Bone and Mineral Disease in Kidney Transplant Recipients

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Introduction

After kidney transplantation, disorders of mineral and Bone metabolism are common and are important causes of morbidity and mortality .

Post-transplantation mineral and bone disease (MBD) is defined by clinical features that are similar to, but distinct from, MBD occurring prior to transplantation.

Transplantation 87: 1846–1851, 2009

Introduction

Over the past 2 decades, high-dose glucocorticoids have become less integral to maintenance immunosuppression regimens, resulting in relatively stable central skeleton (i.e., spine and hip) bone mineral density (BMD).

In contrast, worsening BMD at the peripheral skeleton (i.e., forearm and leg) continues to be seen.(PTH effect)

Cortical losses were linear and driven by greater severity of post-transplantation hyperparathyroidism.

However, for trabecular bone and bone biomechanical competence, the effects of PTH levels were bimodal: more deterioration occurred at the lowest and highest levels of PTH.

J Am Soc Nephrol 25: 1331–1341, 2014

Bone and Mineral Disease in Kidney Transplant Recipients

- Disorders in Calcium and Phosphorus
- Vitamin D Deficiency
- Hyperparathyroidism
- Bone Disease

Disorders in Calcium and Phosphorus

Hypercalcemia affects up to 59%, 45%, and 21% of recipients at 3 and 12 months and 5 years, respectively.

Serum calcium levels peak by 2 months post-transplant and remain elevated in 18% of recipients by 12 months post-transplant, and in 6%, levels remain high even by 10 years post-transplantation.

Transplantation 100: 184–193, 2016

Hypercalcemia

Increased urinary calcium absorption secondary to hyperparathyroidism in a well-functioning kidney

Vitamin D repletion

Calcium release from the skeleton

Hypercalcemia

Importantly, hypercalcemia may be associated with the development of calcifications in the allograft that consequently, affect graft survival .

Am J Transplant 5: 1934–1941, 2005

Hypophosphatemia

Develops in up to 90% of posttransplant recipients.

It typically develops in the first 3 months post-transplant and improves in approximately 86% of recipients by 12 months post-transplant

Hypophosphatemia

FGF-23 is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, and parathyroid hormone (PTH).
High fibroblast growth factor 23 (FGF-23) levels result phosphaturic that inhibits renal 1 alpha-hydroxylase activity.

Hyperparathyroidism-induced urinary phosphate wasting

Immunosuppressant effects

Nat Rev Nephrol 11: 656–666, 2015

Vitamin D Deficiency

- Vitamin D deficiency, defined as 25-hydroxy vitamin D levels < 30 ng/ml, is highly prevalent following transplantation, occurring in up to 80% of recipients by 3 months post-transplantation and persisting in the short- and long-term periods post-transplantation

- Vitamin D deficiency results in hypocalcemia and subsequent bone loss

Other effect of vitamin D

Immunoregulatory role:

- Diminished dendritic cell maturation
- Antigen-presenting capacity
- Enhanced regulatory T cell differentiation
- Improved pathogen clearance differentiation of immune inhibitory cell proliferation

Vitamin D deficiency result:

- Reduce transplant tolerance
- Increase infections
- Higher risk of malignancies

Major risk factors for persistent vitamin D deficiency post transplantation

Decreased allograft function

Elevated FGF-23 levels

Am J Transplant 7: 1193–1200, 2007

Hyperparathyroidism

- Parathyroid hormone (PTH) levels improve quickly after transplantation.
- Hyperparathyroidism completely resolves in only 30% and 57% of recipients within the first and second years post transplantation, respectively.
- Persistent hyperparathyroidism:

✓**Severe pretransplant hyperparathyroidism**

✓**Poor allograft function**

✓**Low vitamin D levels**

Kidney Int 54:1704–1713, 1998

Nephrol Dial Transplant 13: 436–442, 1998

Increased Risk of All-Cause Mortality and Renal Graft Loss in Stable Renal Transplant Recipients With Hyperparathyroidism

