **Transplant Recipients.** | -Older age-Alcoholism-Hypogonadism-Abnormal vitamin D metabolism-Primary biliary cirrhosis-Cholestasis-Hyperbilirubinemia. |
| **Factors Specific to Heart****Transplant Recipients.** | -Low levels of vitamin D-Hypogonadism-Long-term heparin-Loops diuretics-Secondary hyperparathyroidism-Physical inactivity, -Therapy with loop diuretics, -Tobacco, alcoholism. |
| **Factors Specific to Lung****Transplant Recipients.** | -Glucocorticoid therapy-Tobacco-Physical inactivity-Low body weight-Malnutrition-Hypogonadism-Hypercapnia-Hypoxia-Hypogonadism-Cystic Fibrosis |
| **Post-Transplant Factors Affecting All Patients** | -Glucocorticoids-Immunosuppressors: cyclosporine, Tacrolimus.-Older age-Kidney dialysis-Diabetes Mellitus-High or low PTH**-**Cholestatic liver disease, -Primary Biliary Cirrhosis |

This article will review the causes, prevention, and treatment of post-transplant bone loss and fractures in recipients of major organs involved in transplantation, such as kidney, liver, cardiac, and lung.

**BONE AND FRACTURES BEFORE TRANSPLANTATION**

Patients referred for solid organ transplantation due to various diseases (kidney, liver, heart, and lung) have a high prevalence of osteoporosis and fractures, with distinct characteristics specific to each transplanted organ (Table 2).

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| **Table 2.- Prevalence of Osteoporosis and Fractures in Patients Pre-Transplantation \***  |
| **Organ** | **Osteoporosis** | **Fracture incidence** |
| **Spine** | **Hip** |
| **Renal** | **22%**  | **20%**  | **24%-38%** |
| **Liver** | **12%-55%** | **-** | **22% (5)** |
| **Heart** | **7%-40%** | **25%** | **40%** |
| **Lung** | **9%-69%** | **-** | **15%-50%**  |

**\*** Using dual X-ray densitometry, Vertebral fracture incidence in the first years post-transplantation. References: 1,2,3,4,5,6,9,120,122,123.

**Renal Disease**

End-stage renal disease (ESRD) is associated with a form of bone disease known as renal osteodystrophy. This condition develops due to factors such as Vitamin D deficiency, hypercalcemia, hyperphosphatemia, secondary hyperparathyroidism, metabolic acidosis, adynamic bone disease, osteomalacia, and aluminium overload which can lead to low bone BMD. In ESRD, cortical bone is predominantly lost, often resulting in peripheral fractures. The combination of fractures and the classic risk factors of chronic kidney disease significantly increases mortality.

Osteoporosis was found in 27.6% of 221 patients awaiting kidney transplantation and was associated with vascular calcification in 75% and parathyroid hyperplasia in 93.4% of cases. In many of these patients, there is a preference for appendicular fractures, which is different from other solid transplant recipients.

Elevated bone markers of formation (PINP) and resorption markers (B-CTX) were also linked to decreased BMD, confirming a disruption in bone remodelling. This suggests that sustained PTH levels indicate abnormal osteoblast function characterized by high turnover and increased resorption which contributes to a higher fracture risk (11).

Early renal dysfunction is associated with a 38% increase in fracture risk in men over 65 years old. In a cohort of 1477 participants from the Longitudinal Aging Study Amsterdam, followed for six years, patients with chronic kidney disease (CKD) stages 3a and 3b had a 28% and 46% higher fracture risk, respectively, compared to those with stages 1 and 2 (eGFR >60 ml/min/1.73 m2) (12). Early renal dysfunction was linked to lower femoral neck BMD, only in men, likely due to higher PTH levels. Several factors, including hemodialysis and diabetes mellitus further increase fracture risk. Patients with renal insufficiency, low bone turnover, and reduced BMD are at the highest risk for fractures.

**Liver Disease**

Osteoporosis and osteopenia are frequent complications of chronic liver disease, with a higher prevalence in patients awaiting liver transplantation, particularly in those with cholestatic liver diseases (14,15). Low BMD before transplantation is a major risk factor, influenced by inadequate calcium intake, malabsorption, malnutrition, vitamin D deficiency with secondary hyperparathyroidism, and an abnormal sex hormone ratio. In cirrhotic patients, factors such as hypogonadism, steroid use, and alcoholism can further accelerate bone loss (16). Heavy alcohol consumption affects bone metabolism by modulating Wnt and mTOR signaling [17], leading to decreased bone formation and increased adipogenesis. Additionally unconjugated bilirubin in patients with cholestasis has been shown to exert harmful effects on osteoblasts, reducing their viability. Studies have demonstrated that sera from jaundiced patients can upregulate the RANKL/OPG ratio promoting osteoclastogenesis, while downregulating Runx2, a key transcription factor involved in osteoblast differentiation (18).

Calcium and serum PTH levels are typically normal, but two-thirds of patients may have low levels of 25OHD, due to impaired hepatic hydroxylation of cholecalciferol. Histomorphometric studies have revealed decreased cortical bone volume, low bone formation, poor mineralization, and slightly elevated osteoclastic activity (19)

**Cardiac Disease**

Bone loss in candidates for cardiac transplantation is associated with the underlying disease and is commonly found in those with congestive heart failure. The prevalence of osteoporosis at the time of cardiac transplantation has been reported to range from 7% to 23% (20). Older studies indicate that 7% of these patients had lumbar osteoporosis and 20% had hip osteoporosis, meaning that fewer than 50% had normal BMD (21). In another study of 51 cardiac transplant candidates, the prevalence of osteoporosis was 27%, with longer waiting times before transplantation identified as a major risk factor for its development. (22).

