Osteoporos Int (2011) 22:2107–2118
DOI 10.1007/s00198-010-1523-8

REVIEW

Vitamin D in organ transplantation

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Received: 12 August 2010 / Accepted: 10 November 2010 / Published online: 5 January 2011

Abstract Vitamin D deficiency is prevalent among patients with end-stage organ failure awaiting transplant. Low serum 25-hydroxyvitamin D (25-OHD) levels in these patients may be related to many disease-specific factors, as well as decreased sunlight exposure and limited intake of foods containing vitamin D. Low serum 25-OHD levels are also extremely common following solid organ transplantation, both during the immediate postoperative period and in long-term graft recipients. Demographic and lifestyle factors are important in determining D status in transplant recipients. Worse vitamin D status is associated with poorer general health, lower albumin, and even decreased survival among these patients. Although several studies have demonstrated that active forms of vitamin D and its analogues prevent bone loss following transplantation, the data do not show consistent benefit. These therapies may have particular utility after renal transplantation. However, given the narrow therapeutic window with respect to hypercalcemia and hypercalciuria, and the demonstrated efficacy of bisphosphonates to prevent post-transplantation bone loss, we regard these agents as adjunctive rather than primary therapy for transplantation osteoporosis. The effects of $1,25(OH)_2D$ on the immune system, which are still being elucidated, may have potential for reducing infections and preventing allograft rejection after transplantation.

Keywords Bone loss · Fracture · Organ transplantation · Osteoporosis · Vitamin D deficiency

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Introduction

The many skeletal and extraskeletal sequelae of vitamin D deficiency are of particular consequence in the population of patients who have received an organ transplant. Musculoskeletal effects of vitamin D deficiency include secondary hyperparathyroidism, bone loss, and fracture, as well as indirect effects on muscle weakness and falls [1, 2]. Extraskeletal sequelae include insulin resistance, hypertension, and malignancy [3, 4]. Among transplant patients, a potentially important role of vitamin D relates to its regulation of immune function [5]. In this article, we will review the prevalence of vitamin D deficiency in organ transplant candidates and in long-term transplant recipients, with assessment of vitamin D status based upon 25-hydroxyvitamin D (25-OHD) measurements, the most reliable and stable indicator of vitamin D stores. We will summarize interventional trials evaluating vitamin D, 1,25 $(OH)_2D$, and its analogues for the prevention and treatment of bone loss following solid organ transplantation. Finally, we will review the role of vitamin D in immune function as it relates to the transplant population. In this review, the term parent vitamin D will be used to refer to cholecalciferol and ergocalciferol. We will not differentiate between these two forms as there are no data comparing them in transplant patients and data in healthy populations are conflicting [6–8].

Vitamin D deficiency in organ transplant candidates

Vitamin D insufficiency and deficiency are extremely common among patients with end-stage organ failure; insufficient vitamin D levels have been documented in organ transplant candidates with congestive heart failure

[9], end-stage pulmonary disease [10], liver failure [11, 12], and chronic kidney disease [13, 14]. Several factors place patients with end-stage organ failure at particular risk for vitamin D deficiency (Table 1). These include limited sunlight exposure and low dietary intake of vitamin D-containing foods. In addition, hepatic dysfunction, which can result from intrinsic liver disease or from hepatic congestion in heart failure patients, may contribute to vitamin D deficiency. For the purposes of this review, we will define insufficiency as 25-OHD <30 ng/mL, deficiency as 25-OHD <20 ng/mL, and severe deficiency as 25-OHD <10 ng/mL. As categorization of vitamin D status differs in the various published reports, it is not always possible to ascertain the percentage of subjects in each of these categories. We have tried to present the data available in a uniform manner.

Vitamin D deficiency in patients with congestive heart failure

In patients with congestive heart failure, we reported that mean 25-OHD was in the deficient range (18 ng/mL). Furthermore, 18% of patients had severe deficiency (<9 ng/mL). Lower 25-OHD was associated with lower serum calcium, phosphorus, and albumin and higher total alkaline phosphatase activity and bone resorption markers, but not with serum $1,25(OH)_2D$. Those patients in the highest tertile of 25-OHD had significantly lower parathyroid hormone (PTH) levels [9]. In another study of patients with end-stage heart failure, lower circulating calcitriol was associated with poor clinical outcomes, including death and the need for transplantation [15].

