



Published in final edited form as:

Curr Opin Nephrol Hypertens. 2012 July ; 21(4): 389–403. doi:10.1097/MNH.0b013e3283546ee0.

Management of Minerals and Bone Disorders after Kidney Transplantation

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Abstract

Purpose of review—Mineral and bone disorders (MBD), inherent complications of moderate and advanced chronic kidney disease (CKD), occur frequently in kidney transplant recipients. However, much confusion exists about clinical application of diagnostic tools and preventive or treatment strategies to correct bone loss or mineral disarrays in transplanted patients. We have reviewed the recent evidence about prevalence and consequences of MBD in kidney transplant recipients and examined diagnostic, preventive and therapeutic options to this end.

Recent findings—Low turnover bone disease occurs more frequently after kidney transplantation according to bone biopsy studies. The risk of fracture is high, especially in the first several months after kidney transplantation. Alterations in minerals (calcium, phosphorus and magnesium) and biomarkers of bone metabolism (PTH, alkaline phosphatase, vitamin D and FGF-23) are observed with varying impact on post-transplant outcomes. Calcineurin inhibitors are linked to osteoporosis, whereas steroid therapy may lead to both osteoporosis and varying degrees of osteonecrosis. Sirolimus and everolimus might have a bearing on osteoblasts proliferation and differentiation or decreasing osteoclast mediated bone resorption. Selected pharmacologic interventions for treatment of MBD in transplant patients include steroid withdrawal, the use of bisphosphonates, vitamin D derivatives, calcimimetics, teriparatide, calcitonin and denosumab.

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Relevant Potential Conflict of Interest:

Dr. Kalantar-Zadeh has received grants and/or honoraria from Abbott, Amgen, DaVita, Fresenius-Kabi, Genzyme, Otsuka, and Shire.

Summary—MBD following kidney transplantation is common and characterized by loss of bone volume and mineralization abnormalities often leading to low turnover bone disease. Although there are no well-established therapeutic approaches for management of MBD in renal transplant recipients, clinicians should continue individualizing therapy as needed.

Keywords

Renal osteodystrophy; bisphosphonates; fracture; calcineurin inhibitor; adynamic bone

Introduction

Transplantation of solid organs is a common and effective treatment modality for end-stage failure of those organs. Kidney is by far the most frequently transplanted solid organ both in the US and throughout the world.¹ Advances in immunosuppressive therapy and transplant techniques over the last decades have improved allograft and patient survival, although long-term survival advantage of some of these agents still remains to be demonstrated.² Successful transplantation is capable of reversing many complications of end-stage kidney disease; however, disturbances of bone and mineral metabolism, also referred to as “mineral and bone disorders” (MBD), may persist, while new bone disorders may also emerge as a result of transplant related medications. The MBD is inherent features of chronic kidney disease (CKD) and commonly observed both in non-dialysis dependent CKD³ and maintenance dialysis patients.⁴ Although bone disease has been recognized as a common complication in kidney transplant recipients, the routine application of adequate diagnostic tools and preventive or treatment strategies to correct bone loss or mineral disarrays may often be suboptimal. In this review we summarize the updated information about prevalence and consequences of mineral-and-bone disorders (MBD) in kidney transplant recipients and examine diagnostic, preventive and therapeutic options for these conditions.

Types of Bone Disorders in Kidney Transplant Recipients

The hallmark of MBD is renal osteodystrophy, also known as “kidney bone disease”,⁴ which is classified into four major groups (Figure 1): (1) high turnover bone disease, (2) adynamic or low turnover bone disease, (3) mixed renal osteodystrophy, and (4) osteomalacia.^{5,6} Recent evidence suggests that renal osteodystrophy and its primary causes including disordered parathyroid function and disarrays in vitamin D and FGF-23 are related to cardiovascular disease and mortality. Table 1 shows the main characteristics of the 4 traditional types of uremic bone disease.⁷ The findings from earlier reports on bone abnormalities in patients after renal transplantation are somewhat conflicting.⁸⁻¹⁵ Heterogeneity of bone lesions has been noted in these early studies,^{9,13} whereas other studies report a wide range of histopathologic findings including high prevalence of high bone turnover associated with persistence of secondary hyperparathyroidism;^{8,10,11,16} normal bone formation;⁹ or low bone turnover (see Table 1).^{14,15} Prolonged mineralization without osteoid accumulation has been found in some studies as well,^{8,14,15} whereas frank osteomalacia has been rarely observed in kidney transplant recipients.^{12,13,17}

Findings from Bone Biopsy Studies

In a study by Monier-Faugere et al¹⁸ in 56 prevalent kidney transplant patients who underwent bone biopsy, cancellous bone volume/tissue volume was below normal in most patients compared to age- and gender-matched control subjects. Similar bone biopsy findings were reported in a longitudinal study by Cruz et al¹⁹ in 20 patients before and then 6 months after kidney transplantation. Pre-transplant bone histomorphometric diagnoses were adynamic bone disease (n=12); mixed bone disease (n=3); mild disease (n=3); and osteitisfibrosa (n=2). After transplantation most patients (n=11) had adynamic bone disease.

19 Rojas et al.²⁰ showed that osteoid volume, osteoid thickness, osteoid resorption surface, and osteoclast surface were above the normal range before transplant and remained so approximately 35 days after transplantation; however, osteoid and osteoblast surfaces significantly decreased within 35 days post-transplant.²⁰ There was also inhibition of bone formation and mineralization as well as apoptosis, which correlated with the dose of administered glucocorticoids.²⁰ In contrast to the above findings, a longitudinal study by Lehman et al.²¹ reported more heterogeneous biopsy findings.

