

Post-Transplantation Osteoporosis: Prevention and Treatment

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Osteoporosis is a major complication following solid organ transplantation and is associated with an increased incidence of fractures and related morbidity in transplant recipients. The risk of osteoporosis is directly related to the cumulative dose of corticosteroids used for immunosuppression. The maximum loss of bone occurs in the first three months after solid organ transplantation. To assess bone loss double emission x-ray absorptimetry (DEXA) scan is used. Assessments should be performed at the time of transplant and yearly thereafter. In addition patients should be on 1000 mg elemental calcium and 800 IU of vitamin D daily. Bisphosphonates are useful adjunct therapy to prevent bone loss and increase bone density. Gastric irritation is the major limiting side effect of oral bisphosphonates. In the renal transplant recipient, hyperparathyroidism contributes to bone loss. Hence PTH levels should be measured periodically and maintained close to normal levels.

POST-TRANSPLANTATION BONE LOSS:

Bone loss occurring after solid organ transplantation.

Introduction

The incidence of osteoporosis after solid organ transplantation is very high. The recent increase in the number of solid organs transplanted and the prolonged survival of these patients make this a major clinical problem. Post-transplant osteoporosis often results in total joint replacement, extended hospitalization, and mortality. So this complication has significant morbidity, increased mortality and financial implications. It has been observed in kidney transplant recipients, the incidence of vertebral fractures at one year post-transplant was 5.7%. When bone density of the same population was studied, the incidence of osteopenia in the femoral neck was 10.6% and at the lumbar spine was 28.6%.¹ In heart transplant recipients, where higher levels of corticosteroids and other pro-osteoporotic medications are used, the incidence of vertebral fractures at one year is 30%.²

Bone loss after solid organ transplantation occurs rapidly within the first few months after transplantation. In one study of 105 women who received liver transplantation for primary biliary cirrhosis, bone loss, as measured by bone density studies at the lumbar spine, was greatest at three months post-transplant (mean rate 18.1%). Subsequently there was improvement in bone densities measured at

12, 24 and 36 months.³ In a similar study of cardiac allograft recipients, the incidence of fractures after heart transplantation was highest at three months, but subsequently decreased but remained higher than pre-transplant patients.⁴ Similar results have been noted in renal transplant patients.

Pathophysiology

Bone is constantly undergoing remodeling. The osteoclasts when activated, start resorption of the bone. This is followed by osteoblastic activity, which leads to osteoid formation. The osteoid undergoes mineralization and forms new bone. When there is relative increase in osteoclastic activity compared to the osteoblastic activity, there is bone loss.

Kidney transplant recipients have reduced bone density at the outset because of pre-existing renal osteodystrophy. Hyperparathyroidism, vitamin D deficiency and a dynamic bone disease contributes to reduced bone density in end stage renal disease patients. Soon after kidney transplantation, it is observed that there is a significant reduction in bone density in these patients.⁵ This bone loss is greater in women and diabetics.⁶ After the initial rapid post-transplant bone loss, the bone loss continues in renal transplant recipients although at a slower rate.

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Though secondary hyperparathyroidism improves after kidney transplantation, some patients continue to have persistent hyperparathyroidism.⁷ This may be due to mild persistent renal insufficiency or secondary to clonal hyperplasia of the parathyroid glands. This leads to hypophosphatemia. Hypophosphatemia also occurs due to disturbances in tubular resorption of phosphate. This may be due to the ischemic injury after transplantation or the corticosteroid effect. Hypophosphatemia contributes to post-transplantation bone loss. In living related kidney transplantation, it is estimated the bone loss in the first six months is 6.8% of the initial bone density in the first six months and is 9% at 18 months.⁸ Similarly after cadaveric kidney transplantation, the bone loss in the initial six months was found to be 1.6% per month.⁹ This is similar to the bone loss following transplantation of other solid organs.²⁻⁴

