Vitamin D in Kidney Transplant Recipients: Mechanisms and Therapy

Giuseppe Cianciolo^{a, b} Andrea Galassi^c Irene Capelli^{a, b}
Maria Laura Angelini^{a, b} Gaetano La Manna^{a, b} Mario Cozzolino^{d, e}

^aNephrology Dialysis and Renal Transplant Unit, S. Orsola University Hospital, and ^bDepartment of Experimental Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, ^cRenal and Dialysis Unit, Desio-Vimercate Desio Hospital, Desio, ^dRenal Division, San Paolo Hospital, and ^eDepartment of Health Sciences, University of Milan, Milan, Italy

Key Words

Vitamin D · Renal transplant · Chronic kidney disease-mineral and bone disorder · Proteinuria · Parathyroid hormone · Fibroblast growth factor-23

Abstract

Chronic kidney disease-mineral and bone disorder (CKD-MBD) is common in kidney transplant recipients (KTRs), where secondary hyperparathyroidism (HPTH) and post-transplantation bone disease (PTBD) are potential effectors of both graft and vascular aging. Reduced 25(OH)D levels are highly prevalent in KTRs. Experimental and clinical evidence support the direct involvement of deranged vitamin D metabolism in CKD-MBD among KTRs. This review analyzes the pathophysiology of vitamin D derangement in KTRs and its fall out on patient and graft outcome, highlighting the roles of both nutritional and active vitamin D compounds to treat PTBD, cardiovascular disease (CVD) and graft dysfunction. Fibroblast growth factor-23-parathyroid hormone (PTH)-vitamin D axis, immunosuppressive therapy and previous bone status have been associated with PTBD. Although several studies reported reduced PTH levels in KTRs receiving nutritional vitamin D, its effects on bone mineral density (BMD)

remain controversial. Active vitamin D reduced PTH levels and increased BMD after transplantation, but paricalcitol treatment was not accompanied by benefits on osteopenia. Vitamin D is considered protective against CVD due to the widespread pleiotropic effects, but data among KTRs remain scanty. Although vitamin deficiency is associated with lower glomerular filtration rate (GFR) and faster estimated GFR decline and data on the anti-proteinuric effects of vitamin D receptor activation (VDRA) in KTRs sound encouraging, reports on related improvement on graft survival are still lacking. Clinical data support the efficacy of VDRA against HPTH and show promising evidence of VDRA's effect in counteracting post-transplant proteinuria. New insights are mandatory to establish if the improvement of surrogate outcomes will translate into better patient and graft outcome.

© 2016 S. Karger AG, Basel

Background

Kidney transplantation is the best renal therapy for eligible end-stage renal disease (ESRD) patients. Kidney transplant recipients (KTRs) have better survival rates than dialysis patients, with lower morbidity, lower car-

cardiovascular risk, improved quality of life and reduced health economic costs [1, 2]. Despite recent improvements in graft survival up to 1–3 years after transplantation, graft failure remains a frequent cause of dialysis-dependent ESRD [3]. Transplant patients with graft failure are prone to a threefold greater mortality risk than patients with functioning grafts, with a 3.5–5% annual risk of fatal or nonfatal cardiovascular events [4, 5]. Identification of modifiable factors responsible for a hampered glomerular filtration rate (GFR) would improve targeted interventions against allograft deterioration and the related cardiovascular burden.

Chronic kidney disease-mineral and bone disorder (CKD-MBD), including secondary hyperparathyroidism (HPTH) and post-transplantation bone disease (PTBD), can be considered among the effectors of allograft and vascular aging. A deranged vitamin D system, which is an established trigger of CKD-MBD [6], was associated with worse clinical outcomes even in KTRs, where reduced synthesis of vitamin D and impairment of its pleiotropic effects may account for the clinical links between vitamin D, PTBD and graft survival [7].

The present review analyzes vitamin D derangement in KTRs, moving from experimental to clinical evidence to discuss the potential therapeutic application of nutritional and active vitamin D supplementation in terms of graft survival and PTBD and cardiovascular disease (CVD).

Vitamin D System: Pathophysiology

Vitamin D is crucially involved in mineral homeostasis. It regulates intestinal and renal handling of calcium and phosphate [8], as well as bone turnover through PTH downregulation with a direct effect on osteoclast and osteoblast activity [9]. Vitamin D metabolism is described in figure 1.

Vitamin D deficiency has been associated with poor outcomes in the general population and in CKD patients [6, 10, 11]. A univocal definition of 25(OH)D deficiency is still lacking, as no randomized controlled trials (RCTs) have yet been designed to investigate the best 25(OH)D targets to improve hard endpoints in humans. In the general population, serum 25(OH)D levels <20 ng/ml are considered deficient, 20–29.9 ng/ml insufficient, and levels ≥ 30 ng/ml sufficient [8]. Optimal vitamin D levels may vary according to the specific disease and outcome of interest. 25(OH)D levels >10 ng/ml were shown to be adequate to prevent rickets and osteomalacia, whereas

25(OH)D levels >30 ng/ml may be required to prevent secondary HPTH or osteoporosis [12].