Vitamin D deficiency in patients with end-stage pulmonary disease

In patients with end-stage pulmonary disease, 25-OHD deficiency is common and profound. Severe vitamin D deficiency has been reported in 20–50% of subjects [10, 16, 17]. In cystic fibrosis (CF), a common indication for lung transplantation, vitamin D deficiency is an important factor associated with osteoporosis and fractures [18–20]. We have observed that vitamin D deficiency, related in part to pancreatic insufficiency, is extremely common in CF patients despite supplementation; bone density is significantly lower in D-deficient patients [19]. In patients with advanced pulmonary disease, low 25-OHD is associated with lower fat mass, obstructive pulmonary disease, and low dietary vitamin D intake and was a predictor of decreased walking distance [21].

Vitamin D deficiency in patients with liver failure

Vitamin D deficiency is also common among liver transplant candidates. In 45 patients awaiting transplantation, mean 25-OHD was 9 ng/mL [11]. A study of 58 patients with cirrhotic end-stage liver disease referred for liver transplantation [22] reported that serum 25-OHD, $1,25(OH)_2D$, intact PTH, and osteocalcin (a marker of bone formation) were lower and urinary hydroxyproline excretion (a marker of bone resorption) was higher in cirrhotic patients than controls. Liver transplant candidates with a model for end-stage liver disease score of >15, indicative of worse disease and poorer health, had lower serum 25-OHD levels [23]. However, patients with severe liver disease may

Table 1 Risk factors for vitamin D deficiency in organ transplant patients

- •African-American race
- •Limited sunlight exposure, northern latitude, and winter months
- •Low dietary intake of vitamin D
- •Low fat mass
- •Low serum albumin
- •Hepatic dysfunction
- •Obstructive pulmonary disease
- •Renal insufficiency
- •Diabetes
- •Malabsorption
- •Poor general health
- •Female sex[a]
- •Glucocorticoid use[a]—increases catabolism of 25-OHD
- •Organ transplanted[a]—liver transplant recipients may be at increased risk
- •Recent transplantation[a]
- •Proteinuria[a]
- •Use of ACE inhibitors or aldosterone receptor blockers[a]

[a] Risk factor specifically demonstrated following transplantation

have lower levels of vitamin D binding protein as a result of reduced synthetic capacity, and consequently, free vitamin D levels may not be as low as suggested by total serum 25-OHD measurements.

Vitamin D deficiency in patients with chronic kidney disease

In patients with chronic kidney disease (CKD), calcitriol deficiency worsens with declining renal function as a result of glomerular loss [24, 25]. Deficiency of 25-OHD is also common among patients with CKD [13, 14, 25], and lower levels are associated with poorer kidney function [26]. In a population based study, 25-OHD insufficiency was found in 71% of patients with stage 3 and 83% with stage 4 CKD; severe deficiency was found in 14% of patients with stage 3 and 26% with stage 4 CKD [14]. A recent study of patients with chronic kidney disease found a similar prevalence; 39% of patients had 25-OHD between 16 and 30 ng/mL, 33% <16 ng/mL, and 6% <5 ng/mL [13]. Factors that have been associated with low 25-OHD in CKD patients include female sex, African-American race, latitude, season, diabetes, and low serum albumin [25]. Baseline 25-OHD was shown to be an independent predictor of death over 6 years in 168 patients with CKD [26]; however, this finding likely reflects the poorer general health of the subjects with vitamin D deficiency at baseline. Calcitriol treatment is associated with improved mortality in patients on hemodialysis [27, 28] and pre-dialysis patients [29]. However, studies finding a mortality benefit have not differentiated between patients with high turnover and adynamic bone disease. Whether there may be differential effects of treatment with active vitamin D analogies on cardiovascular outcomes or mortality requires further investigation.

Vitamin D deficiency in transplant recipients

The reported prevalence of vitamin D insufficiency after transplant ranges from 51% to 97% and of severe deficiency from 26% to 33% [30–34]. Variability in these estimates relates to the patient population, type of organ transplanted, and assay utilized for measurement of 25-OHD as significant variability exists with commercial assays [35–37]. Transplant recipients are at risk for vitamin D deficiency because of poor health following transplant, which can lead to decreased dietary intake of vitamin D-containing foods. In addition, because of an increased risk of skin cancer in organ transplant recipients, many patients dramatically limit their sun exposure [38, 39]. Furthermore, data from animal studies suggest that glucocorticoids, commonly used for immunosuppression, can increase catabolism of 25-OHD [40, 41]. Vitamin D deficiency in transplant recipients may result in secondary hyperparathyroidism which can further contribute to bone loss and fracture [42]. Patient-specific factors associated with worse vitamin D status after transplant include African-American race [34, 43], avoidance of sun, low dietary intake [33], and transplant during winter months [43]. Not all studies have observed variations related to sun exposure [30], perhaps because in the most severely ill patients there is less variation.