There are many studies showing that the main cause of osteoporosis in post-transplantation state is the use of corticosteroids as an immunosuppressant.¹⁰ Corticosteroids cause osteoporosis by three mechanisms.¹¹ Firstly they reduce osteoblast activity in the bone. This leads to relative hyperactivity of the osteoclasts and directly causes bone resorption. The second mechanism is through the effect of corticosteroids on calcium metabolism. Corticosteroids decrease calcium absorption at the small bowel and increase its excretion in the kidney. This stimulates the parathyroid glands to secrete more parathyroid hormone (PTH), signaling resorption of bone to maintain serum free-calcium levels, again contributing to osteoporosis. The third mechanism of corticosteroid induced osteoporosis is through its effect on the sex hormones. Corticosteroids decrease gonadal estrogen and testosterone secretion as well as adrenal androgen secretion. These sex hormones are important in maintaining the balance between the osteoclastic and osteoblastic activity. Lack of sex hormones lead to increased osteoclastic activity and this leads to osteoporosis.

While corticosteroids are the major cause of post-transplant osteoporosis, other immunosuppressants also have deleterious effect on the bone. Calcineurin inhibitors, tacrolimus and cyclosporine, induce increased osteoclastic activity. Osteoblastic activity also increases but not enough to compensate for the osteoclastic activity. This leads to a high turnover bone loss.¹² Azathioprine and mycophenolate mofetil do not have any significant effect on bone

loss. Rapamycin has not been shown to have any significant bone loss when used as an immunosuppressant.¹³

Diagnosis

Pretransplant bone health is a major factor in the incidence of post transplantation osteoporosis. Postmenopausal women, patients who have been on corticosteroids for long periods like patients with lupus nephritis have reduced bone mass to start with and hence are more predisposed to osteoporosis. So detailed history must be obtained which should include the menopausal status in women, history to suggest androgen deficiency in men, use of corticosteroids and other immunosuppressants prior to transplantation, and history of fractures.

The most commonly used method of assessing the bone density is anteroposterior Dual Energy Xray Absorptiometry (DEXA) scan of the lumbar spine and the dominant hip.¹⁴ This is a specific study to assess the risk of fractures. Although some reports suggest that lateral DEXA scan of the lumbar spine may be more useful,¹⁵ it is used less frequently than anteroposterior DEXA scans and is not standardized. Quantitative computer tomography and quantitative ultrasound of the calcaneus are other methods of measuring bone density.¹⁶

WHO has classified bone density according to the T score.¹⁷ This is the bone density of the individual compared to the bone density of a race and gender matched young person at the peak of bone density. The T score is expressed as standard deviations (SD) from the control. If the T score is 0 to -1 SD from the control, it is considered normal. Osteopenia is defined by T values -1 to -2.5 SD from control, while osteoporosis is present if the T score is ≥ 2.5 SD. For renal transplantation recipients, the baseline DEXA scan should be done at transplantation or within three months after transplantation. At the same time a baseline PTH, serum bicarbonate and if clinically suspected, free testosterone or estradiol should be measured.

Prevention

Post-transplant bone loss correlates best with the cumulative dose of corticosteroids, and thus, attempts should be made to minimize the cumulative dose of corticosteroids (Fig. 1).¹⁸ The maintenance levels of corticosteroids should be brought below

DEXA SCAN:

Double emission x-ray absorptiometry.

OSTEOPENIA:

Bone density (T score) measurement by DEXA scan between -1 and -2.4.