Interestingly, despite 80% of these patients having vitamin D deficiency, 55% of cardiac transplant candidates, had BMD levels comparable to those of healthy individuals (23). This discrepancy may be explained by seasonal variations and the fact that these patients were ambulatory rather than on the transplant list. It is therefore recommended that patients on the waiting list be evaluated for bone loss prevention. The high prevalence of osteoporosis in this population is linked to chronic illness, poor nutrition, limited mobility, weight loss, gonadal dysfunction, and medications that negatively affect bone health (24). Additionally, patients with congestive heart failure, are often treated with medications such as loop diuretics, which increase urinary calcium losses. Furthermore, azotemia is known to impair vitamin D metabolism leading to elevated PTH levels and further contributing to bone loss.

**Lung Disease**

Patients who are candidates for lung transplantation are also highly likely to have osteoporosis before surgery. In many cases, chronic exposure to glucocorticoids is the primary risk factor. However, several other risk factors may also contribute to bone loss.

A retrospective study of patients with diffuse parenchymal lung disease referred for lung transplantation found that 30% had lumbar osteoporosis and 49% had femoral osteoporosis (25). Another study reported even higher rates, with 50% of patients having lumbar osteoporosis and 61% having femoral neck osteoporosis (26,27). Additionally, most of these patients had a history of glucocorticoid therapy.

Cystic Fibrosis (CF) in advanced stages, is another lung disease associated with a high prevalence of osteoporosis and fractures in patients awaiting lung transplantation. A meta-analysis found that bone complications are common in CF, with a prevalence of 23.5% for osteoporosis, 14% for vertebral fractures, and 19.7% for non-vertebral fractures (28). In younger patients, potential risks such as calcium and vitamin D malabsorption, malnutrition, delayed puberty, hypogonadism, and glucocorticoid therapy have been identified as contributors to bone loss.

**BONE LOSS AND FRACTURES AFTER TRANSPLANTATION**

Bone loss and fracture rates are higher in patients who had osteoporosis before transplant (Table 3). In these cohorts, post-transplantation fractures are associated with increased mortality rates (29). The highest fracture risk has been reported in heart and lung recipients, as well as in those with comorbidities such as rheumatoid arthritis, gout, and chronic obstructive pulmonary disease (COPD. Regarding diabetes mellitus, no clear association has been established between this condition and fracture risk in post-transplanted patients.

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| **Table 3.- Prevalence of Osteoporosis and Fractures in Patients Post-Transplantation** |
| **Organ** | **Osteoporosis** | **Fracture incidence** |
| **Spine** | **Hip** |
| **Renal** | **7%-44%**  | **11%-56%** | **7-21%)** |
| **Liver** | **11%-52% (6)** | **-** | **24-65%**  |
| **Heart** | **28%-50%** | **25%** | **22%-44%** |
| **Lung** | **31%-84%**  | **-** | **18-37%**  |

\* Using dual X-ray densitometry, Vertebral fracture incidence in the first years post-transplantation. References: 1,2,5,6,7,8,9,10,38,120,121,122,123,124, 125,126.

Bone loss appears to be more significant during the first year after transplantation across all types of organ transplants, primarily affecting trabecular bone, including the vertebrae and peripheral skeleton. When analysing the incidence rate of osteoporosis per 1000 person-years, heart and lung transplants have the highest rates at 6.00, compared to 4.17 and 4.09 for liver and kidney transplants, respectively. A significant increase was also observed in heart and lung transplant recipients, with a rate of 9.36 per 1.000 person-years, compared to 2.44 for liver transplants and 1.98 for kidney transplants. (27). These differences are likely influenced by variations in immunosuppressive regimens and the use of lower steroid doses.

There are inconclusive findings regarding bone mass recovery in transplant recipients beyond the first year, with studies reporting decreases, increases, or stabilization (30,31). After five years of follow-up, hip BMD often remains lower than pre-transplant levels in many patients, similar to trends observed in quality-of-life assessments. (32). There is considerable overlap in BMD values between individuals who develop fractures and those who do not. This suggests factors affecting bone quality -such as geometry, microarchitecture, and intrinsic properties of bone- may play a more significant role in fracture risk than bone quantity alone in transplant patients.

Trabecular Bone Score (TBS) a surrogate of bone quality, has been shown to deteriorate for up to a year after solid organ transplantation, even with therapeutic interventions, such as risedronate, ibandronate, vitamin D, and calcium, and without correlation with BMD. However, after one year, TBS improved and has been identified as a strong and independent predictor of fragility fractures (33,34).

**Kidney Disease**

As with other organ transplants, BMD loss in the first six months after kidney transplantation primarily affects cortical bones, largely due to persistent hyperparathyroidism and glucocorticoid use. It is estimated that 30% to 50% of patients continued to have hyperparathyroidism post-transplant (35). Specific risk factors for bone loss in kidney transplant recipients include previous chronic kidney disease, duration of dialysis, and hypomagnesemia. Additionally, patients with diabetes mellitus and nephropathy, have an increased risk of bone loss.

Post-transplant treatment factors, such as the use of tacrolimus and steroids, along with older age and elevated body mass index, further contribute to the risk of developing post-transplant diabetes (36). In kidney transplant recipients, those with vitamin D deficiency, have a 2.4 times higher risk of developing post-transplant diabetes compared with those with normal serum 25OHD (>30 ng/ml). Cross-sectional studies report osteoporosis prevalence rates ranging from 17% to 29% at the spine, 11% to 56% at the femoral neck, and 22% to 52% at the radius (11). Although most fractures occur within the first three years post-transplant, the risk continues to increase over time in some patients.