Vitamin D deficiency at the time of organ transplantation

Very few studies have examined vitamin D levels at the time of transplantation. We recently reported that severe vitamin D deficiency was extremely prevalent among heart and liver transplant recipients at the time of transplantation; 91% of patients had vitamin D insufficiency, 55% had deficiency (25-OHD 10 to <20 ng/mL), and 16% had severe deficiency. Liver transplant recipients had significantly lower vitamin D levels than heart transplant recipients (Fig. 1), likely because of disease-related factors such as malabsorption and impaired hepatic 25-hydroxylation of vitamin D [30]. In one study that evaluated vitamin D status in patients at the time of renal transplant, vitamin D insufficiency and deficiency were also prevalent; 59% had 25-OHD<30 ng/mL and 29% had 25-OHD<10 ng/mL [43].

Vitamin D deficiency in long-term transplant recipients

Most studies of vitamin D status in patients after organ transplantation have been performed in kidney transplant recipients and have focused on patients several years after

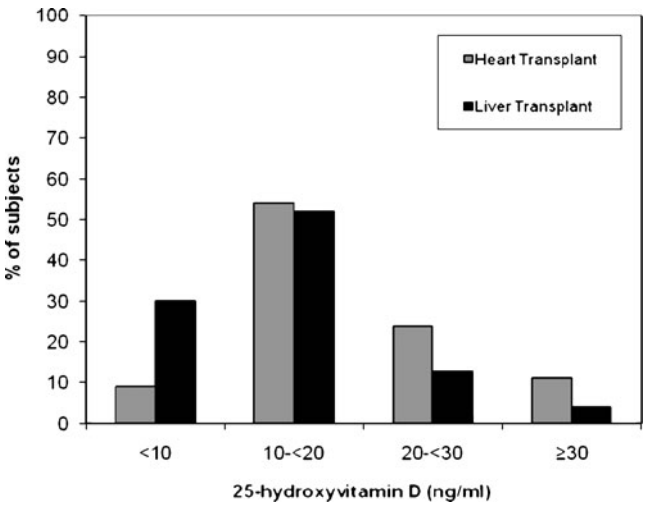

Fig. 1 Comparison of serum 25-hydroxy vitamin D levels in heart and liver transplant recipients at the time of organ transplantation. Adapted from Stein et al. [30]

transplantation. Vitamin D deficiency is common and severe in patients after kidney transplantation [31, 34, 44]. In one study, 31 renal transplant recipients, who were on average 7 years post-transplant, were found to have significantly lower levels than age-matched controls [31]. Among transplant recipients, mean serum 25-OHD was 10 ng/mL, and one third of patients had undetectable levels (<4 ng/mL) [31]. Factors associated with low 25-OHD in renal transplant recipients include African-American race [34]; inadequate dietary vitamin D intake, reported in 87–91% of renal transplant recipients [45]; female sex; measurement in autumn and winter months [34]; recent transplantation [44]; proteinuria [46]; and use of ACE inhibitors or aldosterone receptor blockers [44]. Persistent elevations in FGF-23 after kidney transplantation are associated with lower calcitriol levels [47].

Insufficient 25-OHD levels were reported in 97% of cardiac transplant recipients in another recent study. Though not directly associated with vertebral fractures, low 25-OHD was associated with higher PTH, which was significantly associated with vertebral fractures [42]. Relevant metabolic changes that occur after cardiac transplantation include sustained increases in serum creatinine [48–50] and decreases in $1,25(OH)_2D$ [49, 51]. Furthermore, low concentrations of $1,25(OH)_2D$ measured 21 days post-transplantation were associated with 1-year mortality in cardiac transplant recipients (Fig. 2) [51]. Whether this observation reflects a causal relationship between calcitriol and mortality, the effects of calcineurin inhibitors on renal function, or rather the role of low calcitriol as a marker of renal dysfunction or poorer health is unclear.

In long-term liver transplant recipients, 65–68% had 25-OHD levels below 15 ng/mL [32, 52]. Low 25-OHD was

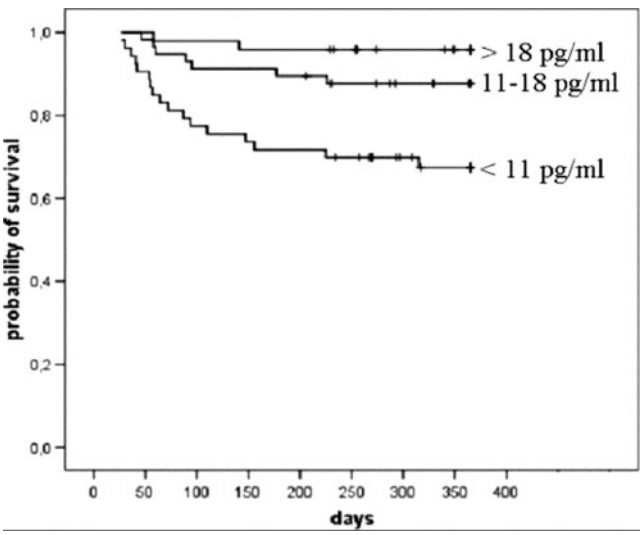

Fig. 2 Kaplan–Meier survival estimates in cardiac transplant recipients according to categories of serum calcitriol concentrations 21 days after transplant (log-rank test $P<0.001$). From Zittermann et al. [51]