Pooling together the bone biopsy studies in kidney transplant recipients, low turnover bone diseases including a dynamic bone and osteomalacia appear to be common. Most kidney transplant recipients exhibit decreased mineral apposition rate and delayed mineralization which may be accompanied by the dramatic decrease in PTH levels including in patients who had relatively mild bone disease prior to transplantation¹⁴ and who received high doses of glucocorticoids.¹⁸ Many studies mainly show alterations consistent with a dynamic bone disease and increased deposition of iron in the mineralization front;¹⁵ however, some studies suggest decreased bone formation and prolonged mineralization lag time in the presence of persisting bone resorption.^{8,22,23} Hence, notwithstanding the discrepancies among various bone biopsy studies, the main alteration in bone remodeling after renal transplantation is decrease in bone formation and mineralization in face of persistent bone resorption, which may lead to an imbalance in remodeling favoring resorption. Likewise, the defective bone formation may be a consequence of alterations in osteoblast function, decreased osteoblastogenesis, or increased osteoblast death rate. More bone biopsy studies in larger number of kidney transplant recipients are needed to better understand the combined impact of prior bone disease and immune suppressive regimen on bone histology in this patient population.

Decreased Bone Mineral Density and Osteoporosis

Loss of bone mass after kidney transplantation leading to osteopenia or osteoporosis occurs primarily in the first 12 months, predominantly in cortical bone. The most rapid decrease in bone mineral density (BMD) [not to confuse with MBD] measured by dual-energy X ray absorptiometry occurs in the first 6 months post-transplantation, and seems to slow down thereafter, possibly reflecting reduced corticosteroid dose. BMD has been reported to decrease considerably at a mean of 5.5% to 19.5% during the first 6 months after transplantation,^{14,24,25} but only 2.6–8.2% between months 6 and 12,^{26,27} and 0.4–4.5% thereafter.^{28,29}

Risk of Fracture

The overall fracture risk after renal transplantation is 3.6–3.8-fold higher than in healthy individuals,^{30,31} and is 30% higher during the first 3 years after transplantation than in patients on dialysis.³⁰ In a retrospective study with follow-up time up to 33 years, more advanced age and history of diabetic nephropathy were independent predictors of fracture risk, whereas higher activity status was protective.³¹ Additional risk factors for fracture in kidney transplant recipients include female gender and combined kidney–pancreas transplantation.^{32–35} Similar to an increased mortality risk during the first few weeks after kidney transplantation followed by a substantial decline in mortality thereafter when compared to waitlisted dialysis patients, the relative risk of hip fracture was 34% greater in the first few weeks after transplant surgery compared to dialysis patients, but decreased by at least 1% per month until the estimated risk became equal for dialysis and transplant recipients approximately 630 days after transplantation.³⁰ It is important to note that renal transplant recipients are at particular risk of vertebral fracture and that this risk is greater than their risk of lower extremity fractures.³¹

Mineral Metabolism after Kidney Transplantation

Alterations in mineral metabolism including such biomarkers of bone disease as PTH and alkaline phosphatase are common following successful kidney transplantation. The most recent Kidney Disease Initiative Global Outcomes (KDIGO) guidelines³⁶ proposed periodic monitoring of serum calcium, and phosphorus every 6–12 months, 3–6 months, 1–3 months, in CKD stages 1–3T, 4T, and 5T, respectively, while PTH should also be measured at 3–12 month intervals according to the severity of CKD. Measurement of alkaline phosphatase should be performed annually or more frequently in the presence of elevated PTH according to the same guidelines.

Serum Calcium

There are several factors that may precipitate or worsen hypercalcemia after successful kidney transplantation: (1) persistently elevated serum PTH, (2) correction of hyperphosphatemia; and (3) improved 1,25(OH)₂ vitamin D production from the allograft. Although severe hypercalcemia (>3 mmol/l or >12 mg/dL) is rarely observed, hypercalcemic episodes (defined as total serum calcium >2.62 mmol/l or >10.5 mg/dL) were reported in 30% and 12% of renal transplant recipients, 1 year and 5 years after transplantation, respectively.³⁷ In a recent study, post-transplant hypercalcemia was not associated with a specific bone turnover abnormality.³⁸ In one study hyperkalemia appeared to correlate with interstitial micro-calcifications in the renal allograft and poor long-term graft outcomes.³⁹

Serum Phosphorus

Hyperphosphatemia (phosphorus >4.5 mg/dL) is more prevalent in pre-transplant patients, while hypophosphatemia (phosphorus <2.5 mg/dL) is observed much more frequently after renal transplantation especially in the first few weeks postoperatively.^{17,40–42} Decreased phosphorus reabsorption in the proximal tubule, potentially related to persistently elevated PTH or FGF-23 levels, and a quasi “hungry bone syndrome” seem to be mechanisms responsible for post-transplantation hypophosphatemia. Hypophosphatemia has been associated with severe alterations in bone turnover that include a decrease in osteoblast activity that leads to rickets and osteomalacia.^{17,43} Several recent studies indicate that post-transplantation hypophosphatemia frequently is independent of PTH,⁴⁴ suggesting that FGF-23,^{45–47} or perhaps additional humoral factors (other phosphatonins) contribute to phosphaturia in the early post-transplant period.^{41,42} Both pre-transplant⁴⁸ and post-transplant⁴⁹ serum phosphorous derangements appear to be associated with anemia⁵⁰ and mortality risk in kidney transplant recipients.

Serum Magnesium

Hypomagnesemia, which is a common condition especially in the first few weeks after kidney transplantation, is also an independent predictor of new onset (de novo) diabetes mellitus in renal transplant recipients.⁵¹ Seventy to 80% of serum magnesium is freely filtered at the glomerulus and most (up to 97%) is reabsorbed throughout the nephron. Calcineurin inhibitors including cyclosporine A may interfere with magnesium metabolism leading to decreased magnesium reabsorption, urinary magnesium wasting and hypomagnesaemia in renal transplant recipients receiving these immunosuppressive medications.⁵² A recent study suggested that low serum magnesium levels were associated with a faster rate of decline in kidney allograft function and increased rates of graft loss in renal transplant recipients with chronic cyclosporine nephropathy.⁵² Whether hypomagnesemia per se contributes to cyclosporine nephropathy, or whether magnesium supplementation may lessen the cyclosporine nephropathy is not clear.