The extra-renal expression of CYP27B1, CYP24A1 and vitamin D receptor (VDR) is considered the cornerstone of vitamin D's pleiotropic effects [13]. VDR is a ubiquitous nuclear receptor, with a major genomic regulatory effect, currently considered a crucial modulator of the human genome. Systemic expression of CYP27B1 allows the local hydroxylation of 25(OH)D into 1,25(OH)₂D and subsequent VDR activation (VDRA) at autocrine and paracrine level [11]. Thus, widespread VDR activity may safeguard homeostasis in different organs and systems.

Vitamin D is an endocrine suppressor of the renin angiotensin aldosterone system (RAAS), downregulating renin expression and the pro-inflammatory pathway pivoted by the transforming growth factor β [14, 15]. Experimental research investigated the effect of vitamin D in reducing CKD progression through the improvement of glomerular and tubular interstitial fibrosis [16]. A more recent study showed that vitamin D and its analogs are able to reduce proteinuria in CKD patients [17].

Epidemiology of Altered Vitamin D Metabolism in KTRs

Reduced 25(OH)D levels are common in KTRs, with an extensive prevalence of deficiency and insufficiency up to 30 and 81%, respectively [18]. Low 25(OH)D levels have been observed after transplantation (fig. 2) [19] with only 12% of KTRs showing 25(OH)D levels higher than 30 ng/ml during the first year after transplant [20] and at longer follow-up [21]. Conversely, 1,25(OH)₂D₃ levels reached normal values within 3–6 months after transplantation (fig. 2) [22, 23].

Vitamin D metabolism may be influenced by impaired allograft function as well as by persistently elevated PTH and fibroblast growth factor-23 (FGF23) levels. HPTH is a frequent and possibly severe complication after renal transplantation. Persistently high PTH levels were reported at 1–2 years and even at 5 years after transplantation in 20% of cases (fig. 2) [24]. By contrast, FGF23 declines 3 months after transplant but remains higher than in CKD patients matched for estimated GFR (eGFR; fig. 2) [25]. Further, FGF23 reductions were repeatedly observed at longer follow-up, approximating normal levels 1–3 years after transplantation [26–28].

Fig. 1. Physiology of vitamin D metabolism. Vitamin D derives from ergocalciferol and cholecalciferol. Ergocalciferol derives from UV irradiation of yeast sterol ergosterol, present in sun-exposed mushrooms, while cholecalciferol derives from UVB irradiation of 7-dehydrocholesterol. Ergocalciferol and cholecalciferol are transformed into 25(OH)D₂ and 25(OH)D₃, respectively, by hepatic 25-α-hydroxylase. 25(OH)D₂ is not produced in humans and almost 80% of human 25(OH)D derives from UVB irradiation

as 25(OH)D₃ with only a minor contribution from nutrients. Renal and extrarenal 1-α-hydroxylase transform 25(OH)D into the active form 1,25(OH)₂D, which thereafter activates VDR. Calcitriol is catabolized by the 24-α-hydroxylase; PTH increases vitamin D activation by upregulating 1-α-hydroxylase in proximal tubular cells, whereas FGF23 counteracts vitamin D activation decreasing 1-α-hydroxylase and enhancing 24-α-hydroxylase. UV = Ultraviolet.

Pathogenesis of Impaired Vitamin D Metabolism in KTRs

Specific alterations in vitamin D metabolism are still incompletely understood in KTRs. A physiology-driven approach suggests that the vitamin D system may be regulated by kidney function, PTH and FGF23 in agreement with evidence from non-transplant CKD patients. How-

ever, alterations in the vitamin D system in KTRs show peculiarities related to post-transplant specific derangement of the PTH-FGF23 axis, immunosuppressive regimen and environmental factors [21, 29].

Recovery of graft function, inappropriately high PTH levels and hypophosphatemia accelerate the conversion of 25(OH)D into 1,25(OH)₂D₃ after renal transplantation [30]. Conversely, high FGF23 levels during the first months

Fig. 2. Trends of mineral metabolism after renal transplantation. In a well-functioning graft, the rise in $1,25(\text{OH})_2\text{D}_3$ levels after transplantation follows, within the first months, the recovery of $1-\alpha$ -hydroxylase. Persistently high PTH and the rapid reduction of FGF23 levels enhance the $1-\alpha$ -hydroxylase activity. Also FGF23

resistance can promote this enhancement. Levels of $25(\text{OH})\text{D}$ are reported to remain inappropriately low even during long follow-up after transplantation. Years after transplantation, PTH can remain persistently high, alongside normal or slightly high FGF23 levels.

post-transplant could inhibit $1-\alpha$ -hydroxylase and enhance $24-\alpha$ -hydroxylase, thereby reducing $1,25(\text{OH})_2\text{D}_3$ and $25(\text{OH})\text{D}$ levels, respectively (fig. 2) [31]. The interactions between FGF23 and PTH are very complex and have a fall-out on vitamin D metabolism. FGF23 and PTH mutually regulate each other in a negative feedback loop, where PTH stimulates FGF23 production, and FGF23 in turn suppresses PTH synthesis acting by the Klotho-FGFR1 complex in the parathyroid gland and via a calcineurin-dependent signaling pathway, although their relative contributions are unknown. In uremic patients, PTH

secretion remains elevated despite extremely high FGF23 levels. A decreased expression of the Klotho-FGFR1 complex in the parathyroid gland causes this parathyroid resistance to FGF23. Speculatively, the clinical use of calcineurin inhibitors (CNI) that block calcineurin signaling may increase the susceptibility to develop, or aggravate pre-existing, HPTH in patients with reduced Klotho expression such as in KTRs [32, 33]. At any rate, decreased FGF23 levels within 1 year [26] associated with FGF23 resistance, may account for the restored $1,25(\text{OH})_2\text{D}_3$ levels within 3–6 months after transplantation [22, 23].