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Background. Hyperparathyroidism is reported in 10% to 66% of renal transplant recipients (RTR). The influence of persisting hyperparathyroidism on long-term clinical outcomes in RTR has not been examined in a large prospective study. **Methods.** We investigated the association between baseline parathyroid hormone (PTH) levels and major cardiovascular events, renal graft loss, and all-cause mortality by Cox Proportional Hazard survival analyses in 1840 stable RTR derived from the Assessment of LEscol in Renal Transplantation trial. Patients were recruited in a mean of 5.1 years after transplantation, and follow-up time was 6 to 7 years. **Results.** Significant associations between PTH and all 3 outcomes were found in univariate analyses. When adjusting for a range of plausible confounders, including measures of renal function and serum mineral levels, PTH remained significantly associated with all-cause mortality (4% increased risk per 10 units; $P = 0.004$), and with graft loss (6% increased risk per 10 units; $P < 0.001$), but not with major cardiovascular events. Parathyroid hormone above the upper limit of normal (65 pg/mL) indicated a 46% ($P = 0.006$) higher risk of death and an 85% higher risk of graft loss ($P < 0.001$) compared with low/normal values. **Conclusions.** Hyperparathyroidism is an independent, potentially remediable, risk factor for renal graft loss and all-cause mortality in RTR.

(*Transplantation* 2015;99: 351–359)