associated with low femoral neck Z-score [52]. Biochemical changes following liver transplantation include increases in both 25-OHD and PTH [11, 12, 53, 54]. These increases appear to be sustained for at least 3–4 years following transplantation [11, 53], although some authors have not found significant changes [55–57]. Despite this increase, most authors have found that 25-OHD remains in the insufficient range. Factors associated with vitamin D deficiency in transplant recipients are detailed in Table 1.

Treatment of post-transplant bone loss with vitamin D and analogues

Administration of vitamin D or its analogues is often recommended to prevent or treat osteoporosis after transplantation [58]. There are several potential mechanisms by which vitamin D and its analogues may influence post-transplantation bone loss. They may overcome GC-induced decreases in intestinal calcium absorption, reduce secondary hyperparathyroidism, promote differentiation of osteoblast precursors into mature cells, or influence the immune system and potentiate the immunosuppressive action of calcineurin inhibitors or prednisone, thus reducing the required dose of immunosuppressive drugs [59–61]. There are several limitations common to the interventional studies evaluating treatment of bone loss following transplantation. Most are single-center studies, with small sample sizes. Most importantly, the majority have had inadequate power to detect differences in fracture.

Since the observation or control arm of most studies of bone loss after organ transplantation have included at least 400 IU of parent vitamin D in the post-transplant regimen [62–65], it is clear that the RDA for vitamin D is not sufficient to prevent transplantation osteoporosis. In two recent studies, parent vitamin D, at doses of 800 IU daily in 40 patients [66] or 25,000 IU monthly in 90 patients [67], also did not prevent bone loss after kidney transplantation.

Active forms of vitamin D may be more effective. Calcidiol (25-OHD) prevented bone loss and increased lumbar spine (LS) bone mineral density (BMD) after cardiac transplantation [68]. Alfacalcidiol (1-α-OHD) prevented or attenuated LS and femoral neck (FN) bone loss when given immediately after kidney transplantation [69–71]. De Sevaux et al. [70] found that treatment with alfacalcidiol for the first 6 months following renal transplant resulted in the attenuation of bone loss at the lumbar spine and greater trochanter and prevented loss at the femoral neck (Fig. 3).

Studies of calcitriol have found contradictory results, although some report beneficial effects at doses >0.5 μg/day. Calcitriol may be of particular benefit in kidney transplant recipients in whom calcitriol produc-