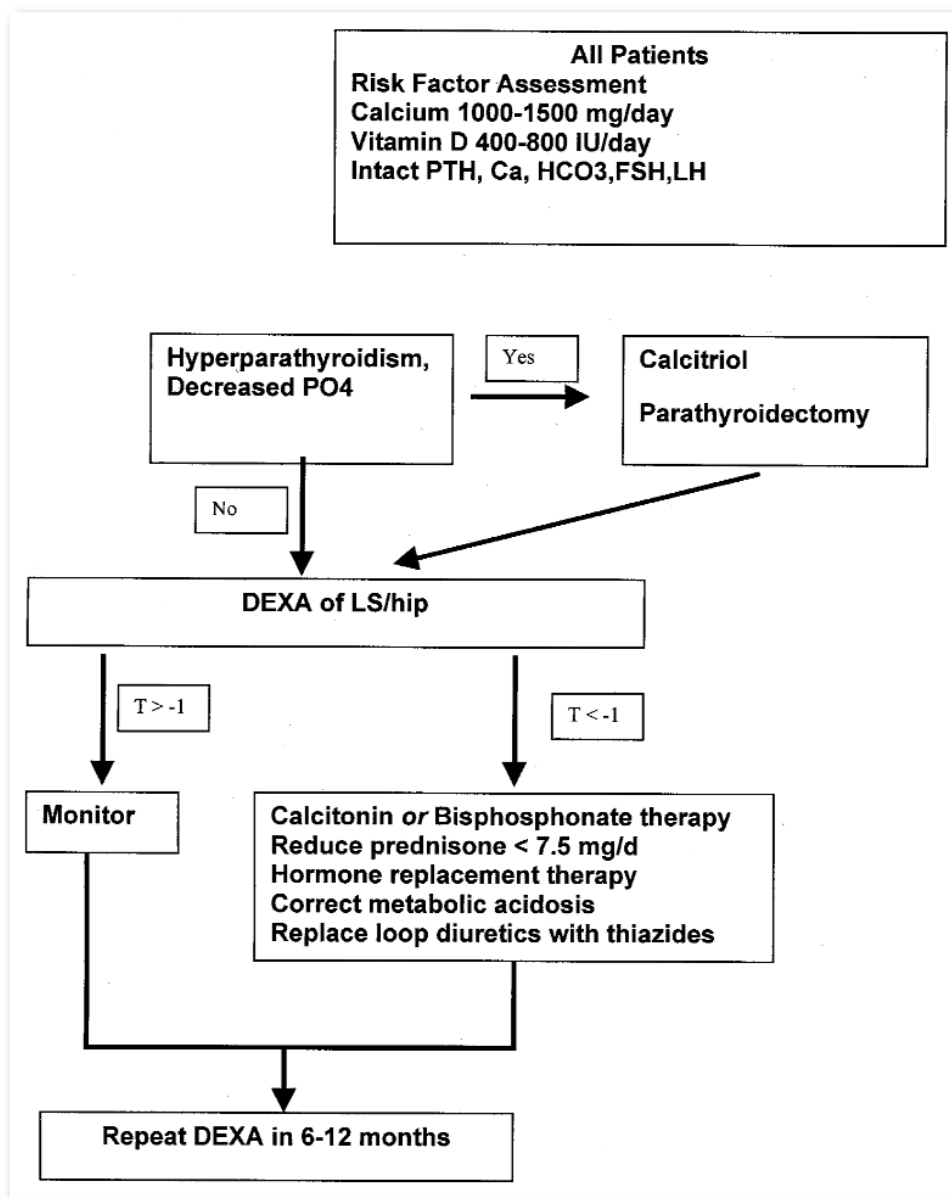


Figure 1. Recommendations for preventing and treating post-transplantation bone loss. T = T score by DEXA scan.

7.5 mg/day at the earliest. For the same reason, the corticosteroid sparing regimens cause less bone loss. As cyclosporine and tacrolimus contribute to bone loss, their dose should be minimized when possible.

Sustained hyperparathyroidism is also a cause of continued bone density loss, and PTH values should be checked periodically and maintained closer to normal. The dietary intake of elemental

calcium from all sources should be between 1000 and 1500 mg.¹⁹ If the diet is not sufficient to supply as much calcium, calcium supplement should be used. Also 800 IU of vitamin D should be taken everyday. Patients are encouraged to get involved in weight bearing exercises and aerobic activities to strengthen their bone. They should also avoid alcohol and tobacco as they have a deleterious effect on the bone.

Treatment of hypertension can worsen osteoporosis. Loop diuretics like furosemide have a calciuric effect and can make osteopenia worse. So when patients need diuretics, thiazide diuretics which reduce calcium excretion by the kidney should be used. Serum calcium and phosphate levels should be maintained near normal levels. All these measures prevent hyperparathyroidism in kidney transplant recipients. During immobilized states, the bone loss is increased. During this period antiresorptive agents like intravenous pamidronate or subcutaneous injection of calcitonin when used reduces bone loss.