Hyperparathyroidism outcome

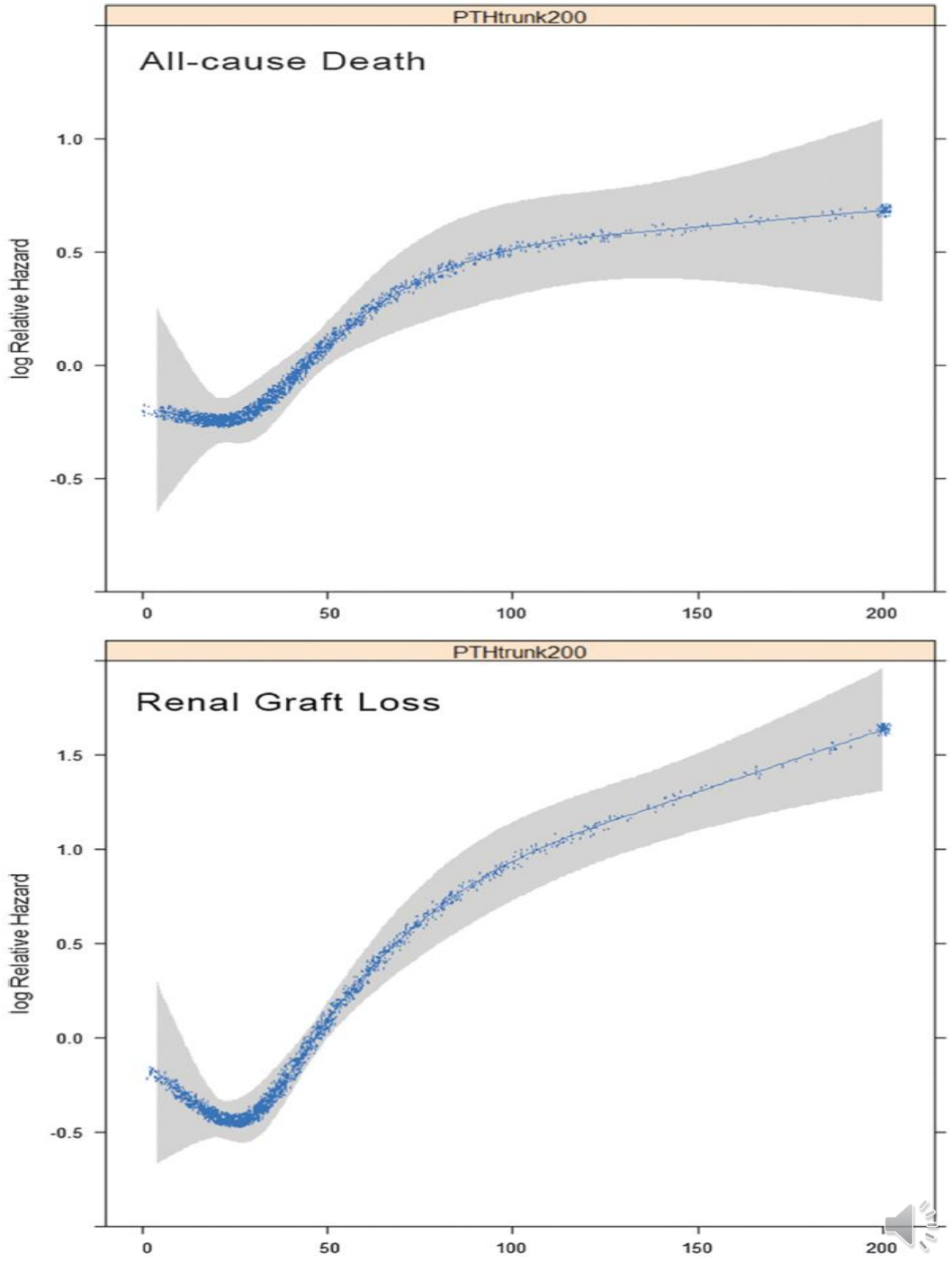
- Mortality

Transplantation (ALERT) trial, parathyroid hormone (PTH) values >65 pg/mL were associated with an increase in all-cause mortality.

- Allograft loss

ALERT trial, PTH >65 pg/mL (6.9 pmol/L) was associated with an 85 percent increase in death-censored graft loss.

- Bone disease and fractures



Calcimimetics & parathyroidectomy

No study has demonstrated a benefit on bone density, fractures, vascular calcifications, or nephrocalcinosis after transplantation.
As such, it is not currently approved by the US Food and Drug administration for the treatment of post-transplant MBD.

Parathyroidectomy should be preferred over cinacalcet in patients who require long-term management of MBD abnormalities, including persistent hypercalcemia, nephrocalcinosis/nephrolithiasis, or high bone turnover states resistant to medical therapies. Langenbecks Arch Surg 400: 907–927, 2015

Bone Disease

Major bone diseases

Osteoporosis

Osteonecrosis (avascular necrosis)

Both of which cause significant long-term morbidity

Bone strength

Bone density

Bone density refers to the Amount of bone mineral (hydroxyapatite) per centimeter squared of bone tissue (i.e., gmHA/cm2), and in the clinic, it is measured by dual energy x-ray absorptiometry.

+

Bone quality

Bone tissue material properties (i.e., microarchitecture, turnover, mineral content and structure, microcracks, collagen content, and structure) and is measured by tetracycline double-labeled bone biopsy with quantitative histomorphometry.

Bone Loss

Kidney transplant recipients come to transplant with significant impairments in bone strength, characterized by high rates of osteopenia and osteoporosis (32% and 15%, respectively) and fractures (two- to 14-fold greater than that of the general population) .Clin Transplant 22: 462–468, 2008

Patients had a history of a fragility fracture at the time of transplantation, and osteopenia or osteoporosis at the femoral neck was observed in 77%, Kidney Int 2019; 95:1461

1.7 percent per year over a mean time of 8.1 years after transplantation. Am J Kidney Dis 1996; 28:105

Historically, the first 12–18 months of transplantation were associated with dramatic decreases in bone density of up to 9% at the spine and hip.

PATHOGENESIS AND RISK FACTORS

Bone loss is principally due to a reduction in trabecular bone mass, although cortical bone may also be affected .

Fractures can occur in either peripheral or central locations, although some evidence suggests that peripheral fractures (involving hands, ankles, and feet) may be more common.