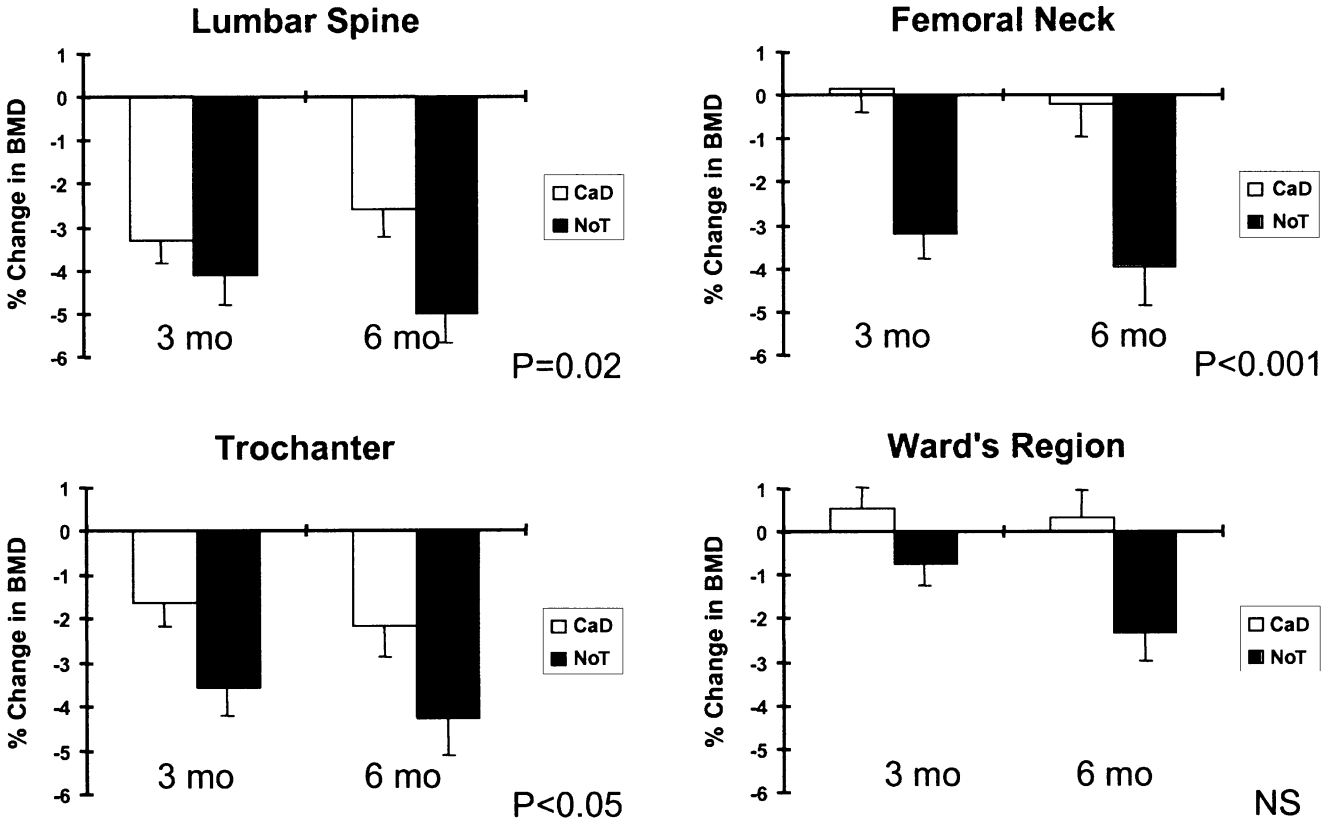

Fig. 3 Change in bone mineral density in renal transplant recipients treated with calcitriol or placebo (% from baseline ± SE; significance shown for differences between groups at 6 months). From de Sevaux et al. [70]

tion by the transplanted kidney may be inadequate to suppress excess PTH secretion by hyperplastic parathyroid tissue [72]. Treatment with calcitriol may prevent hyperparathyroidism after both renal [73] and cardiac [62] transplantation. Calcitriol given during the first year after kidney transplantation was associated with an increase in LS, FN, and forearm BMD [74]. In another study of renal transplant recipients, intermittent calcitriol and calcium prevented total hip (TH) but not LS bone loss [75]. In a stratified, placebo-controlled randomized study in which heart and lung transplant recipients received calcitriol or placebo for 12 or 24 months after transplantation [76], LS bone loss was equivalent between groups, and the amount of FN bone loss at 24 months was significantly reduced only in the group that received calcitriol for the entire period. While these results suggest that the protective effects of calcitriol are not sustained after cessation of treatment, we found no bone loss when we discontinued calcitriol after the first post-transplant year [77]. In contrast to the above findings, studies of long-term kidney [78] and heart transplant patients [79, 80] have failed to find any benefit of calcitriol. The randomized trials evaluating vitamin D analogues for prevention of bone loss following transplantation are summarized in Table 2.

The efficacy of vitamin D analogues compared to bisphosphonates has been evaluated by several studies, again with mixed results. In a randomized trial, we found that both alendronate (10 mg daily) and calcitriol (0.25 μg twice daily) given immediately after cardiac transplant provided similar protection against bone loss at the LS, FN, and TH 1 year after transplant (Fig. 4) compared with a reference group receiving only calcium and vitamin D [62]. BMD remained stable during the second year after cardiac transplant, after discontinuation of both drugs [77]. Calcitriol (0.5–0.75 mcg/day) prevented spine and hip bone loss during the first 6 months after heart or lung transplantation and was as effective as cyclic etidronate [64]. Kidney transplant patients treated with alendronate, calcitriol (0.25 μg daily), and calcium carbonate had marked increases in LS BMD compared to decreases in those who received only calcium and calcitriol [81]. A trial of 40 long-term kidney transplant patients who were started on alendronate, calcitriol, and calcium or only calcitriol and calcium approximately 5 years after transplantation documented significant improvements in LS and FN BMD in the alendronate group, while BMD in the other group was stable [82]. In a small, randomized trial of 80 long-term kidney transplant recipients that compared alendronate and alfacalcidiol plus alendronate for 1 year, BMD improved at

Table 2 Randomized clinical trials of active vitamin D analogues for the prevention of bone loss immediately following solid organ transplantation