PTH and Alkaline Phosphatase

PTH levels usually decline rapidly (>50%) during the first 3–6 months after kidney transplantation because of a reduction in functional parathyroid gland mass,⁵³ followed by a more gradual decline probably attributable to the slower involution of these glands.^{16,37} However, persistently elevated levels of serum PTH despite normalization of renal function have been reported in up to 25% of renal transplant recipients 1 year after transplantation.^{37,54} These so-called refractory (or tertiary) hyperparathyroidism cases may be the result of monoclonal glandular hyperplasia.^{55,56} There are several factors which are associated with persistent post-transplant hyperparathyroidism such as prolonged end stage kidney disease prior to transplantation,^{37,57,58} decreased residual renal function,⁵⁹ low levels of 1,25(OH)₂-and 25(OH) vitamin D, and reduced expression of vitamin D and calcium-sensing receptors and also reduced expression of FGF-23 receptors in the parathyroid gland.^{54,60-62} Both pre-transplant⁶³ and post-transplant³⁹ serum PTH level are associated with unfavorable outcomes including worse graft function. However, it is important to note that two studies that assessed bone biopsy samples in kidney transplant recipients did not find a correlation between serum PTH levels and bone turnover,^{18,38} and the diagnostic accuracy of PTH is not quite clear.⁶⁴ Treatment options for hyperparathyroidism are summarized below. Serum bone-specific alkaline phosphatase is significantly correlated with calcitriol and adequately reflects increased bone formation after renal transplantation.⁶⁵ Higher levels of alkaline phosphatase, but not PTH in the months prior to kidney transplantation may herald poor post-transplant outcomes (Miklos Z. Molnar and colleagues, personal communication).

Vitamin D and FGF-23

Low serum 25-OH-D levels are common following solid organ transplantation, both during the immediate postoperative period and in long-term graft recipients.⁶⁶ According to the KDIGO guidelines³⁶ kidney transplant patients should be assessed for the presence of vitamin D deficiency by examining circulating levels of 25-(OH) vitamin D (calcidiol), and vitamin D deficiency and insufficiency should be corrected using treatment strategies recommended for the general population. Even though the level of 1,25(OH)₂ vitamin D (calcitriol) usually increases after successful kidney engraftment, it may still remain lower compared to normal population.⁷ The most important predictor of low 1,25(OH)₂ vitamin D levels are immunosuppressive therapy, PTH level and residual renal function.⁴⁵ The study by Evenepoel et al. found elevated pre-transplantation PTH levels and low post-transplantation levels of FGF23 to be additional predictors of improved post-transplantation 1,25(OH)₂ vitamin D levels, although these were weaker than renal graft function.⁴⁵ FGF-23 per se appears to be a strong and independent predictor of mortality in prevalent kidney transplant recipients.⁶⁷

Preexisting Osteodystrophy

Virtually all patients who receive a kidney allograft suffer from some degree of preexisting bone disorders. The incidence and prevalence of pre-existing low turnover bone disease may have increased recently, probably due to higher dialysate calcium concentrations (1.75 mmol/L [3.5 mEq/L]), high doses of calcium containing phosphate binders and the potentially overzealous utilization of active vitamin D metabolites. It is not clear whether the pre-existing MBD has significant consequences on post-transplant outcomes; nevertheless, some transplant centers consider dialysis patients with high PTH level as unfavorable candidates for kidney transplantation, which is similar to the policies pertaining to body mass index and obesity that have recently been challenged.⁶⁸

Effects of Transplantation-Specific Therapies on Bone

Post-transplantation immunosuppressive therapy may have a major impact on the pathogenesis of bone disease.⁶⁹⁻⁷² The role of corticosteroids is well-known. During the first several months after transplantation, rapid bone loss secondary to steroid-induced acceleration in bone remodeling occurs in cancellous bone.¹⁴ A study that involved serial bone biopsies at 22 days and 160 days after transplantation showed impaired osteoblastogenesis and early osteoblast apoptosis probably related to steroid therapy.²⁰ The etiology of glucocorticoid induced bone disorder is multi-factorial.⁷³⁻⁷⁵ Steroids can be directly toxic to osteoblasts and lead to increased osteoclast activity.⁷⁵ Other steroid effects include decreased calcium absorption in the gut, reduced gonadal hormone production, diminished insulin-like growth factor-1 (IGF-1) production, decreased sensitivity to PTH, increase in receptor activator of NF-kappa beta ligand (RANKL), and increased osteoclastogenesis.⁷⁵⁻⁷⁷

Calcineurin inhibitors including cyclosporine and tacrolimus have been linked to osteoporosis.^{78,79} Epidemiologic studies that have examined fracture risk, however, could not establish an association between use of calcineurin inhibitors and fracture risk.^{31,80} Although mycophenolatemofetil, sirolimus, and azathioprine do not affect bone volume in rodents,⁸¹⁻⁸³ a recent in vitro study suggests sirolimus might interfere with the proliferation and differentiation of osteoblasts,⁸⁴ while everolimus reduces cancellous bone loss in ovariectomized rats by decreasing osteoclast mediated bone resorption.⁸⁵ Calcineurin-inhibitor induced pain syndrome may happen as a result of osteonecrosis, along with transient marrow edema.⁸⁶ These painful conditions, which can be diagnosed by X-ray, radionuclide scan or magnetic resonance imaging are associated with increased intraosseous pressure, compromised vascular supply, marrow edema and the development of a 'bone compartment syndrome'.⁸⁶ Steroid therapy is another known risk factor for osteonecrosis in renal transplant recipients.⁸⁷ Mechanisms may include the differentiation of mesenchymal stem cells to adipocytes causing increased intraosseous pressure and collapse of marrow sinusoids, and increased osteoblast and osteocyte apoptosis. Calcineurin-inhibitors, particularly cyclosporine A, may increase the risk of osteonecrosis because of vasoconstrictive effects, and sirolimus may influence the development of osteonecrosis by potentiating the effects of calcineurin inhibitors or by influencing the lipid profile.⁸⁶