Fig. 3. Effects of immunosuppressive therapy on bone and vitamin D metabolism. Steroids unbalance bone homeostasis between osteoblastic and osteoclastic activity. Steroids impair osteoblasts, enhancing apoptosis and impairing their genesis and functionality. At the same time, steroids enhance osteoclastic activity, by upregulation of the RANKL/OPG ratio. Steroids are also associated with

high PTH levels and also increase vitamin D catabolism, directly or via a potential activation of FGF23. CNI can increase the osteoclastic activity and induce vitamin D resistance through a direct downregulation of VDR. Sirolimus has been reported to be a bone-sparing immunosuppressor free from side effects on bone and vitamin D metabolism.

Immunosuppressive therapy anyhow contributes to vitamin D derangement, although the scientific literature is still scanty on the topic. Glucocorticoids alter vitamin D metabolism, expressing enzymes involved in vitamin D catabolism [34, 35] and increasing PTH and FGF23 levels (fig. 3). The cumulative prednisone dose was inversely correlated with $1,25(\text{OH})_2\text{D}_3$ levels 2 years after transplantation [30], and low $1,25(\text{OH})_2\text{D}$ levels could also be favored by higher FGF23 concentrations induced by steroid therapy [27, 36–38].

Discrepancies were observed between the effects of CNI and mTOR inhibitors on the vitamin D system (fig. 3). CNI was associated with lower $25(\text{OH})\text{D}$ levels among 289 KTRs, in agreement with previous experimental data [39] and animal models showing CNI-induced vitamin D resistance through VDR downregulation [40, 41]. By contrast, sirolimus had no effect on renal calcium excretion, vitamin D metabolism, calcium channel expression or calcium-binding proteins [38].

PTBD: Epidemiology and Mechanisms

KTRs commonly present PTBD, a disorder characterized by altered mineral metabolism with reduced bone quality, bone loss and an increased fracture risk. PTBD requires special attention when dealing with vitamin D derangement and vitamin D therapy for transplant recipients.

Significant bone loss was described during first year after transplantation with a 14.5% rate in the first 6 months, followed by mild improvement only after the second year post-transplant [42, 43]. Restoration of bone mineral density (BMD) within pre-transplant range was observed only 8 years after transplantation [44]. Although bone loss and bone frailty are well-established drawbacks in KTRs, reports on their prevalence vary widely. Osteoporosis ranged from 11 to 56% among long-term KTRs and paralleled the fracture risk between 5 and 44% [30]. Although the risk of fracture is high in KTRs, it was considerably lower up to 1–3 years after transplantation compared to that in dialysis patients [45].

The limitations of the diagnostic techniques available to assess PTBD merit particular consideration. Extraskel-etal calcifications and osteosclerosis impair the accuracy of dual-energy X-ray absorptiometry in assessing BMD, thereby limiting its reliability in predicting the risk of fractures. Furthermore, biomarkers of bone metabolism (PTH, osteocalcin, 25OHD) do not correlate with histological patterns. Bone biopsy remains the gold standard for the diagnosis of bone disease in KTRs, although it has limited routine applicability due to its invasive characteristics. Few studies have reported histological patterns of PTBD, describing a considerable prevalence of adynamic bone disease (5–50%), and high bone turnover (25–50%) [46–48]. More recent investigations observed a 48% rate of delayed mineralization, a 26% rate of low bone turnover, a 26% rate of high turnover and a 12% rate of mixed uremic bone disease 2 years after transplantation [36].

Persistent bone resorption associated with reduced osteoblastogenesis, impaired osteoblast function and increased osteoblast apoptosis represent the main triggers of impaired bone formation and mineralization in KTRs [30]. Similar derangements are influenced by (1) an imbalanced FGF23-PTH-vitamin D axis, (2) immunosuppressive therapy, (3) previous bone status, (4) allograft function and (5) hypophosphatemia. Among these conditions, HPTH seems to be predominant. Post-transplant HPTH can be differentiated into a maladaptive response (persistent HPTH) vs. a compensatory-adaptive response (de novo HPTH). Persistent HPTH results from

pre-existing CKD-MBD with secondary HPTH, likely to complicate post-transplant follow-up with hypercalcemia, hypophosphatemia, fracture risk [49, 50], vascular calcification [51] and loss of graft function [52–54]. Conversely, de novo HPTH results in raised PTH levels along with deterioration of graft function to maintain normophosphatemia and normocalcemia.