**Liver Disease**

After liver transplantation, bone density declines rapidly within the first six months, followed by a gradual increase in the subsequent months, with a tendency toward recovery within two years. However, not all patients regain normal BMD levels. Fracture incidence is highest during the first six months post-transplant, particularly in patients with primary biliary cirrhosis. While lumbar BMD tends to improve over time, hip BMD often remains lower for an extended period after transplantation (39).

Previous studies have reported an osteoporosis prevalence of 40.8% in 82 liver transplant recipients with various etiologies who were followed for one year (38). Similarly, a more recent study found a prevalence of 34.5% in 83 patients who were followed for an average of 80 months (39). After the first year, bone loss tends to slow, likely due to reduced use of glucocorticoids and immunosuppressants (40). Additionally, the decrease in bilirubinemia, known to negatively affect osteoblast differentiation and mineralization, may also play a role in this stabilization. However, it is accepted that approximately one-third of liver transplant recipients, still have lumbar spine BMD below the fracture threshold two years post-transplant, despite improvements in survival and quality of life (41). Reported fracture rates after liver transplantation range from 24% to 65%.

**Cardiac Disease**

Bone loss progresses rapidly after transplantation in these patients, with an estimated decline of 6%-11% at the vertebral site within the first six months, and a similar rate at the hip within the first year (21). Most studies report vertebral fracture incidence ranging from 33 to 36% in the first one to three years post-transplant stabilizing in subsequent years (15). During the initial months after transplantation, bone resorption markers are elevated, while bone formation markers (such as osteocalcin), are reduced. The levels typically return to normal by the end of the first year (38).

Patients with congestive heart failure patients are particularly prone to significant bone loss compared to other cardiac transplant candidates (7). Higher exposure to glucocorticoids, vitamin D deficiency, and testosterone deficiency in men, are linked to reduced bone formation in the first year (Table 3). By the third-year post-transplant, a significant recovery in lumbar BMD is observed. While both men and women experience similar rates of bone loss, women are more prone to fractures due to lower pre-transplantation BMD.

In some patients, bone recovery has not been observed, with a reported fracture prevalence of 40% among 180 individuals who underwent cardiac transplantation over 10 years (44). Furthermore, significant bone loss has been documented, with decreases ranging from 3% to 10% in the lumbar spine, 6% to 11% in the femoral neck, and fracture rates between 12% and 36% within one year. These rates of bone loss are notably higher compared to the 1.41% and 0.35% annual decreases observed at the lumbar spine and femoral neck, respectively, in the healthy population (44,45).

**Lung Disease**

Patients with chronic obstructive pulmonary disease (COPD) have a high prevalence of osteoporosis which can reach 57% to 73% in the first year after lung transplantation (46). Fracture rates continue to rise in some cases, with an average prevalence of 53% by the fifth-year post-transplant (47). Lung transplants have reported the highest fracture rates, likely due to prolonged and intensive immunosuppressive therapy, along with additional life-risk factors. Among lung diseases, patients with COPD are particularly prone to bone loss.

**OSTEOPOROSIS AFTER BONE MARROW TRANSPLANTATION**

Allogenic or autologous stem cell transplantation is used to treat a variety of hematologic diseases. Advances in histocompatibility testing and improvements in infection control have significantly increased patient survival. Risk factors for osteoporosis include the underlying disease, comorbidities (such as diabetes and obesity), the use of glucocorticoids, and immunosuppressants.

The pathogenesis of bone loss in this context is not well understood. It has been postulated that implanted bone marrow stromal cells may have a reduced capacity to develop into osteogenic lineage. Bone loss is most prominent during the 6 to 12 years following transplantation. Osteoporosis has now been recognized as a common condition in these patients, with a reported prevalence of up to 23% within the first-year post-transplant. Therefore, bone marrow-related osteoporosis following stem cell transplantation appears to be less severe compared to that seen in solid organ transplantation. However, there are still relatively few publications addressing this issue.

**PATHOGENESIS OF OSTEOPOROSIS POST-TRANSPLANTATION**

Bone loss after solid organ transplantation is caused by numerous factors, including pre-transplant underlying disease, individual risk factors, and the use of glucocorticoids and immunosuppressor drugs. Additional contributors include age, limited mobility, smoking, excessive alcohol consumption, and lifestyle habits.

**Glucocorticoids**

Glucocorticoids are essential for managing rejection episodes. They are typically administered at high doses initially and then gradually reduced. However, if rejection occurs, the dosage is increased. Recent protocols have aimed to minimize glucocorticoid doses to reduce side effects. High doses of glucocorticoids play a significant role in bone loss. However, it has been shown that even small doses of glucocorticoids are associated with an increased fracture risk (48). The potential impact of glucocorticoid dose on bone loss is supported by the evidence showing no significant bone loss at the lumbar spine and proximal femur in renal transplant patients treated with low doses of steroids and tacrolimus. Additionally, studies have reported that steroid withdrawal in liver transplant patients accelerates lumbar spine bone density recovery without compromising graft tolerance (5,54).

The mechanisms contributing to glucocorticoid-induced bone loss are discussed in the Endotext chapter entitled “An Overview of Glucocorticoid-Induced Osteoporosis” in the Bone Mineral section.

DIRECT EFFECTS OF GLUCOCORTICOIDS ON OSTEOBLASTS AND OSTEOCYTES

Glucocorticoids inhibit bone formation by impairing the proliferation and differentiation of osteoblasts, as well as reducing their lifespan (49,50, 51). This occurs through the inhibition of the canonical Wnt/B catening pathway, and the upregulation of sclerostin and other peptides, which further suppress osteoblast formation.