Chronic Allograft Nephropathy Associated MBD

Gradually failing allografts may lead to post-transplantation CKD stage 3-5T leading to increased risk of worsening or de novo development of hyperparathyroidism, active vitamin D deficiency and the whole spectrum of "classic" MBD that is observed in transplant-naïve-CKD patients.^{3,59} In a study of more than 900 transplant patients PTH exhibited a negative correlation with estimated GFR in CKD stages 3-5T ($r = -0.29$, $P < 0.001$).⁵⁹ High PTH values correlate with significant bone loss at the hip and other areas.⁸⁸ Given recent data that delaying the return to dialysis therapy may be associated with better survival in gradually failing kidney transplant recipients,^{89,90} higher rates of MBD are to be expected in the prevalent transplant population.

Management of MBD in Kidney Transplant Recipients

Several practice guidelines and expert reviews can be used to lay out pragmatic recommendations for the prevention, diagnosis and management of bone disease and mineral disorders in kidney transplant recipients.^{36,91,92} To date, no randomized controlled trials in kidney transplant recipients have examined the effect of bone-specific therapies on relevant clinical outcomes, including mortality, quality of life or fracture risk.³⁶ In heart transplant patients alendronate was as effective as calcitriol to prevent bone loss.⁹³ Table 2

shows a list of selected studies pertaining to MBD management in renal transplant recipients. The KDIGO guidelines³⁶ recommend treatment with active vitamin D (calcitriol or alfacalcidol) or bisphosphonates in the first 12 months after kidney transplant in those with estimated GFR > 30 mL/min/1.73 m² and low bone mineral density, and bone biopsy consideration to guide treatment, specifically before the use of bisphosphonates due to the high incidence of a dynamic bone disease. The Cochrane Database review, however, indicate that no type of MBD treatment was associated with better survival in kidney transplant recipients, although treatment reduces the risk of fractures.⁹² Selected pharmacologic interventions for treatment of MBD in transplant patients are listed in Table 3 and include steroid withdrawal, bisphosphonates, vitamin D derivatives, calcimimetics, teriparatide, calcitonin and denosumab.

Steroid withdrawal or avoidance

The rationale for minimizing corticosteroid exposure is compelling and based on well-established risks of osteoporosis, avascular necrosis and other side effects. Some studies found beneficial effects of early tapering of prednisolone on BMD.^{123,124} In contrast, however, randomized controlled trials have shown that steroid withdrawal, when carried out weeks to months after kidney transplantation, is associated with an increased risk of acute rejection.^{125,126} Hence, the current KDIGO guidelines³⁶ do not currently recommend steroid withdrawal and avoidance as a routine course of action.

Bisphosphonates

Bisphosphonates (also known as diphosphonates) consist of two phosphonate (PO₃) groups and are used to prevent bone mass loss and to treat osteoporosis and other osteopenic conditions. Figure 2 shows an overview of the results of the bisphosphonates studies in kidney transplant recipients. In four studies of multiple doses of pamidronate during the initial months after renal transplantation, prevention of bone loss occurred even after treatment was discontinued.⁹⁹⁻¹⁰² Most, if not all, studies suggest that pamidronate administration prevents bone loss shortly after transplantation, although low turnover bone disease may develop or worsen in many patients.^{99,100} Similar results were found when alendronate was administered.^{94,105} Intravenous ibandronate was used by Grotz et al.¹⁰³ in 80 randomly assigned transplant recipients at a dose of 1 mg immediately before the transplant and 2 mg at 3, 6, and 9 months after transplantation and demonstrated prevention of bone loss, spinal deformation, and loss of body height during the first year after kidney transplantation.¹⁰³ Another randomized controlled trial of 20 kidney transplant recipients showed that zoledronate improved the calcium content of cancellous bone.⁹⁷ As to whether this early short-term intervention exhibits a sustained bone-sparing effect later in time, in another study zoledronate therapy conferred no sustained benefit versus placebo at 3 year post-transplantation.⁹⁸ Weekly oral risedronate immediately after renal transplantation can improve BMD, particularly in the femoral neck at 6-month follow-up, without major side effects.¹⁰⁴ Hence, bisphosphonate therapy may significantly improve bone mineral density at the femoral neck and lumbar spine and reduce the risk of acute rejection and might reduce the risk of fracture,¹²⁷ although bisphosphonates do not appear to have any effect on patient survival or graft loss.⁹²

Vitamin D derivatives and D-mimetics with or without calcium supplement

Several forms of vitamin D derivatives and their therapeutic classification are shown in Table 3. In a well-controlled, blinded study, Josephson et al.¹¹⁰ showed that kidney transplant recipients who were given calcium and calcitriol had significantly less bone loss in the lumbar spine and increased BMD in the distal radius and femoral neck compared with transplant patients given calcium alone or placebo. The treated patients did not develop

significant hypercalcemia or deterioration of kidney function during the two years of the study.¹¹⁰ Torres et al reported that therapy with low-dose calcium supplements during 1 year, plus intermittent calcitriol for 3 months after transplantation was safe, decreased PTH levels more rapidly, and prevented bone loss at the proximal femur.¹⁰⁹ Compared to placebo, calcidiol and oral calcium increased BMD at the lumbar spine and femoral neck.^{107,108,128} Paricalcitol, a selective vitamin D receptor activator, also known as D-mimetic,^{4,129} is indicated in the prevention and treatment of secondary hyperparathyroidism. Preliminary results of a randomized controlled trial showed that changes in the profile of urinary peptides occurred due to treatment with paricalcitol;¹¹¹ however, no study has assessed the association between bone fracture, BMD or outcomes and administration of paricalcitol.