Immunosuppressive drugs may have a major impact on bone loss. Experimental models observed an association between the skeletal toxicity of immunosuppressive drugs and impaired vitamin D metabolism, increased PTH and FGF23 synthesis and altered bone remodeling mediated by the osteoprotegerin (OPG)-receptor activator of nuclear factor Kappa-B ligand (RANKL)-RANK pathway (fig. 3) [55–57]. Steroids directly worsen bone formation by impaired genesis and increased apoptosis of osteoblasts and enhanced osteoclastogenesis through an increased RANKL/OPG ratio [30]. Both cyclosporin and tacrolimus similarly promote bone loss via direct osteoclast activation [58], but sirolimus is administered as a bone-sparing immunosuppressive agent due to its capability to inhibit osteoclast generation [57, 59].

Vitamin D and Main Outcomes in KTRs: Observational Data

CVD is the leading cause of mortality in transplant recipients accounting for 36–55% of deaths with a functioning graft, representing 42% of total graft losses per se [60]. Vitamin D is currently considered protective against CVD due to the widespread pleiotropic effects elicited by VDRA.

The benefits of vitamin D on CVD have received widespread attention in CKD, but data among KTRs remain scanty. Although low vitamin D levels were not associated with a 3-year increased risk of CVD [61], more recent data from stable KTRs showed an independent association between 25(OH)D levels <12 ng/ml and all-cause mortality [21]. Flow-mediated dilation consensually proved to increase 25(OH)D levels close to restored renal function and reduced FGF23 levels [62].

Observational studies have investigated the correlation between vitamin D deficiency and graft outcomes. Reduced 25(OH)D levels, assessed 3 months after transplantation, were independently associated with lower GFR at 12-month follow-up [22] and a worse annual eGFR decline [21]. The strength of the association between 25(OH)D levels and graft function may be negatively influenced by the length of follow-up. Obi et al. [63]

observed a significant association between 25(OH)D deficiency and a rapid decline in kidney function only within 10 years after kidney transplantation. An inverse correlation between 25(OH)D levels and acute rejection may contribute to a time-dependent link between 25(OH)D deficiency and graft function [64]. No associations between 1,25(OH)₂D₃ levels and GFR trends have been observed in KTRs [21].

Interventional Studies with Native and Active Vitamin D on Graft Survival

Although effective management of acute rejection improves clinical outcomes during the early post-transplant period, loss of graft function secondary to chronic allograft damage remains a frequent complication for KTRs in the long run. Proteinuria is an important risk factor for graft loss in KTRs [65]. Accumulating experimental, epidemiological and clinical evidence supports raised proteinuria as a modifiable effector of fibrogenesis and glomerulosclerosis typical of non-transplant CKD progression [66–68]. The prevalence of proteinuria in KTRs varies considerably from 7.5 to 45% [69]. Furthermore, mild proteinuria (<500 mg/24 h) 1 year after transplant was associated with a fourfold increased risk of graft failure [65]. Nephrotic range proteinuria was even more closely associated with a 19 times higher risk of graft failure compared to non-proteinuric KTRs [65]. In 2009, the KDIGO guidelines suggested assessing proteinuria at least once within the first month after transplantation, every 3 months during the first year and annually thereafter [70].

The etiology of post-transplant proteinuria is likely to be multifactorial, including both allograft pathologies and the renal toxicity of immunosuppressive drugs. Reports on vitamin D therapy to improve graft survival are still scanty. Cholecalciferol supplementation 3–12 months after kidney transplant did not retrospectively modify the progression of GFR, or the onset of interstitial fibrosis/tubular atrophy and proteinuria (fig. 4) [71]. The ongoing VITALE study is comparing the effect of cholecalciferol at high vs. low doses (respectively 100,000 or 12,000 IU every 2 weeks for 2 months then monthly for 22 months) on proteinuria and graft survival as secondary outcomes [72]. Indeed, we are waiting to know the results of the VITA-D study, a randomized, placebo-controlled, double-blind study including a total of 200 KTRs, designed to investigate the immunomodulatory and renoprotective effects of cholecalciferol. KTRs found

to have vitamin D deficiency have been randomly assigned to receive either oral cholecalciferol therapy at a daily dose of 6,800 IU over a time period of one year or placebo [73].

Data on the anti-proteinuric effects of VDRA in KTRs sound encouraging (fig. 4). Paricalcitol at low doses (3 µg/week) was retrospectively associated with a significant 24-month reduction of proteinuria (from 1.1 ± 0.7 to 0.7 ± 0.7 g/24 h) among 58 KTRs, independently from changes in renal function or blood pressure [74]. Trillini et al. [75] described a significant 6-month reduction of proteinuria from 0.27 to 0.14 g/24 h ($p < 0.05$) in KTRs randomized to paricalcitol at escalating doses (1 µg/day for 3 months and then uptitrated to 2 µg/day if tolerated) without significant changes in the control arm. However, it should be noted that in this study, similarly with previous investigations in CKD patients [76, 77], paricalcitol treatment was associated with a slight increase in serum creatinine and creatinine clearance decrease. This finding was most likely explained by decreased creatinine tubular secretion, increased creatinine generation, or both. Authors concluded that a worsening of kidney function was unlikely because comparative analyses showed that activators of VDRs do not affect inulin clearance [77]. Lastly, the RAAS blockage is a known mechanism of renal protection with paricalcitol treatment, so we would expect to observe similar effects to RAAS blockers.