DIRECT EFFECT OF GLUCOCORTICOIDS ON OSTEOCLASTS

Glucocorticoids increase the production of RANKL (receptor activators of nuclear factor kappa-B ligand) and decrease the production of osteoprotegerin, leading to enhanced bone resorption.

INDIRECT EFFECTS

Similar to other conditions with hypercortisolism, glucocorticoids in post-transplant patients can induce hypogonadism, by directly inhibiting the secretion of estrogens and androgens. They also impair calcium absorption, and negatively affect the synthesis of 25OHD, by inhibiting the 25 hydroxylases.

**Calcineurin Inhibitors: Cyclosporine A (CsA) and Tacrolimus**

The impact of various immunosuppressor drugs used in post-transplant patients on bone health remains partially unknown and, in some cases, controversial. This uncertainty is likely due to differences in dosage, duration of use, and combination with other medications (Table 4). Among these drugs, two are considered the cornerstone of immunosuppressive therapy for maintaining graft survival. Calcineurin inhibitors work by inhibiting cytokines synthesis, such as interleukin-2, through binding to immunophilin and suppressing the activity of calmodulin-dependent protein phosphatase calcineurin. This suppression reduces by downregulating genes regulatory products, including interleukin 2, interleukin receptors and H-ras and c-myc (55). Studying the effect of these drugs on bone health is challenging due to their frequent coadministration with glucocorticoids. The effects of these drugs are difficult to study, due to their coadministration with glucocorticoids.

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| **Table 4. Effect of Immunosuppressor Drugs on Bone of Post-Transplant Patients** |
| **Drug**  | **Effect on Bone** |
| **Glucocorticoids**  | Inhibition of bone formationStimulation of bone resorptionReduce intestinal calcium absorptionIncrease urinary calcium excretionDecrease secretion of GH, estrogens and androgens |
| **Calcineurin inhibitors**Cyclosporine A & Tacrolimus  | Marked stimulation of bone resorption Minor increase in bone formation |
| **Sirolimus (Rapamycin**) | No effects on bone volumeInhibits longitudinal growthDecrease bone formation |
| **Everolimus**  | Decrease bone resorption |
| **Azathioprine**  | No effect on bone volume |
| **Mycophenolate mofetil** | No change in bone volume |

Studies in rats have shown that CsA stimulates both osteoblast and osteoclast activity (56). However, administration of CsA in rodents has been associated with severe trabecular bone loss and induced high turnover bone loss, due to increased bone resorption and formation, accompanied by elevated levels of osteocalcin and 1,25(OH)2D3 (57). In a one-month comparative study in rats, both CsA and tacrolimus were found to reduce bone strength. CsA induced high-turnover bone loss by stimulating both bone formation and resorption whereas tacrolimus primarily stimulated bone resorption (58). Additionally, in a small study of renal transplant patients, steroid withdrawal was associated with lower bone loss when CsA was used alone (59). Consequently, the overall effect of CsA on bone density remains unclear.

Tacrolimus has been shown to induce trabecular bone loss without significantly affecting bone formation in the rat (57). Compared to Csa, Tacrolimus-based regimens may allow for a decrease in glucocorticoids use and result in a more modest reduction in BMD. In a study of 350 liver transplant recipients with chronic cholestatic liver disease, patients treated with CsA experienced lower post-transplant bone gain and higher incidence of fractures than those receiving tacrolimus (60). Other studies suggest that tacrolimus induces only a modest reduction in bone mass, while some reports indicate liver transplant recipients treated with tacrolimus had significantly higher femoral neck BMD compared to those receiving CsA (61).

**mTOR Immunosuppressors: Sirolimus and Everolimus**

Both drugs, inhibited the activity of the mammalian target of rapamycin (mTOR) a key protein kinase involved in regulating cellular metabolism, catabolism, immune responses, autophagy, survival, proliferation, and migration, to maintain cellular homeostasis.

Sirolimus, also known as rapamycin, has the advantage of not causing nephrotoxicity. In-vitro, Sirolimus inhibits the proliferation and differentiation of osteoclasts, making it a potential bone-sparing agent (61). Additionally, lower bone resorption markers observed in a study of renal transplant recipients suggest that this drug helps preserve bone mineral density (62). However, potential side effects seen in animal studies, including impaired growth, delayed callus formation, and interference with IGF1- indicating that sirolimus should be used with caution in clinical practice (63).

Everolimus is a derivative of rapamycin, targets the mTOR pathway, and inhibits interleukin-2 (IL”)-induced cell proliferation, thereby suppressing the immune response. Using mouse models everolimus has been shown to act as a potent inhibitor of osteoclast formation and activity (64).

**Other Immunosuppressors: Mycophenolate Mofetil (Mn) and Azathioprine**

Mn inhibits B and T lymphocyte proliferation while azathioprine, a purine antagonist, reduce lymphocyte count and immunoglobulin synthesis. In animal studies, neither drug has shown an adverse effect on bone mass, and their use may contribute to reduced glucocorticoid co-administration. Currently, many recommended post-transplant regimens consist of a calcineurin inhibitor -such as tacrolimus or cyclosporine A in combination with an antiproliferative agent Mm), with or without low-dose corticosteroids (e.g., prednisolone).

Azathioprine, another purine antagonist, further decreases B and T lymphocytes. The impact of sirolimus, tacrolimus, and Mn on osteoclasts has been studied in cell-cultured systems. The authors detected that the inhibition of osteoclast precursors and proliferation, with Mn and tacrolimus, was lower compared to sirolimus (65). Both drugs are given in protocols combined with other immunosuppressors, which makes it difficult to determine their effects on bone.