Major risk factors for osteoporosis

- Glucocorticoids
- Calcineurin inhibitors
- Persistent hyperparathyroidism

Other risk factors for osteoporosis

- Deceased donor
- Diabetes
- Low eGFR

Glucocorticoid

Glucocorticoid-induced suppression of bone formation is the most important risk factor for bone loss .

Glucocorticoids are directly toxic to osteoblasts and lead to increased osteoclast activity .

Glucocorticoids also have other effects that promote negative calcium balance and osteoporosis:

- Decreased calcium absorption in the gut,
- Reduced gonadal hormone production,
- Diminished insulin-like growth factor 1 production,
- Decreased sensitivity to parathyroid hormone (PTH),
- Increased activity of nuclear factor kappa-beta ligand (RANKL),
- Increased osteoclast genesis .

Calcineurin inhibitors

Cyclosporine may contribute to bone loss among patients treated with glucocorticoids , although this may not occur in patients who are not treated with glucocorticoids

The effect of tacrolimus on bone mineral density (BMD) in transplant patients is uncertain.

Although one study suggested that tacrolimus had similar effects as cyclosporine on BMD , other studies have not shown this, possibly because the use of tacrolimus permitted lower doses of glucocorticoids .

However, one small study found that kidney transplant recipients with higher blood concentrations of tacrolimus (≥6 ng/mL) had lower BMD compared with those who had lower blood concentrations (<6 ng/mL), suggesting a possible dose-related effect of tacrolimus on bone loss.(Int Immunopharmacol2012; 13:69).

Persistent hyperparathyroidism

Patients with a PTH concentration that is **two to three times** the upper limit of normal are considered to have persistent hyperparathyroidism.

Persistent hyperparathyroidism occurs in approximately 15 to 50 percent of patients after transplantation and is associated with cortical bone loss and fractures.

In one retrospective study, PTH of >130 ng/L three months posttransplant was an independent risk factor for fractures.

Am J Transplant 2013; 13:2653.

Persistent hyperparathyroidism

Another retrospective study found that more intensive treatment of the mineral and bone disorders of chronic kidney disease (CKD-MBD) prior to transplantation was associated with lower rates of persistent hyperparathyroidism and fewer fractures in the first year after transplantation.(Transplantation 2016)