Amer et al. [78] randomized 100 incident KTRs to oral paricalcitol 2 µg/day vs. no treatment for the first year after transplantation, showing that changes in proteinuria after 1 year were comparable among patients receiving paricalcitol (from 169 to 91 mg/24 h) and controls (from 195 to 118 mg/24 h). Although the rate of mild interstitial fibrosis in 38 biopsies at 1 year was equally distributed in both study groups, moderate fibrosis was absent in the paricalcitol arm compared to controls (4 cases, $p = 0.04$). Notably, neither of these RCTs was designed to investigate the effect of paricalcitol on proteinuria as a primary outcome. Further dedicated RCTs are advocated to clarify whether active vitamin D administration may improve graft survival through a direct antiproteinuric effect.

Interventional Studies with Native and Active Vitamin D for Post-Transplant Bone Disorder

Several international guidelines recommend replenishment of vitamin D deficiency but show wide discrepancies concerning 25(OH)D target levels, specific indications across CKD stages and therapeutic schedules for

Fig. 4. Indications for vitamin D supplementation in KTRs. Data on the effect of nutritional vitamin D replacement on post-transplant proteinuria and PTBD are still scanty. More encouraging interventional studies reported the efficacy of VDRA on both

PTBD and proteinuria in KTRs. No RCTs have yet investigated whether the protective effect elicited by vitamin D on proteinuria and PTBD could improve graft survival and the risk of fractures in the long run.

supplementation [66, 79–82]. No specific guidelines currently address nutritional vitamin D replenishment in KTRs, leading to heterogeneous interventions to correct vitamin D deficiency in clinical studies. Although several studies reported a significant improvement in PTH and calcium levels in KTRs receiving nutritional vitamin D, the effects of ergocalciferol and cholecalciferol on BMD remain controversial (fig. 4) [83–85]. As previously mentioned, the VITALE trial has raised great expectations, as its secondary analysis will also compare the effect of high vs. low dose cholecalciferol on BMD at 2 years of follow-up [72].

Active vitamin D reduced PTH levels and improved BMD after transplantation (fig. 4) [86–88], thereby becoming a well-accepted preventive therapy against bone loss in KTRs with osteopenia or osteoporosis [30, 89]. A clinical investigation by Gonzalez et al. [74] reported that paricalcitol induced a 30% reduction of PTH levels in 78% of 58 KTRs at 24 months of follow-up, although no data were provided on the BMD trend. Amer et al. [78] found a greater PTH reduction and a lower prevalence of HPTH (29–63%) in KTRs receiving paricalcitol compared to controls. However, improved HPTH was not accompanied by benefits on osteopenia [78]. In the

previously mentioned RCT by Trillini et al. [75], patients randomized to paricalcitol improved L3 and L4 vertebral BMD as well as reduced serum levels of bone formation biomarkers like osteocalcin and bone alkaline phosphatase, and reduced urinary levels of deoxypyridinoline, a biomarker of osteoclastic-mediated bone resorption. In addition, paricalcitol therapy was not associated with a higher risk of hypercalcemia, the few hypercalcemic episodes being easily reversed by a down-titration of dosage.

Conclusion and Future Perspectives

KTRs commonly present vitamin D derangement consisting in both 25(OH)D deficiency and reduced levels of 1,25(OH)₂D₃. The resulting impairment of VDRA is likely to contribute to PTBD, graft aging and vascular disease. Perturbation of the vitamin D system after transplantation is multifactorial, being influenced by allograft function, HPTH, altered FGF23 levels and immunosuppressive therapy.

Unfortunately, specific recommendations on the optimal 25(OH)D targets in KTRs and the relative interventions to achieve them are still lacking. While awaiting an appropriately designed RCT to investigate this issue, the KDIGO guidelines could be applied in KTRs to replenish 25(OH)D levels <30 ng/ml as a first-line therapy against HPTH. Although the protective effect of nutritional vitamin D supplementation in KTRs seems reasonable against post-transplant proteinuria, CVD and PTBD, further ad hoc RCTs are advocated to test its real effectiveness compared to placebo.

Clinical data support the efficacy of VDRA against HPTH and show promising evidence of VDRA's protective effect in counteracting post-transplant proteinuria. However, new insights are mandatory to establish if the

improvement of surrogate outcomes will translate into better graft survival with a lower incidence of PTBD and cardiovascular events.

Immunosuppressive therapy can significantly modulate the vitamin D system and bone turnover. Steroids and CNIs are associated with vitamin D derangement and increased osteoclast activity, whereas sirolimus had no effect on either vitamin D or skeletal health. Further studies are advocated to investigate vitamin D therapies tailored to specific immunosuppressive regimens.