**POST-TRANSPLANTATION SERUM PTH, VITAMIN D, TESTOSTERONE, AND MAGNESIUM**

Changes in serum PTH levels vary following solid organ transplants. No significant alteration in PTH levels has been observed after cardiac transplants, whereas liver transplant recipients often experience a moderate increase. In kidney transplant patients, PTH levels may initially decrease by approximately 50% within the first six months post-transplantation (2). Notably, secondary hyperparathyroidism is observed in some kidney transplant recipients, particularly those with prolonged pre-transplant dialysis duration, reduced glomerular filtration, and low serum 25OHD levels (66). The exact causes of elevated serum PTH levels remain unclear but may be associated with the decline in renal function, which affects approximately 20% of transplant recipients. For a detailed discussion of hyperparathyroidism in patients with renal disease see the Endotext chapter entitled “Hyperparathyroidism in Chronic Kidney Disease” in the Bone and Mineral section.

Serum 25OHD levels are often low before transplantation in all transplant candidates before the procedure and remain low afterward. Following transplantation, 91% of patients experience vitamin D insufficiency, and 55% have a deficiency, with the more severe cases observed in liver transplant recipients (68). However, a tendency toward higher levels is typically seen, likely due to supplementation. This deficiency, along with factors such as immobilization, low sunlight exposure, and inadequate vitamin D intake, contributes to an increased risk of bone loss. Additionally, excess glucocorticoid leads to an increased catabolism of 25OHD.

Furthermore, the frequently observed lower testosterone levels found in transplant patients, which contribute to bone loss, generally recover within one year.

Hypomagnesemia is commonly observed in kidney and cardiac transplant recipients and has been associated with the use of calcineurin inhibitors, particularly tacrolimus. Hypomagnesemia can lead to bone loss by increasing the number of osteoclasts and decreasing osteoblasts, resulting in the deterioration of trabecular bone mass and stiffness, along with elevated PTH levels (127).

**POST-TRANSPLANT OSTEOPOROSIS MANAGEMENT**

**Pre-Transplant Considerations**

The evaluation of bone metabolism and fracture risk in candidates for solid organ transplantation should include the following components **(Table 5):**

**-Medical History, Physical Examination, and Assessment of Traditional Osteoporosis Risk Factors:** Key elements include age, sex, low body weight, nutritional status, history of fragility fractures, and prior falls. Notably, a history of falls is an important independent risk factor for fractures in the general population (68)

**-Evaluation of Potential Secondary Causes of Osteoporosis:** These may include endocrinological, nutritional, gastrointestinal, nephrological, rheumatological, hematological, and pharmacological factors (69)

**-Bone Turnover Markers (BTMs):** Although not diagnostic for osteoporosis, BTMs may serve as surrogate markers for bone remodeling activity and may aid in estimating fracture risk. In a study involving patients with chronic kidney disease (CKD) in the pre-transplant setting, BTMs were inversely associated with BMD, although no significant association with fracture prevalence was observed (70)

**-Lumbar Spine Radiography:** This modality is useful for detecting vertebral fractures, many of which are asymptomatic (71). Radiographic screening is recommended for all solid organ transplant candidates and is particularly advised in lung transplant recipients, given a reported vertebral fracture prevalence of approximately 25%, often without correlation to BMD measurements (72).

-Dual-energy X-ray absorptiometry (DXA)**:** DXA scanning is recommended for all solid organ transplant candidates. In patients with CKD stages 3–5, DXA has demonstrated predictive value for fracture risk (73). However, its accuracy may be compromised by spinal deformities, degenerative changes, and vascular (e.g., abdominal aorta) or articular calcifications, which can lead to BMD overestimation.

**-Fracture Risk Assessment Tool (FRAX):** The FRAX algorithm estimates the 10-year probability of hip and other major osteoporotic fractures using clinical risk factors, with or without BMD input (74). Although CKD is not included in the FRAX model, its use is still recommended for renal transplant candidates, as predictive utility has been demonstrated in non-dialysis populations (75).

**-Trabecular Bone Score (TBS):** Derived from DXA images of the lumbar spine, TBS evaluates bone microarchitecture through texture analysis (76). Its value as an independent predictor of fragility fractures has been confirmed in patients with CKD (77).

-Bone biopsy: In patients with CKD stages 3a–5D, bone biopsy should be considered when there are unexplained fractures, persistent bone pain, hypercalcemia, hypophosphatemia, or suspicion of aluminum toxicity.

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| **Table 5. Clinical Evaluation in Patients with Solid Organ Transplantation** |
| **History** -Age-History of previous fractures-Gonadal status-Dietary intake calcium/vitamin D-Alcohol abuse-Smoking-Physical Activity: sedentarism, exercise, mobility-Chronic disease: Diabetes, renal osteodystrophy, end-stage pulmonary disease, hepatic diseases.-Medications |
| **Physical examination**-Weight-BMI-Presence of imbalance, complications |
| **Laboratory****-**Serum Ca, P04, Mg-Serum intact PTH-Serum 25OHD-Renal function parameters-Bone mineral density-Trabecular Bone Score-Bone turnover markers (formation/resorption)-Gonadal hormone levels (testosterone in men, estradiol, LH levels in women)-Thyroid function studies-Urinary calcium excretion |
| **Densitometry: DXA****Fracture Risk Assessment: FRAX® test**  |

**Preventive Management and Post-Transplant Osteoporosis Treatment**

Although numerous studies in solid organ transplant recipients have demonstrated the beneficial effects of antiresorptive agents in preventing bone loss, the majority have been limited by insufficient statistical power to detect significant differences in fracture incidence. Nonetheless, two reports have provided evidence supporting the effectiveness of initiating treatment with bisphosphonates or vitamin D supplementation in reducing the risk of post-transplant fractures (78,79) (Table 6).