Treatment

Postmenopausal women should be placed on hormone replacement therapy, if there is no contraindication. Women who are amenorrheic should be investigated for estrogen deficiency. Estradiol levels, FSH and LH should be measured in them. Estrogen replacement should be accompanied by progesterone in women who have not had hysterectomy to reduce the risk of uterine cancer. Risk of venous thrombosis and increased risk of breast cancer should be considered before starting hormone replacement. In men, if there is a clinical suggestion of low testosterone level (e.g. impotence), early morning testosterone levels should be checked. If low levels of testosterone are present, and there is reduced bone mass in the initial DEXA scan, patients should start testosterone replacement therapy. Once on testosterone replacement therapy, it is important that patients are periodically screened for prostatic cancer. Complicated patients with multiple abnormalities, for example hyperprolactinemia and androgen insufficiency, should be referred to an endocrinologist for a more extensive evaluation.

Bisphosphonates are the mainstay in treating osteoporosis. Bisphosphonates when administered early after kidney transplantation prevents the early bone loss that occurs after the procedure. Intravenous pamidronate (0.5 mg/kg) given to kidney recipients at the time of transplantation, and at three months afterwards, prevents accelerated bone loss following transplantation.²⁰ The mean DEXA score of the lumbar spine remained unchanged from pre-transplant values, while in the placebo group the mean T score decreased by 6.4% ($p < .05$). Similarly in lung transplant recipients, intravenous administration of 30 mg pamidronate within the first weeks after transplantation significantly reduced post-transplant bone loss.²¹

Oral etidronate, when administered cyclically with calcium for 12 months to patients having glucocorticoid induced osteoporosis, also produces an improvement in bone density by 5.7% compared to a fall by 3.4% when treated with calcium alone.²² Etidronate is not commonly used as this has to be administered cyclically with calcium and the newer oral bisphosphonates do not have the same limitations.

Alendronate when given daily at doses of 5 mg or 10 mg/day, to patients receiving 7.5 mg of glucocorticoids showed significant increases in bone density at the lumbar spine, femoral neck and femoral trochanter, compared to placebo alone. For 5 mg alendronate the increase of BMD at 48 weeks was 2.1% and for 10 mg it was 2.9%. This difference was significant when compared to a decrease of 0.4% for the placebo group.²³

Risedronate is another bisphosphonate that can be used to prevent and treat glucocorticoid induced osteoporosis. When administered to 228 patients initiated on glucocorticoid therapy, there was a reduction in vertebral fractures at one year and also a significant increase in the BMD at the lumbar spine femoral neck and femoral trochanter.²⁴ Similarly when given to patients who have been on more than 7.5 mg/day of glucocorticoid for more than 6 months, risedronate reduced the incidence of vertebral fracture at 12 months.²⁵

As bisphosphonates are inhibitors of osteoclastic activity they can produce hypocalcemia and hypophosphatemia. So blood tests should be done regularly to monitor calcium and phosphate. Alendronate and risedronate are excreted through kidneys and are contraindicated when the creatinine clearance is less than 30 ml/min. The major side effect of oral bisphosphonates is gastric irritation, which manifests as nausea vomiting and dyspepsia. Hence these agents should be taken with a glass of water and the patients should remain upright for at least 30 minutes after ingestion. If patients cannot be upright for 30 minutes due to any physical ailment, then oral bisphosphonates are contraindicated.

When oral bisphosphonates are not tolerated because of gastrointestinal side effects or are contraindicated because of renal insufficiency, intranasal calcitonin can be tried; 200 IU calcitonin along with calcium supplements have shown to increase BMD in transplant recipients at one year. When calcitonin is administered as a nasal spray it should be given by alternating nostril everyday.

OSTEOPOROSIS:

Bone density (T score) measurement of DEXA scan less than -2.5.

Unfortunately, calcitonin tolerance frequently develops after about 6 months of its use. Calcitonin is very useful in reducing pain that occurs from osteoporotic fractures.

Recommendations

After the initial DEXA scan, patients with osteopenia or osteoporosis (t score ≤ 1) should be placed on bisphosphonate therapy. Patients with normal bone density (t score ≥ 1) should be monitored closely, with a repeat DEXA scan yearly. All patients should receive calcium 1000 to 1500 mg/day and vitamin D 400 to 800 IU/day. Metabolic acidosis should be corrected and hormone replacement therapy should be initiated when indicated. A repeat DEXA scan should be performed at 6-12 month intervals. If there is less than a 5% change in BMD, continue the same management. If the change is more than 5%, medication regimen should be modified.

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