Calcimimetics

In the past several years the calcimimetic agent cinacalcet has been frequently evaluated for the treatment of hypercalcemia in renal graft patients with ongoing refractory hyperparathyroidism. As shown in some post-transplant trials cinacalcet successfully corrects elevated serum calcium and PTH levels with no negative effect on renal function,^{114,115,120,121} and it appears to be safe in kidney transplant recipients.^{117,122} A favorable effect of cinacalcet on BMD in renal transplant patients was reported by several small studies (see Table 2).^{116,118,119} Interestingly, cinacalcet might also have favorable effect on blood pressure in kidney transplant recipients, but not on outcomes.¹³⁰

Other potential MBD treatment modalities

Another therapeutic agent studied in patients after kidney transplantation is teriparatide, a recombinant human PTH. A recent trial showed that teriparatide administered to kidney transplant patients for 6 months was safe but did not alter BMD in the lumbar spine or distal radius compared with the placebo group.¹³¹ However, BMD at the femoral neck remained stable in those given teriparatide, compared with a decrease in the placebo group. In addition, after 6 months, no significant differences between the two groups were detected in fractures, bone histology, vitamin D levels, PTH levels, kidney function, or serologic bone markers.¹³¹ Teriparatide can be considered as an alternative treatment of MBD in kidney transplant patients with low PTH and refractory hypocalcemia.¹³² Another potential therapeutic agent is calcitonin, although it has no effect on mortality, graft loss and risk of fracture in patients after kidney transplantation.^{92,133,134} Exercise training and hormonal therapy are other potential interventions. The effect of regular exercise or hormone replacement therapy on bone loss or risk of fracture has not yet been examined in kidney transplant recipient, although data from other solid organ transplant patients are promising.^{135,136} Denosumab, a RANK-ligand inhibitor for treatment of post-menopausal osteoporosis;⁴ can theoretically reduce osteoclastic resorption of trabecular structures and, hence, be used for treatment of osteonecrosis, but currently there is no human data. Early stages of osteonecrosis are generally managed conservatively or with core decompression accompanied by bone grafting and more recently the injection of bone morphogenetic protein, while iloprost to improve blood flow combined with bisphosphonates deserve further studies.⁸⁶

Conclusions

Mineral and bone disorders following kidney transplantation are common and characterized by loss of bone volume and mineralization abnormalities leading to low turnover bone disease in most patients. There are several contributing factors including pre-existing osteodystrophy, transplantation-specific therapies and reduced renal function due to chronic

allograft nephropathy. At this time there are no well-established therapeutic approaches that would provide bone preserving or anabolic effects with high degree of certainty. However, vitamin D analogues and bisphosphonates are often used for treatment of MBD after kidney transplantation. Whereas more studies are needed to examine the effects of different therapeutic interventions on bone disorders after kidney transplantation, clinicians should continue to individualize therapy according to their expertise and best judgment.

Acknowledgments

Funding Source:

The study was supported by Dr.Kalantar-Zadeh's research grants from the National Institute of Diabetes, Digestive and Kidney Disease of the National Institute of Health (R01 DK078106 and K24 DK091419), and a philanthropic grant from Mr. Harold Simmons. MZM received grants from the National Developmental Agency (KTIA-OTKA-EU 7KP-HUMAN-MB08-A-81231) from the Research and Technological Innovation Fund, and is recipient of the Hungarian Eötvös Scholarship (MÖB/77-2/2012).

None.

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Key bullet points

1. Mineral and bone disorders following kidney transplantation are common and characterized by loss of bone volume and mineralization abnormalities leading to low turnover bone disease in most of these patients.
2. At this time there are no well-established therapeutic approaches that would provide bone preserving or anabolic effects with high degree of certainty in renal transplant recipients.
3. However, vitamin D analogous and bisphosphonates are often used for treatment of mineral and bone disorders after kidney transplantation.
4. More studies are needed to examine the effects of different therapeutic interventions on bone disorders after kidney transplantation, clinicians should continue to individualize therapy according to their expertise and best judgment.