First author	Transplant type	Sample size	Duration (months)	Treatment regimen	Control regimen	Findings
Garcia-Delgado et al. [68]	Heart	40	18	Calcidiol 32,000 IU/week OR etidronate 400 mg/day, 14-day cycle/3 months OR calcitonin 100 IU/day; calcium 1 g/day	No control group	BMD: Only LS measured, improved by 4.9% in calcidiol groups vs. declines of 0.19% in etidronate and 1.2% in calcitonin groups Fracture: 3 vertebral fractures in etidronate group, 4 in calcitonin group. No fractures in calcidiol group
Stempfle et al. [80]	Heart	132	36	Calcitriol 0.25 μg/day; calcium 1,000 mg/day; HRT if hypogonadal	Placebo Calcium 1,000 mg/day; HRT if hypogonadal	BMD: Only LS measured. Increases in both groups during 3 years after transplant. No significant difference between groups Fracture: In calcitriol group, 2 subjects with fractures at 12 months, one subject at 24 months. In placebo, one subject with fracture at 24 months (all vertebral)
Sambrook et al. [76]	Heart and lung	65	24	Calcitriol 0.5–0.75 μg/day for 12 or 24 months; calcium 600 mg/day	Calcium 600 mg/day	BMD: FN (but not LS) bone loss was attenuated in the calcitriol groups at 12 months (−6.6% in controls vs. −3.9% and −1.2% in the treatment groups). LS bone loss was similar among all three groups (−2.7% to 5.6%). In those who discontinued calcitriol after 12 months, FN bone loss was similar to control at 24 months Fracture: 22 new vertebral fractures occurred in four control subjects. One new vertebral fracture occurred in a calcitriol subject (not powered to assess difference in fracture rates)
Henderson et al. [64]	Heart and lung	41	6 (24 months f/u)	Etidronate 400 mg/day for 2 14-day cycles followed by calcium 1.25 g/day OR calcitriol 0.5 μg/day	Untreated reference group	BMD: Similar small losses at LS and FN in both groups during the treatment period. Significantly less bone loss than in the reference group. Loss at 24 months was lower in etidronate group Fracture: 3 fractures in etidronate group (vertebral); 2 in calcitriol group (non-vert); 1 in reference group (non-vert)
De Sevaux et al. [70]	Kidney	111	6	1-hydroxy vitamin D 0.25 μg/day; calcium 1,000 mg/day	No treatment	BMD: Significantly less bone loss at LS and hip in treatment group Fracture: 6 vertebral fractures in non-treatment group
Coco et al. [84]	Kidney	72	12	Pamidronate 60 mg at transplant 30 mg months 1, 2, 3, 6; calcitriol; calcium (variable doses)	Calcitriol; Calcium (variable doses)	BMD: At LS, stable BMD in pamidronate group at 6 and 12 months compared to calcitriol (6% at 12 months). At FN, no significant difference in either group Fractures: 1 vertebral fracture in pamidronate group, 2 in calcitriol group. No non-vert fractures
El-Agroudy et al. [69]	Kidney	40	12	Alfacalcidiol 0.5 μg/day; calcium 500 mg/day	Calcium 500 mg/day	BMD: Increased by 2.1%, 1.8%, and 3.2% at LS, FN, and forearm, respectively, in alfacalcidiol group decreased by 3.2%, 3.8%, and 1.8% in the controls No fracture data
Josephson et al. [74]	Kidney and kidney-pancreas	64	12	Calcitriol 0.25–1.0 μg/day + calcium 1 g/day OR calcium 1 g/day	No treatment	BMD: Significantly less bone loss at the FN and DR in the calcitriol group compared to no treatment No fracture data

Shane et al. [62]	Heart	149	12	Alendronate, 10 mg/day OR calcitriol 0.5 mg/day; calcium, 945 mg/day; vitamin D, 1,000 IU/day	Non-randomized reference group	BMD: similar small losses at LS and TH in both groups. Significantly less bone loss at LS and TH than in reference group Fracture: incidence of vertebral fracture was 6.8% in alendronate group, 3.6% in calcitriol group, and 13.6% in reference group. Differences were not statistically significant
Torres et al. [75]	Kidney	86	3 (12 month f/u)	Calcitriol 0.5 μg qod; calcium 500 mg/day	Calcium 500 mg/day	BMD: Significantly less bone loss at the TH in calcitriol group at 3 and 12 months. No difference at LS or FN Fractures: No fractures occurred in either group
El-Agroudy et al. [71]	Kidney	60	12	Alendronate 5 mg/day OR alfacalcidiol 0.5 μg/day OR calcitonin 200 IU qod; calcium 500 mg/day	Calcium 500 mg/day	BMD: small increases (1–3%) in all treatment groups at the LS, FN, and forearm. Small but significant declines in control group No fracture data

the LS and FN in both groups. The increase was only significant in the combination alendronate–alfacalcidiol group, however, likely because of inadequate power in this small study [83]. Histomorphometric changes after kidney transplantation were examined in a subset (n=14) of a larger study of 72 subjects who received calcitriol with or without pamidronate [84]; paired iliac crest bone biopsies were obtained in six subjects randomized to calcitriol plus pamidronate and eight subjects who received calcitriol alone. Pamidronate plus calcitriol was associated with maintenance of trabecular bone structure. Activation frequency at 6 months was lower in subjects who received pamidronate, but was also low in six of eight subjects who received calcitriol alone.