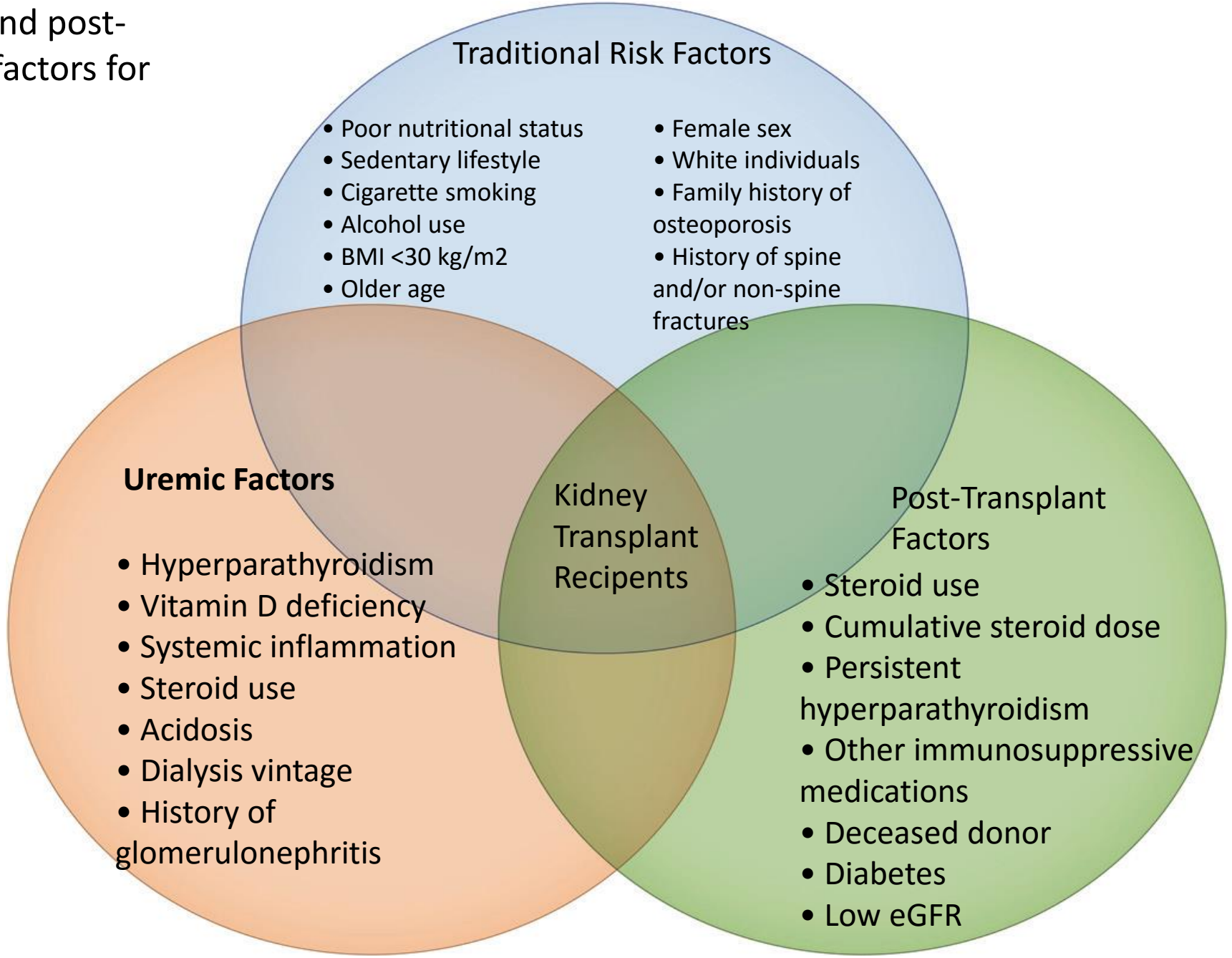
Another study showed PTH and bone turnover markers at the time of transplantation failed to predict incident fractures.

In conclusion, aBMD is low, correlates inversely with bone turnover, and predicts incident fractures in de novo kidney transplant recipients.

Kidney Int 2019; 95:1461).

EVALUATION OF OSTEOPOROSIS AND FRACTURE RISK

Pretransplant and post-transplant risk factors for osteoporosis.



Screening and monitoring kidney transplant candidates

Measure serum parathyroid hormone (PTH) and 25-hydroxyvitamin D levels.

Dual-energy x-ray absorptiometry (DXA) to assess bone mineral density (BMD) of the hip, spine, and forearm.

Imaging of the thoracic and lumbar spine, either with lateral radiographs or by performing vertebral fracture assessment (VFA) using DXA (if available), to assess for the presence of existing vertebral fractures.

Screening and monitoring kidney transplant candidates

Among deceased donor kidney transplant candidates who do not have evidence of osteoporosis or osteopenia on the initial screen and do not develop a fracture while on the transplant waiting list, recommendation is repeat DXA every two years

In those patients who do not have a DXA scan in the year prior to transplant, we obtain a repeat DXA scan as soon as possible within the first three months after transplantation.

Screening and monitoring kidney transplant candidates

- At two to four weeks after transplantation, or when kidney allograft function stabilizes, measure serum calcium, phosphate, PTH, and 25-hydroxyvitamin D levels.
- In addition, some authors obtain fasting morning serum concentrations of bone turnover markers (BTMs), including:

- **C-telopeptide crosslink (CTX)** C-terminal telopeptide of fibrillar collagens such as collagen type I and type II.
- **Bone-specific alkaline phosphatase (BSAP)**

WHO is high risk of incident fracture?

Patients with a history of pretransplant low-trauma fracture or radiologic evidence of vertebral fracture.