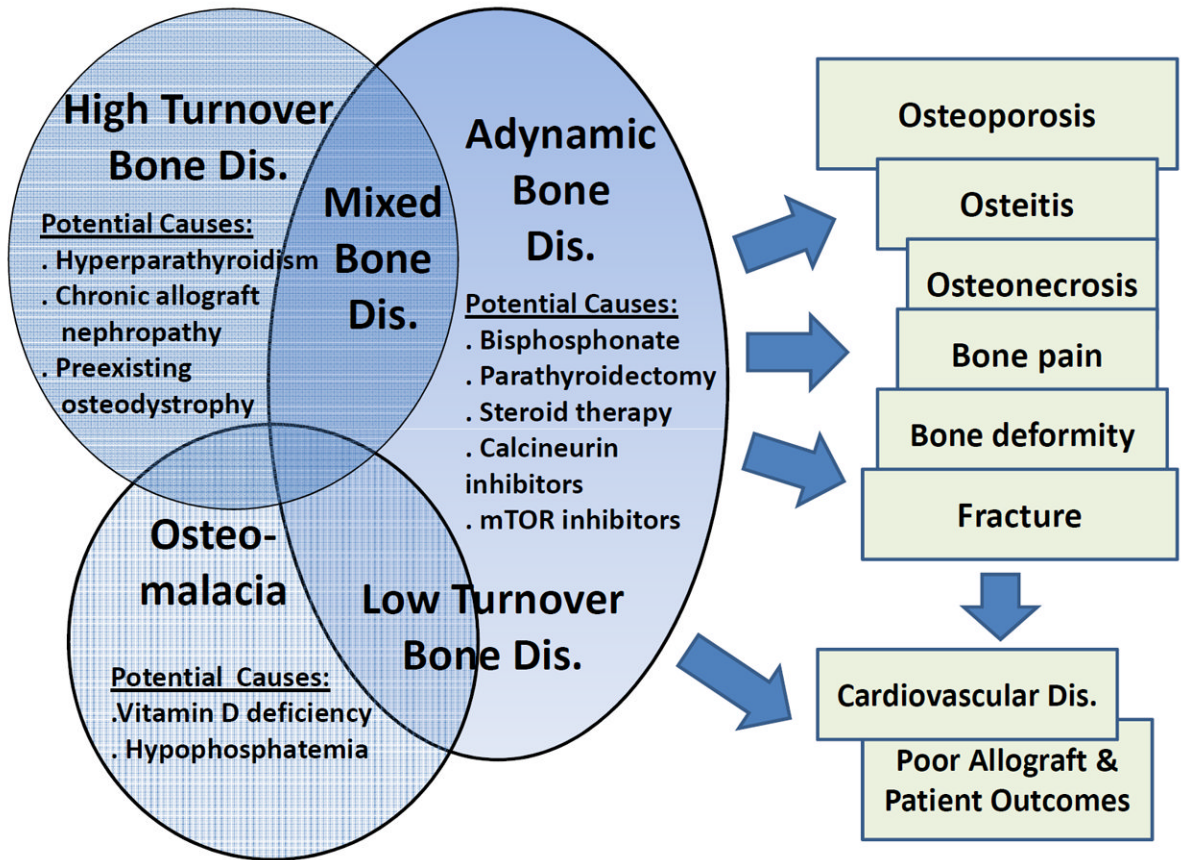


Figure 1. Four main types of renal osteodystrophy in kidney transplant recipients (see also Table 1)

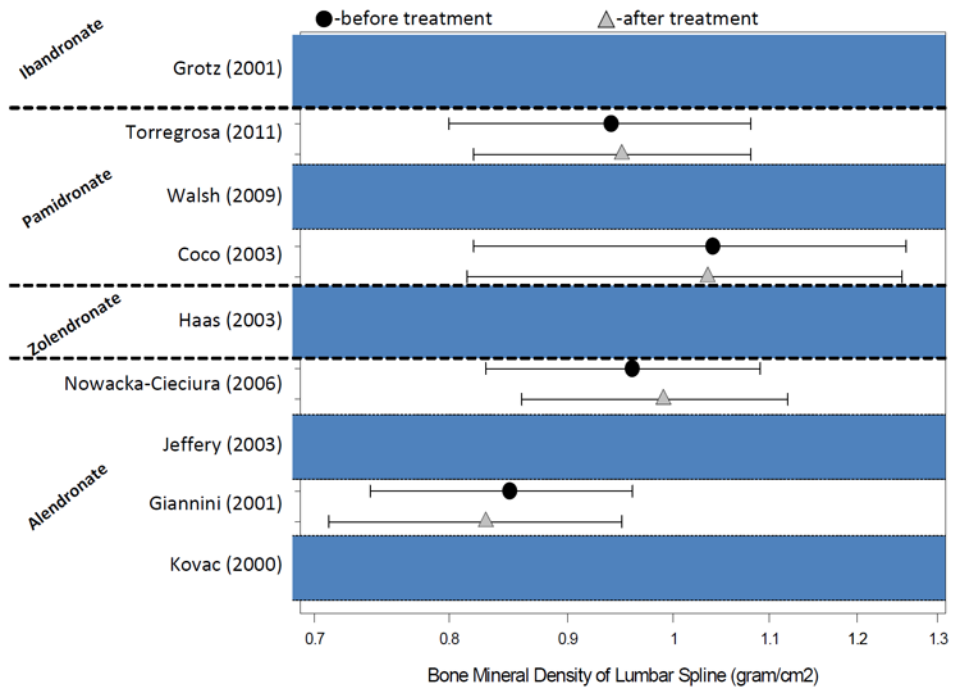


Figure 2. Overview of the results of the bisphosphonates studies in kidney transplant recipients (see also Table 2)

Table 1

Clinical features of four main categories of bone disease (renal osteodystrophy) in kidney transplant recipients (see also Figure 1)

Type	Histopathologic features	Biochemical abnormalities	Clinical consequences
Hyperactive (high turnover) bone disease (including osteitisfibrosa)	Marked increase in bone turnover, irregularly shaped trabecules displaying numerous abnormal remodeling sites, and an unusually high number of bone cells with irregular arrangement and shape	High PTH High AlkPhos * Varying levels of calcium and phos. Low 1,25(OH)D level	Bone pain Increased risk of fracture Higher graft loss risk? Increased risk of vascular calcification? Higher mortality risk?
Adynamic (low turnover) bone disease	Reduced bone volume and mineralization paralleled by a decrease in bone formation. It is also characterized by presence of few osteoid seams and few osteoblasts. Osteoclast number may be low, normal, or high.	Low to normal PTH Low AlkPhos * Varying levels of phos. Calcium tends to be high Varying 1,25(OH)D level	Increased vascular calcifications? Increased risk of fracture?
Mixed renal osteodystrophy	Defective mineralization with or without increased bone formation and increased PTH activity in bone. Increased numbers of heterogeneous remodeling sites and an increase in osteoclast number. Bone volume is variable and depends on a dominant pathogenic cause.	High PTH High AlkPhos * Varying levels of calcium and phos levels. Varying 1,25(OH)D level	Bone pain Increased risk of fracture? Mortality and graft loss risk?
Osteomalacia (may also be included under low-turnover category)	Accumulation of unmineralized matrix in which a decrease in mineralization precedes or is more pronounced than the inhibition of collagen deposition.	Varying levels of PTH, AlkPhos, calcium and phos. Usually low 1,25(OH) ₂ D and 25-OH-D levels	Increased risk of fracture? Higher risk of osteoporosis Bone pain and discomfort

* Bone specific AlkPhos is preferred but total (non-specific) AlkPhos can be used after ruling out liver disease or other non-bone sources of circulating AlkPhos.