Given that patients who have undergone solid organ transplantation are at a higher risk of fractures compared to the general population, particularly within the first year post-transplant, several experts and professional societies recommend preventive treatment during this critical period, especially for heart, lung, and liver transplant recipients. For instance, the International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend preventive therapy for all heart transplant recipients during the first year following transplantation (80). Similarly, the American Association for the Study of Liver Diseases (AASLD) guidelines advocate for the use of bone-protective treatment in all liver transplant recipients (81). In lung transplantation, where the incidence of osteoporosis and osteopenia is significantly higher than in other transplant populations, preventive treatment is also strongly recommended.

In contrast, there is currently no consensus regarding the use of preventive therapy in renal transplantation. Some authors have proposed initiating antiresorptive treatment in patients with osteopenia and a high risk of fracture. They emphasize the importance of a comprehensive fracture risk assessment, which should include factors such as age, sex, history of fragility fractures, bone mineral density (BMD), bone turnover markers, and parathyroid hormone (PTH) levels (82). Preventive treatment is generally recommended for patients with elevated fracture risk and/or evidence of osteopenia.

The management of bone loss in patients undergoing bone marrow transplantation is currently under investigation. A recent meta-analysis suggests that, in patients with a BMD T-score below -1.5, bisphosphonates, particularly zoledronic acid, are effective in preventing bone loss. If renal function is impaired or bisphosphonates are not well tolerated, denosumab is recommended as an alternative. Clinical trials involving teriparatide, abaloparatide, and romosozumab have not yet been published (128).

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| --- |
| **Table 6. Antiresorptive Therapy with Proven Efficacy in Increasing Bone Mineral Density in Solid Organ Transplant Patients** |
| **Medications** | **Dose and route of administration** | **Rare possible long-term Adverse Effects** |
| Bisphosphonates-Alendronate-Risedronate-Ibandronate-Zolendronic acid-Pamidronate | 70 mg PO/week5 mg PO/daily150 mg PO/monthly3 mg IV/3 months5 mg IV/year for 5 yrs30 mg IV/3 months | GI intolerance, hypocalcemia, rare jaw osteonecrosis and atypical femur fractureSame as aboveSame as aboveSame as above plus infusion reactionSame as above |
| Denosumab | 60 mg SC/6 months | Liver safe, fractures rebound after cessation |
| Teriparatide | 20 ug/day SC/2 years only | Hypercalcemia |

PO = per os; SC = subcutaneously

NON-PHARMACOLOGICAL MEASURES

The general recommendations for all transplant patients are as follows:

* Smoking cessation and reduced alcohol consumption (especially in the case of liver transplantation).
* Limiting caffeine intake to fewer than 1–2 caffeinated beverages per day.
* Nutritional assessment to identify patients at risk of malnutrition or those with established malnutrition, enabling appropriate dietary modifications and initiation of nutritional supplementation if needed. It is also crucial to ensure adequate protein intake, as this helps minimize bone loss, particularly in patients with prior hip fractures.
* Avoidance of prolonged immobilization due to the association between sarcopenia, increased risk of falls, and bone fractures. Physical exercise is strongly recommended, including:
	+ A 30- to 40-minute walk per session (3 to 4 times per week).
	+ Back and postural exercises for a few minutes per day (3 to 4 times per week).
	+ Strength training exercises.
* Implementation of fall prevention measures, both at home and outdoors.

Finally, to optimize bone metabolism in transplant patients and reduce the risk of developing osteoporosis, it is recommended to appropriately adjust the doses of steroids and immunosuppressants (maintaining these drugs within the therapeutic range and avoiding overdosing) (83).

CALCIUM AND VITAMIN D SUPPLEMENTATION

Although conclusive data in patients with solid organ transplantation is lacking, it is recommended to achieve and maintain normal levels of calcium and vitamin D, with supplementation provided if necessary. Vitamin D deficiency is particularly common in transplant recipients, making supplementation especially important for these patients. The recommended daily intake of calcium ranges from 1000 to 1200 mg, depending on age and sex (84). If dietary calcium intake is insufficient, supplementation should be considered. Vitamin D deficiency leads to inefficient absorption of dietary calcium and phosphorus, as well as secondary hyperparathyroidism, which can impair bone mineralization. An optimal 25(OH)D level of >30 ng/mL is recommended, similar to the target for steroid-induced osteoporosis.

A study involving pre-renal transplant recipients found that cholecalciferol supplementation with vitamin D and calcium, did not lead to a significant improvement in BMD compared to calcium supplementation alone (85). However, a recent study in renal transplant patients showed that taking 4000 IU/day of cholecalciferol for one year reduced lumbar BMD loss compared to placebo (percentage change in BMD: −0.2% with cholecalciferol vs. −1.9% with placebo). The positive effect on BMD was more pronounced in patients who had significant bone mass impairment at the beginning of treatment with more pronounced bone mass impairment at the start of treatment (86)

CALCITRIOL, PARACALCITOL, ALFACALCIDOL

Calcitriol is the active form of vitamin D, while paricalcitol and alfacalcidol are synthetic analogs of vitamin D. It has been demonstrated that these compounds reduce or stabilize parathyroid hormone (PTH) levels and improve bone histology post-transplantation (84,86). Their use has been proposed as a preventive treatment for osteoporosis in transplant patients who may have contraindications to or intolerance of bisphosphonates.