Meanwhile, we suggest that in the post-transplant phase, vitamin D deficiency be corrected with 25,000 IU on a monthly basis. The prevention of osteoporosis in KTRs may benefit from a timely pre-transplant parathyroidectomy in the presence of uncontrolled HPTH. In the post-transplantation period, we suggest: (a) hip and lateral spine radiographs to screen for bone fragility or fractures (clinically silent) within 1 year after transplantation; (b) in selected patients DEXA scans at the time of transplantation or within the first 3 months, particularly if patients have other risk factors for rapid bone loss. DEXA scans can be repeated at 12-month intervals if BMD decreases by >5% or otherwise every 2 years; (c) in high-risk patients for PTBD, we evaluate the use of steroid-sparing and steroid-withdrawal protocols; (d) calcimimetics in KTRs with persistent HPTH and hypercalcemia or PCT, if the patients have not hypercalcemia and especially if coexists proteinuria; (e) parathyroidectomy if HPTH persists for more than 1 year after transplantation with associated symptomatic bone disease, spontaneous fracture, vascular calcification, and calciphylaxis.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

- 1 Wolfe RA, Ashby VB, Milford EL, et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725–1730.
- 2 Tonelli M, Wiebe N, Knoll G, et al: Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant* 2011;11:2093–2109.
- 3 Sellarés J, de Freitas DG, Mengel M, et al: Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence. *Am J Transplant* 2012;12:388–399.
- 4 Weiner DE, Carpenter MA, Levey AS, et al: Kidney function and risk of cardiovascular disease and mortality in kidney transplant recipients: the FAVORIT trial. *Am J Transplant* 2012;12:2437–2445.
- 5 Ojo AO, Morales JM, González-Molina M, et al: Scientific Registry of Transplant Recipients and; Spanish Chronic Allograft Study Group: Comparison of the long-term outcomes of kidney transplantation: USA versus Spain. *Nephrol Dial Transplant* 2013;28:213–220.
- 6 Galassi A, Bellasi A, Papagni S, et al: Which vitamin D in CKD-MBD? The time of burning questions. *Biomed Res Int* 2013;2013:864012.
- 7 Courbebaisse M, Souberbielle JC, Thervet E: Potential nonclassical effects of vitamin D in transplant recipients. *Transplantation* 2010;89:131–137.
- 8 Holick MF: Vitamin D deficiency. *N Engl J Med* 2007;357:266–281.