Table 2

Overview of relevant clinical trials and observational studies related to MBD management in kidney transplant patients

Study (first author, publication year)	Type of study	Intervention	Number of patients	Outcome/comments
Bisphosphonates (see also Fig 2)				
Kovac et al. ⁹⁴ , 2000	RCT	<i>Alendronate + calcium + Vit D</i> vs Calcium + Vit D	12	BMD increment in lumbar spine in Alendronate group and decrement in control group
Giannini et al. ⁹⁵ , 2001	RCT	<i>Alendronate + calcium + calcitriol</i> vs Calcium + calcitriol	40	BMD increases in Alendronate arm, but not in control arm.
Jeffery et al. ⁹⁶ , 2003	RCT	<i>Alendronate and calcium</i> vs calcitriol and calcium	117	One year of treatment with alendronate or calcitriol, both with calcium supplementation, resulted in significant increases in BMD at the lumbar spine and femur, with a trend toward alendronate being more effective at the spine.
Haas et al. ⁹⁷ , 2003	RCT	<i>Zoledronate + calcium</i> vs placebo + Calcium	20	BMD increment in lumbar spine in Zoledronate group and decrement in control group
Schwarz et al. ⁹⁸ , 2004 (follow up of study by Haas et al. ⁹⁷ , 2003)	RCT	<i>Zoledronate + calcium</i> vs placebo + Calcium	20	The early bone-sparing effect of short-term Zoledronate therapy confers no sustained benefit versus placebo at three year post-transplantation.
Fan et al. ⁹⁹ , 2003	RCT	<i>Pamidronate + calcium + Vit D</i> vs Calcium + Vit D	25	BMD preserved in lumbar spine in Pamidronate group and decrement in control group
Coco et al. ¹⁰⁰ , 2003	RCT	<i>Pamidronate + calcium + Vit D</i> vs Calcium + Vit D	59	BMD preserved in lumbar spine in Pamidronate group and decrement in control group
Walsh et al. ¹⁰¹ , 2009	RCT	<i>Pamidronate + calcium + Vit D</i> vs Calcium + Vit D	93	BMD preserved in lumbar spine in Pamidronate group and decrement in control group
Torregrosa et al. ¹⁰² , 2011	RCT	<i>Pamidronate + calcium + Vit D</i> vs Calcium + Vit D	39	Pamidronate significantly reduced spinal bone loss, but no significant benefit was found for the incidence of fractures.
Grotz et al. ¹⁰³ , 2001	RCT	<i>Ibandronate + calcium</i> vs Calcium	72	BMD preserved in Ibandronate group and decrement in control group
Torregrosa et al. ¹⁰⁴ , 2010	RCT	<i>Risedronate + calcium + Vit D</i> vs Calcium + Vit D	101	Administration of risedronate immediately after renal transplantation contributes to an improved BMD, particularly in the femoral neck at 6-month follow-up, without major side effects.

Study (first author, publication year)	Type of study	Intervention	Number of patients	Outcome/comments
Nowacka-Cieciura et al. ¹⁰⁵ , 2006	Observational	<i>Alendronate/Risedronate</i> vs drug free	66	BMD preserved in treated group
Vitamin D derivatives and vitamin D receptor activators				
Cueto-Manzano et al. ¹⁰⁶ , 2000	RCT	<i>Calcium + Calcitriol</i> vs drug free	30	1,25-dihydroxyvitamin D3 and calcium carbonate did not significantly improve bone loss in long-term renal transplant recipients. However, significant osteoclast suppression and a trend to maintain trabecular bone volume and wall thickness as well as improve the axial BMD were observed in the treatment group.
De Sevaux et al. ¹⁰⁷ , 2002	RCT	<i>Calcium + Calcitriol</i> vs drug free	111	Treatment with a low dose of active vitamin D and calcium partially prevents bone loss at the lumbar spine and proximal femur during the first 6 months after transplantation
El-Agroudy et al. ¹⁰⁸ , 2003	RCT	<i>Alfacalcidol</i> vs placebo	40	In treated group BMD increased and PTH decreased, whereas BMD decreased in control group
Torres et al. ¹⁰⁹ , 2004	RCT	<i>Calcium + Calcitriol</i> vs Calcium	86	Therapy with low-dose calcium supplements during 1 year, plus intermittent calcitriol for 3 months after transplantation, is safe, decreases PTH levels more rapidly, and prevents bone loss at the proximal femur; a more pronounced effect is seen in recipients with at least one at-risk allele of the VDR genotype
Josephson et al. ¹¹⁰ , 2004	RCT	<i>Calcium + Calcitriol</i> vs Calcium vs placebo	64	BMD decrement was detected in placebo group, whereas BMD was small increased and preserved in treated group
Perez et al. ¹¹¹ , 2010	RCT	<i>Paricalcitol</i> vs drug free	42	Profile of urinary peptides was changed due to treatment with paricalcitol
Calcimimetics				
Kruse et al. ⁵⁶ , 2005	Observational	<i>Cinacalcet</i> vs drug free	14	Serum calcium decreased and normalized, whereas serum PTH and phosphate levels did not change significantly
Serra et al. ¹¹² , 2005	Observational	<i>Cinacalcet</i> vs drug free	11	Serum calcium and PTH decreased, whereas serum phosphate increased
Szwarc et al. ¹¹³ , 2006	Observational	<i>Cinacalcet</i> vs drug free	9	Serum calcium, phosphate and PTH did not change
Srinivas et al. ¹¹⁴ , 2006	Observational	<i>Cinacalcet</i> vs drug free	11	Serum calcium decreased, whereas serum phosphate increased and PTH did not change
Bergua et al. ¹¹⁵ , 2007	Observational	<i>Cinacalcet</i> vs drug free	13	Serum calcium and PTH decreased, whereas serum phosphate increased
Bergua et al. ¹¹⁶ , 2008	Observational	<i>Cinacalcet</i> vs drug free	9	Serum calcium, creatinine and PTH decreased, whereas radial BMD increased
Lopez et al. ¹¹⁷ , 2009	Observational	<i>Cinacalcet</i> vs drug free	29	Serum calcium decreased, whereas serum phosphate increased and PTH did not change