In heart transplantation, a clinical trial comparing alendronate and calcitriol over one year demonstrated that calcitriol significantly reduced bone mass loss in the lumbar spine and femoral neck, with no significant differences between the bisphosphonate and calcitriol groups (87). In renal transplant patients with secondary hyperparathyroidism, supplementation with paricalcitol for six months was associated with reductions in PTH levels and proteinuria, as well as an improvement in bone mass loss (88).

A meta-analysis demonstrated a reduction in vertebral fractures with bisphosphonates or calcitriol during the first year of administration in solid organ transplant recipients (89). It is important to note that this meta-analysis showed considerable heterogeneity across the included studies (e.g., type of transplanted organ, type and dose of bisphosphonate used, and immunosuppressive regimen). Furthermore, only two of the eleven studies included calcitriol as the active comparator. Calcidiol was also found to be an effective therapy in 40 patients following cardiac transplantation. After 18 months of treatment, 12,000 IU weekly of calcidiol led to a 4.9% increase in lumbar BMD, compared to −1.19% and −0.19% with calcitonin and etidronate, respectively. Calcidiol causes less hypercalcemia and hypercalciuria than calcitriol (90).

Despite their potential benefits, calcitriol and synthetic analogues should be used with caution, as their use is associated with an increased risk of hypercalcemia and hypercalciuria. Therefore, periodic monitoring of serum calcium and 24-hour urinary calcium levels is recommended.

BISPHOSPHONATES (BFs)

These drugs have been the most widely used treatment for osteoporosis for over two decades (Table 6). They are analogs of inorganic pyrophosphate that inhibit bone resorption. BFs are generally safe and well-tolerated. They are the initial treatment option for both the prevention and management of post-transplant osteoporosis. Numerous studies have demonstrated improvements in bone density with BFs; however, there is currently no specific recommendation favoring one bisphosphonate over another.

In an early trial, the comparison of salmon calcitonin and sodium etidronate over one year showed that BFs were capable of inducing a greater increase in lumbar BMD (6.4% vs. 8.2%) (91). A more recent retrospective study in renal transplant patients with end-stage renal disease demonstrated that BF treatment for 3.5 years was associated with a significant increase in lumbar spine BMD in recipients 15 years post-transplant (92). Additionally, in renal transplant patients, administration of BFs for 12 months was associated with improvements in lumbar and femoral neck BMD, as well as a reduction in fracture risk (RR 0.62; CI: 0.38–1.01) (86).

Two trials with risedronate have been conducted: one involving 101 patients after kidney transplantation and another with 41 liver transplant patients, both with one year of follow-up. In both trials, there was a significant and early increase in lumbar BMD at 6 months (93,94). In a study of 84 patients with liver or heart transplantation, alendronate and zoledronate administered for one year prevented hip bone loss. However, in heart transplant patients, lumbar BMD remained stable with zoledronate but decreased with alendronate (95).

A more recent meta-analysis reported improvements in BMD and reductions in fracture risk with BFs use in liver transplant patients (96). The results indicate that BFs are associated with superior fracture prevention compared to calcium and vitamin D alone (OR = 0.37; CI: 0.17–0.7). Oral BFs were linked to a lower incidence of vertebral and overall fractures, as well as improvements in lumbar spine and femoral neck BMD, compared to intravenous BFs. The potential superiority of oral BFs may be due to several studies using intravenous zoledronate and ibandronate with doses that did not align with those recommended in clinical guidelines.

The tolerability of BFs is generally acceptable, with the common adverse effect being gastroesophageal reflux (97). Therefore, caution should be exercised in liver transplant patients with pre-existing cirrhosis if esophageal pathology is present, especially in those with pre-transplant esophageal varices. In transplant patients with a history of esophageal injuries or who develop esophagitis with oral bisphosphonate use, zoledronate may be considered, as its parenteral administration is not associated with reflux development. Furthermore, treatment with zoledronate is associated with better patient adherence (98) and may be an option to reduce polypharmacy in transplant patients (95). Another complication associated with BF use is hypercalcemia, typically linked to intravenous zoledronate use and pre-existing vitamin D deficiency (86). Finally, due to its potential to exacerbate adynamic bone disease, BFsare not recommended in patients with glomerular filtration rates below 30 mL/min (96).

DENOSUMAB

Denosumabis a monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL), a key factor involved in osteoclast differentiation. By blocking the binding of RANKL to its receptor, RANK, denosumab reduces the formation, function, and survival of osteoclasts. This action decreases bone resorption, increases BMD, and reduces fracture risk in both the short and long term (99).

Therapy with denosumab has demonstrated improvements in BMD in patients undergoing solid organ transplantation, although data are limited. In a study involving 93 renal transplant patients with osteoporosis, after 12 months of denosumab treatment, there was an improvement in bone mineral density of 4.6% (3.3–5.9%) in the lumbar spine and 1.9% (0.1–3.7%) in the total hip (100). Similarly, it was shown that the prevalence of osteoporosis decreased in the lumbar spine from 72% to 50% and in the femoral neck from 78% to 69% in 32 renal transplant recipients (101). High-resolution peripheral quantitative computed tomography has described the beneficial short-term effects of one year of denosumab treatment on bone structure, microarchitecture, and strength in kidney transplant recipients (102).

In a study with various types of transplants (49 renal, 14 liver, and 15 simultaneous kidney-pancreas transplant recipients), denosumab treatment over one year increased lumbar BMD by 11.5 ± 6.2% and femoral neck BMD by 10.4 ± 8.3%, reducing the prevalence of osteoporosis in the spine by 48% and in the proximal femur by 18% (103). In a 4-year trial, denosumab was linked to a significant increase in BMD (9.0 ± 10.7% in the lumbar spine and 3.8 ± 7.9% in the total hip) in renal transplant patients, while the control group showed lower increases in BMD at all sites (104).