Patients with osteoporosis. (T-score of ≤-2.5)

Patients with low bone mass (osteopenia, T-score between -1.0 and -2.5) who have one or more clinical risk factors for fracture or will receive glucocorticoids as part of their maintenance immunosuppression regimen.

Patients who are determined to be at high risk of incident fracture

Monitor DXA annually in order to assess the stability of BMD and the response to treatment.

Patients who are not determined to be at high risk of incident fracture

Rescreen by DXA every two years and use preventive measures.

Role of bone biopsy for Bone quality evaluation

Bone biopsy with double-tetracycline labeling is the gold standard for the diagnosis of posttransplant bone disease in kidney transplant recipients.

However, bone biopsies are not frequently performed, as few centers have the expertise to properly process and analyze bone biopsy specimens.

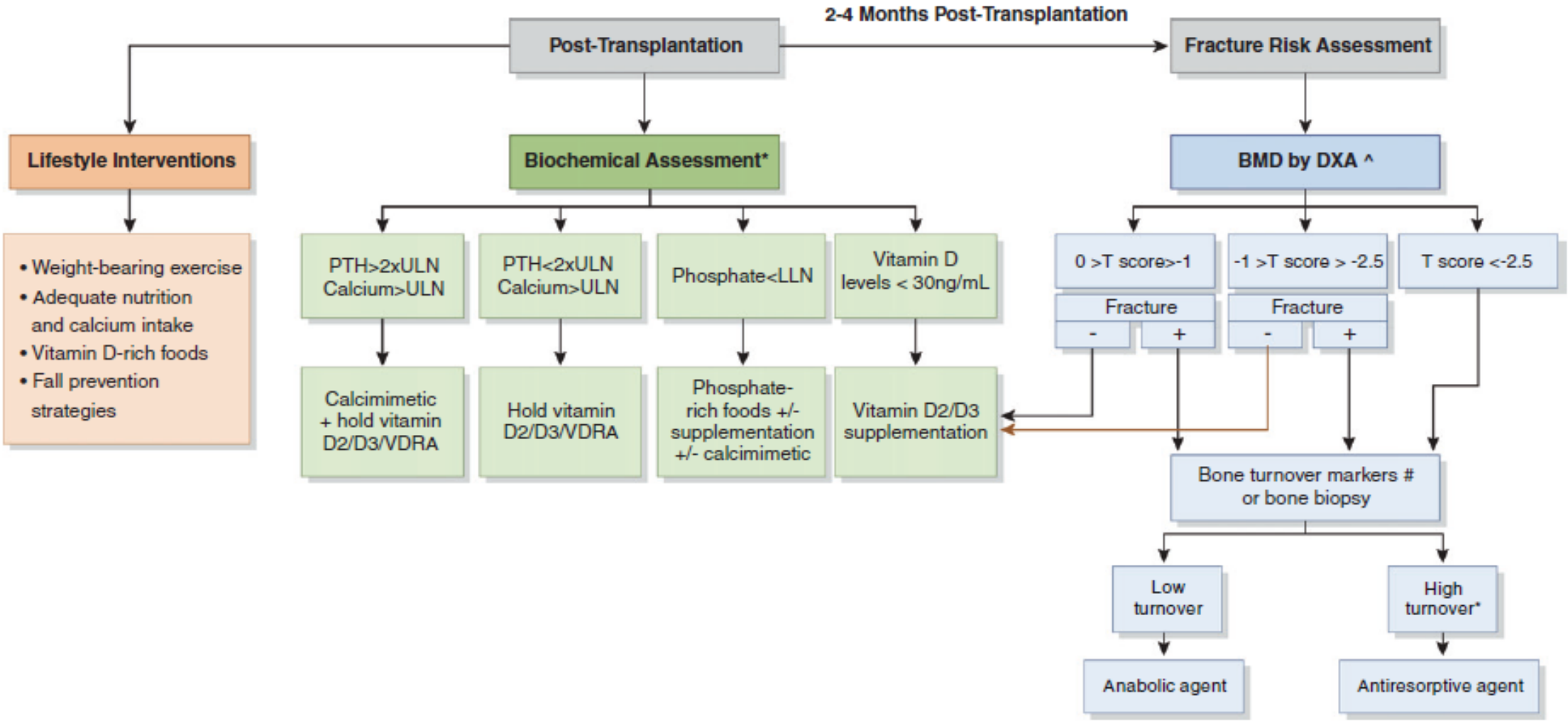
If possible, a bone biopsy should be performed in patients with:

Severe osteoporosis

Frequent fractures

Persistent bone pain to rule out adynamic bone disease prior to initiating treatment with antiresorptive therapy

Risk-based approach to mineral and bone disease (MBD) management after kidney transplantation



PREVENTION OF OSTEOPOROSIS

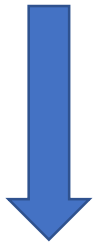
MEDICAL THERAPY PREVENTION OF OSTEOPOROSIS

- Calcium and vitamin D3
- Active vitamin D analogs (Alfacalcidol, calcitriol and eldecalcitol)
- Bisphosphonates
- Denosumab
- Teriparatide

Among all transplant recipients who have a normal bone mineral density (BMD) or osteopenia

- Encourage lifestyle changes.
- Maintain the lowest possible glucocorticoid dose.
- Provided the serum calcium is normal, treat with calcium and vitamin D3.
- Treat persistent hyperparathyroidism

In high-risk patients with biochemical evidence of low bone turnover (ie, C-telopeptide crosslink [CTX] and bone specific alkaline phosphatase [BSAP] concentrations in the lower one-third of the normal range for premenopausal women as provided by the specific laboratory)



Treat with teriparatide for the first year after transplantation.
Some Arthurs treat with an active vitamin D analog (eg, calcitriol) in absence of hypercalcemia

In high-risk patients with biochemical evidence of normal or high bone turnover (ie, CTX and BSAP concentrations in the upper two-thirds of the normal range or above the normal range for premenopausal women as provided by the specific laboratory)

Treat with an oral bisphosphonate (either alendronate or risedronate) or denosumab during the first posttransplant year .

All patients who have received bisphosphonate therapy or denosumab should have a dual-energy x-ray absorptiometry (DXA) scan performed at 12 months post transplantation to reassess BMD.

At 12 months post transplantation to reassess BMD In patients with stable BMD or in whom BMD increased

The decision to continue bisphosphonate or denosumab treatment is based upon whether glucocorticoids are being administered as maintenance immunosuppression and, if so, the dose of glucocorticoids.

Patients who are on 5 mg/day or less of oral prednisone (or 4 mg/day or less of prednisolone) can discontinue bisphosphonate or denosumab therapy.

Those who are on more than 5 mg/day of oral prednisone (or more than 4 mg/day of prednisolone) can continue bisphosphonates or denosumab for another 12 months, and a repeat DXA scan should be performed at the completion of therapy to reassess BMD.

At 12 months post transplantation to reassess BMD in patients who have a significant loss of BMD

Patients who have not been adherent to therapy or have been taking it incorrectly should continue treatment with bisphosphonates or denosumab for another 12 months, after factors contributing to nonadherence or incorrect administration have been addressed, and a repeat DXA should be performed at the completion of therapy to reassess BMD.

Patients who have been adherent to therapy should be evaluated for other causes of bone loss (eg, severe hyperparathyroidism, multiple myeloma, celiac disease, and hyperthyroidism). Such conditions, if identified, should be treated with the appropriate therapy.

If no such conditions are identified, bisphosphonates or denosumab can be continued for another 12 months, and a repeat DXA should be performed at the completion of therapy to reassess BMD.

In patients who develop a fragility fracture while receiving bisphosphonate or denosumab therapy

Patients with stable BMD can continue bisphosphonates or denosumab for another 12 months, and a repeat DXA should be performed at the completion of therapy to reassess BMD.