- 9 Ormsby RT, Findlay DM, Kogawa M, et al: Analysis of vitamin D metabolism gene expression in human bone: evidence for auto-crane control of bone remodelling. *J Steroid Biochem Mol Biol* 2014;144:110–113.
- 10 Vaidya A, Williams JS: Vitamin D and insulin sensitivity: can gene association and pharmacogenetic studies of the vitamin D receptor provide clarity? *Metabolism* 2012;61:759–761.
- 11 Gonzalez-Parra E, Rojas-Rivera J, Tuñón J, et al: Vitamin D receptor activation and cardiovascular disease. *Nephrol Dial Transplant* 2012;27(suppl 4):iv17–iv21.
- 12 Thacher TD, Clarke BL: Vitamin D insufficiency. *Mayo Clin Proc* 2011;86:50–60.
- 13 Bover J, Cozzolino M: Mineral and bone disorders in chronic kidney disease and end-stage renal disease patients: new insights into vitamin D receptor activation. *Kidney Int Suppl* (2011) 2011;1:122–129.
- 14 Li YC, Qiao G, Uskokovic M, et al: Vitamin D: a negative endocrine regulator of the renin-angiotensin system and blood pressure. *J Steroid Biochem Mol Biol* 2004;89–90:387–392.
- 15 Zhang Z, Sun L, Wang Y, et al: Renoprotective role of the vitamin D receptor in diabetic nephropathy. *Kidney Int* 2008;73:163–171.
- 16 Tan X, Li Y, Liu Y: Paricalcitol attenuates renal interstitial fibrosis in obstructive nephropathy. *J Am Soc Nephrol* 2006;17:3382–3393.
- 17 de Borst MH, Hajhosseiny R, Tamez H, et al: Active vitamin D treatment for reduction of residual proteinuria: a systematic review. *J Am Soc Nephrol* 2013;24:1863–1871.
- 18 Boudville NC, Hodsman AB: Renal function and 25-hydroxyvitamin D concentrations predict parathyroid hormone levels in renal transplant patients. *Nephrol Dial Transplant* 2006;21:2621–2624.
- 19 Querings K, Girndt M, Geisel J, et al: 25-Hydroxyvitamin D deficiency in renal transplant recipients. *J Clin Endocrinol Metab* 2006;91:526–529.
- 20 Sadlier DM, Magee CC: Prevalence of 25(OH) vitamin D (calcidiol) deficiency at time of renal transplantation: a prospective study. *Clin Transplant* 2007;21:683–688.
- 21 Keyzer CA, Riphagen IJ, Joosten MM, et al: Associations of 25(OH) and 1,25(OH)₂ vitamin D with long-term outcomes in stable renal transplant recipients. *J Clin Endocrinol Metab* 2015;100:81–89.
- 22 Bienaimé F, Girard D, Anglicheau D, et al: Vitamin D status and outcomes after renal transplantation. *J Am Soc Nephrol* 2013;24:831–841.
- 23 Barros X, Fuster D, Rodríguez N, et al: Rapid calcitriol increase and persistent calcidiol insufficiency in the first 6 months after kidney transplantation. *Nucl Med Commun* 2015;36:489–493.
- 24 Douthat WG, Chiurciu CR, Massari PU: New options for the management of hyperparathyroidism after renal transplantation. *World J Transplant* 2012;2:41–45.
- 25 Economidou D, Dovas S, Papagianni A, et al: FGF-23 Levels before and after renal transplantation. *J Transplant* 2009;2009:379082.
- 26 Evenepoel P, Meijers BK, de Jonge H, et al: Recovery of hyperphosphatonaemia and renal phosphorus wasting one year after successful renal transplantation. *Clin J Am Soc Nephrol* 2008;3:1829–1836.
- 27 Sánchez Fructuoso AI, Maestro ML, Pérez-Flores I, et al: Serum level of fibroblast growth factor 23 in maintenance renal transplant patients. *Nephrol Dial Transplant* 2012;27:4227–4235.
- 28 Mazzaferro S, Pasquali M, Pugliese F, et al: Distinct impact of vitamin D insufficiency on calcitriol levels in chronic renal failure and renal transplant patients: a role for FGF23. *J Nephrol* 2012;25:1108–1118.
- 29 Dusso AS, Finch J, Brown A, et al: Extrarenal production of calcitriol in normal and uremic humans. *J Clin Endocrinol Metab* 1991;72:157–164.
- 30 Alshayeb HM, Josephson MA, Sprague SM: CKD-mineral and bone disorder management in kidney transplant recipients. *Am J Kidney Dis* 2013;61:310–325.
- 31 Sanchez Fructuoso AI, Maestro ML, Calvo N, et al: Role of fibroblast growth factor 23 (FGF23) in the metabolism of phosphorus and calcium immediately after kidney transplantation. *Transplant Proc* 2012;44:2551–2554.
- 32 Krajisnik T, Olauson H, Mirza MA, et al: Parathyroid Klotho and FGF-receptor 1 expression decline with renal function in hyperparathyroid patients with chronic kidney disease and kidney transplant recipients. *Kidney Int* 2010;78:1024–1032.
- 33 Olauson H, Lindberg K, Amin R, et al: Parathyroid-Specific deletion of klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulates PTH secretion. *PLoS Genet* 2013;9:e1003975.
- 34 Pascucci JM, Robert A, Nguyen M, et al: Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. *J Clin Invest* 2005;115:177–186.
- 35 Akeno N, Matsunuma A, Maeda T, et al: Regulation of vitamin D-1 α -hydroxylase and -24-hydroxylase expression by dexamethasone in mouse kidney. *J Endocrinol* 2000;164:339–348.
- 36 Neves CL, dos Reis LM, Batista DG, et al: Persistence of bone and mineral disorders 2 years after successful kidney transplantation. *Transplantation* 2013;96:290–296.
- 37 Bacchetta J, Dubourg L, Harambat J, et al: The influence of glomerular filtration rate and age on fibroblast growth factor 23 serum levels in pediatric chronic kidney disease. *J Clin Endocrinol Metab* 2010;95:1741–1748.
- 38 Wesseling-Perry K, Tsai EW, Ettenger RB, et al: Mineral abnormalities and long-term graft function in pediatric renal transplant recipients: a role for FGF-23? *Nephrol Dial Transplant* 2011;26:3779–3784.
- 39 Filipov JJ, Zlatkov BK, Dimitrov EP, et al: Relationship between vitamin D status and immunosuppressive therapy in kidney transplant recipients. *Biotechnol Biotechnol Equip* 2015;29:331–335.
- 40 Lee CT, Ng HY, Lien YH, et al: Effects of cyclosporine, tacrolimus and rapamycin on renal calcium transport and vitamin D metabolism. *Am J Nephrol* 2011;34:87–94.
- 41 Grenet O, Bobadilla M, Chibout SD, et al: Evidence for the impairment of the vitamin D activation pathway by cyclosporine A. *Biochem Pharmacol* 2000;59:267–272.
- 42 Brandenburg VM, Politt D, Ketteler M, et al: Early rapid loss followed by long-term consolidation characterizes the development of lumbar bone mineral density after kidney transplantation. *Transplantation* 2004;77:1566–1571.
- 43 Kodras K, Haas M: Effect of kidney transplantation on bone. *Eur J Clin Invest* 2006;36(suppl 2):63–75.
- 44 Carlini RG, Rojas E, Weisinger JR, et al: Bone disease in patients with long-term renal transplantation and normal renal function. *Am J Kidney Dis* 2000;36:160–166.
- 45 Ball AM, Gillen DL, Sherrard D, Weiss NS, et al: Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 2002;288:3014–3018.
- 46 Brandenburg VM, Westenfeld R, Ketteler M: The fate of bone after renal transplantation. *J Nephrol* 2004;17:190–204.
- 47 Lehmann G, Ott U, Stein G, et al: Renal osteodystrophy after successful renal transplantation: a histomorphometric analysis in 57 patients. *Transplant Proc* 2007;39:3153–3158.
- 48 Borchhardt K, Sulzbacher I, Benesch T, et al: Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. *Am J Transplant* 2007;7:2515–2521.
- 49 Perrin P, Caillard S, Javier RM, et al: Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. *Am J Transplant* 2013;13:2653–2663.
- 50 Giannini S, D'Angelo A, Nobile M, et al: The effects of vitamin D receptor polymorphism on secondary hyperparathyroidism and bone density after renal transplantation. *J Bone Miner Res* 2002;17:1768–1773.
- 51 Mazzaferro S, Pasquali M, Taggi F, et al: Progression of coronary artery calcification in renal transplantation and the role of secondary hyperparathyroidism and inflammation. *Clin J Am Soc Nephrol* 2009;4:685–690.
- 52 Gwinner W, Suppa S, Mengel M, et al: Early calcification of renal allografts detected by protocol biopsies: causes and clinical implications. *Am J Transplant* 2005;5:1934–1941.
- 53 Nankivell BJ, Borrows RJ, Fung CL, et al: The natural history of chronic allograft nephropathy. *N Engl J Med* 2003;349:2326–2333.
- 54 Schwarz A, Mengel M, Gwinner W, et al: Risk factors for chronic allograft nephropathy after renal transplantation: a protocol biopsy study. *Kidney Int* 2005;67:341–348.