The major side effects of therapy with active vitamin D and analogues are hypercalcemia and hypercalciuria, which may develop suddenly and at any time during the course of treatment. Thus, frequent urinary and serum monitoring is required. If hypercalcemia occurs, it must be recognized and reversed promptly because of the adverse effects on renal function and the life-threatening potential of a severely elevated serum calcium concentration. Given the requirement for serial monitoring, the narrow therapeutic window with respect to hypercalcemia and hypercalciuria, and the demonstrated efficacy of bisphosphonates to prevent post-transplantation bone loss [62, 85], we regard pharmacologic doses of vitamin D and its analogues as adjunctive rather than primary therapy for the prevention and treatment of transplantation osteoporosis. In contrast to active vitamin D metabolites, the therapeutic index for parent vitamin D is wide. Very high and sustained doses of ergocalciferol or cholecalciferol are required to develop toxicity [86].

Deficiency of 25-OHD may complicate treatment of bone loss following transplantation. Bisphosphonates may not be optimally effective in the setting of severe vitamin D deficiency. Furthermore, intravenous bisphosphonate treatment has been reported to precipitate symptomatic hypocalcemia in patients with severe, unrecognized vitamin D deficiency [87].

Effects of vitamin D on immunity and graft rejection

Immune effects of vitamin D

Vitamin D potentiates the innate immune system and has been shown to be protective against bacterial infections and tuberculosis [88]. When $1,25(OH)_2D$ is produced by monocytes and macrophages in sufficient quantities, it has intracellular antimicrobial effects and can also interact with and govern the cytokine profiles of activated T and B lymphocytes in the local environment [89]. The ability of

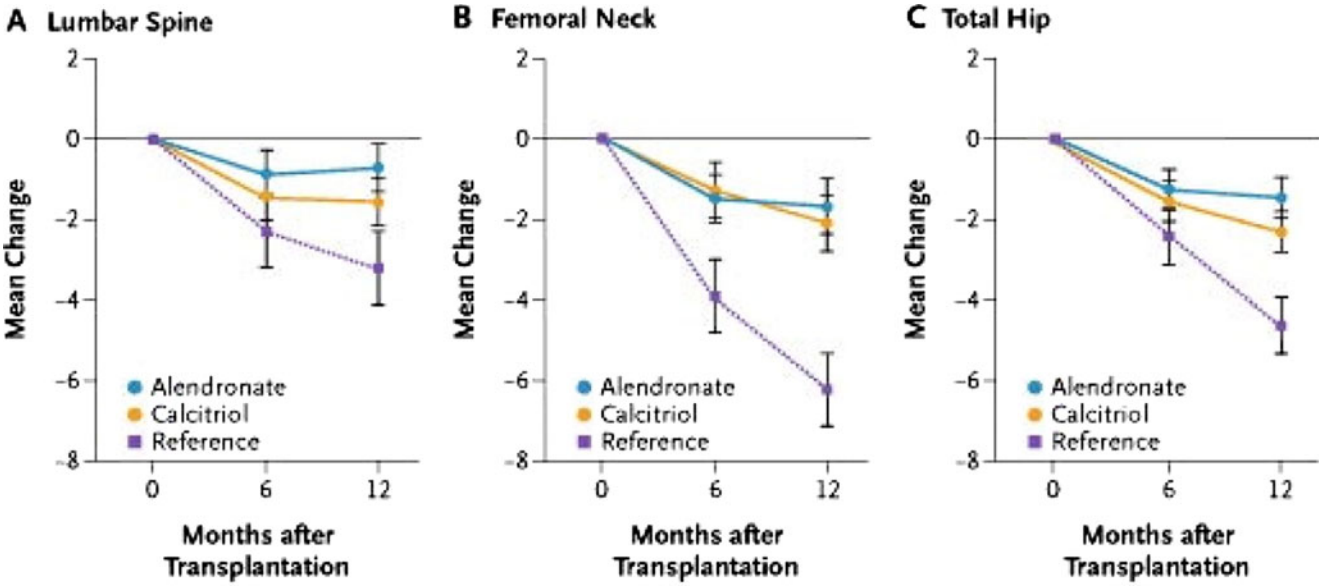

Fig. 4 Comparison of mean (±SE) percent change in bone mineral density from baseline in cardiac transplant subjects treated with alendronate or calcitriol and untreated reference group. From Shane et al. [62]