Patients with a significant loss of BMD who are on an oral bisphosphonate should discontinue the bisphosphonate and initiate treatment with either an intravenous bisphosphonate (if prior treatment with an oral bisphosphonate was used), denosumab, or teriparatide if no contraindications to their use exist.

Significant bone loss on denosumab is unusual, so if this occurs, patients should be reassessed for other causes of bone loss.

Lifestyle changes

All transplant recipients to perform regular weight-bearing exercises after transplant.

Regular weightbearing exercise may help to prevent and/or treat osteoporosis in the general population and in transplant recipients.

All patients should receive counseling regarding smoking cessation, early mobilization after transplantation, and fall prevention, which are beneficial for skeletal health

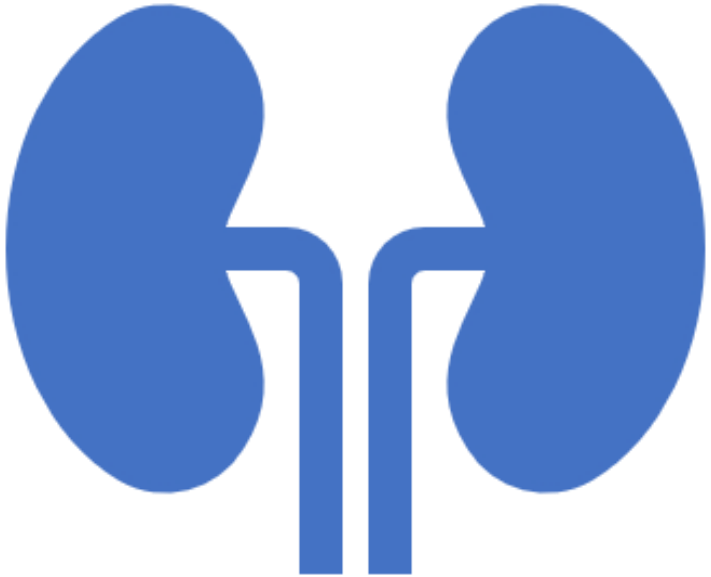
Glucocorticoid dose minimization

For all patients, use the lowest glucocorticoid dose compatible with graft survival.

However, stress that significant osteoporosis has been observed with prednisone doses as low as 7.5 to 10 mg/day , and bone loss occurs even in patients on early corticosteroid withdrawal protocols

TREATMENT OF OSTEOPOROSIS

OTHER FORMS OF POSTTRANSPLANT BONE DISEASE



Osteonecrosis

Osteonecrosis (avascular or ischemic necrosis) is probably the most debilitating of the musculoskeletal complications following transplantation

Previous studies suggested an incidence of approximately 15 percent within three years of transplantation .

However, in a historic cohort study of over 40,000 kidney transplant recipients, the incidence of hospitalization due to osteonecrosis was seven episodes per 1000 person-years .(Kidney Int 2002; 62:2250)

Osteonecrosis

- Among transplant recipients, factors that contribute to osteonecrosis include:
- Uremic-induced defects in mineral metabolism
- Immunosuppressive medications
- Glucocorticoids play a central role.
- Some, though not all, studies have suggested an association between cyclosporine use and osteonecrosis.
- Osteopenia and hyperparathyroidism may also contribute

Bone pain and cyclosporine

A different bone pain syndrome has been described in patients receiving cyclosporine (and, perhaps, tacrolimus) and is often temporally related to increased plasma cyclosporine levels.

The mechanism by which this occurs and its possible relation to the development of osteonecrosis are not clear, but intraosseous vasoconstriction and hypertension may play a role.

Bone pain and cyclosporine

- There are characteristic magnetic resonance imaging (MRI) findings that are consistent with edema and subclinical trauma .

- Administration of calcium channel blockers (such as sustained-release nifedipine, 30 to 60 mg before bedtime) and a reduction in the calcineurin inhibitor dose appear to relieve the symptoms in most patients

Thank you for your attention