Study (first author, publication year)	Type of study	Intervention	Number of patients	Outcome/comments
Borchhardt et al. ¹¹⁸ , 2010	Observational	<i>Cinacalcet</i> vs drug free	10	While cinacalcet might decrease bone formation rate, it did not change bone volume, and bone mineral density of the femur increased
Cho et al. ¹¹⁹ , 2010	Observational	<i>Cinacalcet</i> vs drug free	23	Cinacalcet therapy was associated with significant reduction of serum calcium compared to control. Cinacalcet therapy was associated with greater BMD increase at the hip over the 36-month post-transplant period.
Copley et al. ¹²⁰ , 2010	Observational	<i>Cinacalcet</i> vs drug free	41	Serum calcium and PTH decreased, whereas serum phosphate increased, but estimated GFR did not change
Schwarz et al. ¹²¹ , 2011	Observational	<i>Cinacalcet</i> vs drug free	58	Serum calcium, estimated GFR and PTH decreased, whereas serum phosphate increased
Pinho et al. ¹²² , 2011	Observational	<i>Cinacalcet</i> vs drug free	18	Serum calcium and PTH decreased, whereas estimated GFR did not change

Table 3

Pharmacologic agents used for the management of MBD in kidney transplant patients.

Vitamin D preparation	Type	Serum calcium & phosphorus	Serum PTH and alkaline phosphatase	Availability (and brand name in the USA/Canada)
Bisphosphonates*				
<i>Alendronate</i>	<i>N</i> -containing	↓	↓	Fosamax™
<i>Pamidronate</i>	<i>N</i> -containing	↓	↓	APD™, Aredia™
<i>Zoledronate</i>	<i>N</i> -containing	↓	↓	Zometa™, Aclasta™
<i>Risedronate</i>	<i>N</i> -containing	↓	↓	Actonel™
<i>ibandronate</i>	<i>N</i> -containing	↓	↓	Boniva™
Nutritional Vitamin D				
Ergocalciferol	D2 , prepro- hormone, inactive	↑	?	Generic (<i>Drisdol™</i>)
Cholecalciferol	D3 , prepro- hormone, inactive	↑	?	Generic (<i>Calciol, Vitamin D3</i>)
25(OH)D (calcidiol, calcifediol)	D3 , prehormone	↑	?	Currently not yet available in the USA (<i>Calderol™</i>)
Vitamin D Receptor Activators				
1- α -calcidiol	1- α (OH) D3 , missing 25(OH)	↑	?	Not available in the USA (<i>one-alpha™</i>)
Doxercalciferol	1- α (OH) D2 , missing 25(OH)	↔ to ↑	↓	PO & IV (<i>Hectoral™</i>)
Calcitriol	D3 hormone, non-selective VDRA	↑	↔ to ↓	IV and PO (<i>Calcijex™, Rocaltrol™</i>)
Vitamin D Mimetics				
Paricalcitol	D2 , 19-Nor, selective VDRA	↔ to ↑	↓	IV & PO (<i>Zemlar™</i>)
Maxacalcitol	1,25-dihydroxy-22-oxa-vitamin D3 selective VDRA	↔ to ↑	↓	Not available in the USA (currently only in Japan)
Calcimimetics				
Cinacalcet	Calcimimetic (calcium sensing receptor activator)	Ca: ↓ P: ↓ in ESRD P: ↑ in NDD-CKD	↓	Only in PO form (<i>Sensipar/Mimpara™</i>)
Other agents				
Teriparatide	Recombinant PTH 1-34	Ca: ↑ P: ↓ in non-CKD	↑	Injectable (<i>Forteo™</i>)

Vitamin D preparation	Type	Serum calcium & phosphorus	Serum PTH and alkaline phosphatase	Availability (and brand name in the USA/Canada)
Calcitonin	Salmon-calcitonin	↓	↓	<i>Miacalcin, Fortical, Calcimar</i> (injectable and nasal)
RANK-ligand inhibitors				
Denosumab	IgG2 monoclonal antibody inhibiting osteoclastic bone resorption	Ca: ↓	↓	<i>Prolia</i> TM (60 mg SC q 6 mo) No data in RTR

CKD: chronic kidney disease, HD: hemodialysis; PTH: parathyroid hormone. 25(OH)D: 25-hydroxyvitamin D; 1,25(OH)₂D: 1,25-dihydroxyvitamin D; AP: alkaline phosphatase, MVDRA: vitamin D receptor activators, (OH): hydroxyl; RTR: renal transplant recipients

* Other bisphosphonates include non-nitrogenous (non-N-containing) bisphosphonates Etidronate (DidronelTM), Clodronate (BonafosTM, LoronTM), and Tiludronate (SkelidTM); and other nitrogenous (N-containing) bisphosphonates include Neridronate and Olpadronate.