monocytes and macrophages to synthesize $1,25(OH)_2D$ is dependent on the availability of adequate serum concentrations of 25-OHD and increases in response to vitamin D supplementation [89]. Thus, in the setting of insufficient 25-OHD to serve as substrate, there will be a decrease in local production of $1,25(OH)_2D$. The resultant decreased binding of $1,25(OH)_2D$ to the macrophage vitamin D receptor will result in reduced antimicrobial activity against ingested microbes [89]. This can have deleterious effects on immunity. Of particular importance to transplant recipients is that the antimicrobial actions of $1,25(OH)_2D$ also occur in barrier epithelial cells of the skin [90, 91], gut [92], and lungs [93]. Animals treated with calcitriol were able to resist infection with *Candida albicans* and herpes simplex virus-1 [94], two common opportunistic infections in transplant patients. In a population study, the prevalence of upper respiratory tract infections was greater in individuals with lower 25-OHD levels [95].

Role of vitamin D in allograft rejection

Recent studies have demonstrated a role for vitamin D in the regulation of immune cell proliferation, differentiation, and responsiveness [5]. Evidence from animal studies suggests that administration of 1,25-dihydroxyvitamin D can prevent acute allograft rejection following liver [96, 97], kidney [98], and heart [99] transplantation. There are limited data from human studies. In kidney transplant recipients, calcitriol supplementation was associated with fewer episodes of acute cellular rejection [100], reduced glucocorticoid requirements [73], and decreased expression of co-stimulatory and HLA-DR molecules, suggesting a possible mechanism for allograft survival [101]. In one study, patients treated with calcitriol following heart transplantation had a reduction in their requirement for cyclosporine [59]. However, we did not observe a reduction in cyclosporine or prednisone dose in our clinical trial of heart transplant recipients treated with calcitriol [62]. In a retrospective study, lower preoperative 25-OHD was associated with increased numbers of moderate to severe rejection episodes in the first 2 months after cardiac transplantation [23]. Those patients who were supplemented with cholecalciferol, in a clinical non-experimental setting, had fewer rejection episodes [23]. Further prospective human studies are needed to explore the role of $1,25(OH)_2D$ and of parent vitamin D in the prevention of graft rejection and infection after transplantation.

Conclusions

Given the high prevalence of 25-OHD deficiency in patients with organ failure prior to and following transplantation, patients should be assessed before transplantation and receive treatment for vitamin D insufficiency and deficiency, if present. In addition, long-term transplant recipients should be monitored and treated for vitamin D deficiency as part of broader management of bone disease. We recommend treatment with parent vitamin D for patients with insufficient 25-OHD (<30 ng/mL) regardless of the type of underlying disease. In patients with stage 3 and 4 CKD (estimated GFR 15–60 mL/min), therapy with an active oral vitamin D analogue (calcitriol, alfacalcidol, or doxercalciferol) should be initiated when serum levels of

25-OHD are sufficient (>30 ng/mL) and plasma levels of intact PTH are above the target range for the CKD stage, as outlined in the K/DOQI guidelines [102]. Patients treated with hemodialysis or peritoneal dialysis with serum levels of intact PTH levels >300 pg/mL should receive an active vitamin D sterol to reduce the serum levels of PTH to a target range of 150–300 pg/mL [102]. For patients with other types of end-organ failure, including liver disease, we suggest replacement with parent vitamin D alone. If monitoring during treatment reveals that 25-OHD is not increasing by the expected amount and is suggestive of a significant impairment in 25-hydroxylase activity, we would consider adding an active vitamin D analogue.

Pharmacologic doses of vitamin D and its analogues have clear utility after renal transplant, but should be utilized as adjunctive rather than primary therapy for osteoporosis in patients after other types of solid organ transplantation because of their narrow therapeutic window and inconsistent efficacy.

There is a need for longitudinal studies to evaluate the efficacy of different repletion regimens to restore 25-OHD levels after transplantation and to examine whether restoring 25-OHD at the time of transplant reduces the development of infectious complications and immunosuppressant requirements. Epidemiologic studies and one randomized controlled clinical trial [103] suggest that adequacy of vitamin D is associated with lower incidence of malignancy [103, 104] as well as cardiovascular disease [105, 106] and mortality [107–109] in healthy populations; these data may be applicable to transplant patients as well. At present, physicians who care for transplant patients should screen all patients for 25-OHD deficiency. Treatment of this condition and subsequent improvement in vitamin D status may reduce skeletal and extraskeletal morbidity in transplant patients.

Conflicts of interest None.

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