Few studies have evaluated whether denosumab improves densitometric outcomes compared to BFs. A clinical trial involving 85 renal transplant patients compared the impact of denosumab versus BFs after more than 3 years and found that denosumab treatment resulted in a significant increase in bone density in both the lumbar spine and femoral neck compared to the BFs group (105). A slight increase in mild urinary tract infections and asymptomatic episodes of hypocalcemia (especially in patients with impaired renal function) has been reported with denosumab. To detect hypocalcemia, it is recommended to measure corrected serum calcium and 25(OH)D levels 2–4 weeks after the denosumab dose (106). No severe complications, such as osteonecrosis of the jaw, have been reported in transplant patients using denosumab. As for vertebral fractures observed in postmenopausal osteoporosis following denosumab discontinuation, this complication has not been evaluated in transplant patients.

In summary, the available studies demonstrate that short- and medium-term use of denosumab is a useful option for treating osteoporosis in patients who have undergone organ transplantation. Its use should be considered, particularly in patients with established chronic kidney disease where bisphosphonates may be contraindicated. Moreover, a sub-analysis of the FREEDOM study showed that the reduction in fracture risk remained similar in patients with chronic kidney disease stages I to IV, suggesting that denosumab could be highly beneficial for this group of patients (107).

TERIPARATIDE

Teriparatide is a fragment of parathyroid hormone comprising amino acids 1–34, retaining the activity of the intact peptide. It is an anabolic agent with proven efficacy in reducing both vertebral and non-vertebral fracture risk in postmenopausal women with osteoporosis (108). However, similar to denosumab, publications evaluating the use of teriparatide in solid organ transplant patients are limited.

In a 6-month clinical trial, 26 renal transplant patients received either teriparatide or a placebo. In the teriparatide-treated group, no improvement in BMD at the femoral neck, lumbar spine, or distal radius was observed; rather, BMD remained stable. In contrast, patients receiving a placebo experienced a decrease in femoral neck bone mass over the 6-month study period (109).

In another study, teriparatide treatment in 18 renal transplant patients was associated with a significant improvement in lumbar spine BMD after 1 year, stability of total hip bone mass, and a significant increase in femoral neck BMD after 2 years of treatment (110). No changes were observed in bone microarchitecture, as assessed by the Trabecular Bone Score.

Teriparatide was generally well tolerated, with isolated episodes of mild and transient hypercalcemia and hypophosphatemia.

In a separate retrospective study of renal transplant patients with osteoporosis, the differences in BMD after 1 year of treatment with alendronate or teriparatide were evaluated. Teriparatide was associated with a significant improvement in BMD at all sites, while bisphosphonate use was linked to a lower rate of complications (111).

**SUMMARY OF TREATMENT APPROACHES. WHEN TO START AND STOP ANTIRESORPTIVE THERAPY**

The Bone Health and Osteoporosis Foundation has made the following recommendations for initiating pharmacologic therapy:

1. Patients with lumbar, femoral neck, or total hip BMD T-score ≤-2.5.

2. Postmenopausal women and men aged ≥50 years with lumbar, femoral neck, or total hip BMD between -1.0 and -2.5 and a 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture ≥20%.

3. A hip or vertebral fracture regardless of T-score.

4. A pelvis, proximal humerus, or distal forearm fracture in a person with low bone mass or osteopenia.

It is recommended that glucocorticoids be administered at the lowest dose possible, and reduced or withdrawn when feasible, in order to minimize early bone loss after transplantation.

Supplementation with calcium and vitamin D is advised. Serum 25OHD levels should be above 50 nmol/L. In kidney transplant recipients; alfacalcidiol or calcitriol can be used due to impaired 1 alpha hydroxylation of this metabolite to reduce secondary hyperparathyroidism.

In the presence of osteoporosis, antiresorptive therapy should be administered. BFs are the most widely used, while denosumab is an alternative, especially in cases of intolerance to bisphosphonates. For patients with suppressed bone turnover markers, BFs should be avoided due to the potential risk of exacerbating low bone turnover or adynamic bone disease. Although denosumab is metabolized hepatically and does not accumulate in renal insufficiency, hypocalcemia and the risk of rebound vertebral fractures upon withdrawal require careful monitoring and consideration of initiating BF therapy. There is limited experience with other drugs, such as romosozumab and abaloparatide, which have demonstrated efficacy in treating adult osteoporosis.

**FOLLOW-UP OF POST-TRANSPLANT PATIENTS**

After initiating treatment, BMD should be monitored using Dual-energy X-ray absorptiometry (DXA). Although there are no specific recommendations for transplant patients, it is reasonable to repeat DXA after 1 year if denosumab is used, and after 1 or 2 years if bisphosphonates are the treatment (112). If an adequate densitometric response is not observed after the first or second year, considering an alternative treatment would be logical.

The decision to stop treatment should be individualized based on clinical information. After 3 to 5 years of bisphosphonate treatment, patients with a modest fracture risk (T-score >-2.5) may discontinue treatment, while those at high fracture risk (T-score ≤-2.5) should either continue treatment or begin alternative therapy. Research has shown a residual positive skeletal effect even after discontinuing bisphosphonate treatment for several years. Reassessment of fracture risk is recommended after 2–3 years of bisphosphonate therapy. Discontinuation of denosumab treatment is associated with rapid bone loss and multiple vertebral fractures; therefore, bisphosphonates are recommended as an alternative therapy to maintain the gains in bone density (129).

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