- 55 Fukunaga J, Yamaai T, Yamachika E, et al: Expression of osteoclast differentiation factor and osteoclastogenesis inhibitory factor in rat osteoporosis induced by immunosuppressant FK506. *Bone* 2004;34:425–431.
- 56 Hirotani H, Tuohy NA, Woo JT, et al: The calcineurin/nuclear factor of activated T cells signaling pathway regulates osteoclastogenesis in RAW264.7 cells. *J Biol Chem* 2004;279:13984–13992.
- 57 Westenfeld R, Schlieper G, Wöltje M, et al: Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis – implications for post-transplantation bone disease. *Nephrol Dial Transplant* 2011;26:4115–4123.
- 58 Giannini S, Sella S, Silva Netto F, et al: Persistent secondary hyperparathyroidism and vertebral fractures in kidney transplantation: role of calcium-sensing receptor polymorphism and vitamin D deficiency. *J Bone Miner Res* 2010;25:841–848.
- 59 Campistol JM, Holt DW, Epstein S, et al: Sirolimus European Renal Transplant Study Group: Bone metabolism in renal transplant patients treated with cyclosporine or sirolimus. *Transpl Int* 2005;18:1028–1035.
- 60 Kahwaji J, Bunnapradist S, Hsu JW, et al: Cause of death with graft function among renal transplant recipients in an integrated healthcare system. *Transplantation* 2011;91:225–230.
- 61 Marcén R, Jimenez S, Fernandez-Rodriguez A, et al: Are low levels of 25-hydroxyvitamin D a risk factor for cardiovascular diseases or malignancies in renal transplantation? *Nephrol Dial Transplant* 2012;27(suppl 4):iv47–iv52.
- 62 Yilmaz MI, Sonmez A, Saglam M, et al: Longitudinal analysis of vascular function and biomarkers of metabolic bone disorders before and after renal transplantation. *Am J Nephrol* 2013;37:126–134.
- 63 Obi Y, Hamano T, Ichimaru N, et al: Vitamin D deficiency predicts decline in kidney allograft function: a prospective cohort study. *J Clin Endocrinol Metab* 2014;99:527–535.
- 64 Lee JR, Dadhania D, August P, et al: Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. *Transplantation* 2014;98:292–299.
- 65 Amer H, Cosio FG: Significance and management of proteinuria in kidney transplant recipients. *J Am Soc Nephrol* 2009;20:2490–2492.
- 66 Astor BC, Matsushita K, Gansevoort RT, et al: Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int* 2011;79:1331–1340.
- 67 Gansevoort RT, Matsushita K, van der Velde M, et al: Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int* 2011;80:93–104.
- 68 Ruggenenti P, Perna A, Mosconi L, et al: Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. 'Gruppo Italiano di Studi Epidemiologici in Nefrologia' (GISEN). *Kidney Int* 1998;53:1209–1216.
- 69 Shamseddin MK, Knoll GA: Posttransplantation proteinuria: an approach to diagnosis and management. *Clin J Am Soc Nephrol* 2011;6:1786–1793.
- 70 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group: KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int* 2009;113:S1–S130.
- 71 Courbebaisse M, Xu-Dubois YC, Thervet E, et al: Cholecalciferol supplementation does not protect against renal allograft structural and functional deterioration: a retrospective study. *Transplantation* 2011;91:207–212.
- 72 Courbebaisse M, Alberti C, Colas S, et al: Vitamin D supplementation in renal transplant recipients (VITALE): a prospective, multi-centre, double-blind, randomized trial of vitamin D estimating the benefit and safety of vitamin D3 treatment at a dose of 100,000 UI compared with a dose of 12,000 UI in renal transplant recipients: study protocol for a double-blind, randomized, controlled trial. *Trials* 2014;15:430.
- 73 Thiem U, Heinze G, Segel R, et al: VITA-D: cholecalciferol substitution in vitamin D deficient kidney transplant recipients: a randomized, placebo-controlled study to evaluate the post-transplant outcome. *Trials* 2009;10:36.
- 74 Gonzalez E, Rojas-Rivera J, Polanco N, et al: Effects of oral paricalcitol on secondary hyperparathyroidism and proteinuria of kidney transplant patients. *Transplantation* 2013;95:e49–e52.
- 75 Trillini M, Cortinovis M, Ruggenenti P, et al: Paricalcitol for secondary hyperparathyroidism in renal transplantation. *J Am Soc Nephrol* 2015;26:1205–1214.
- 76 de Zeeuw D, Agarwal R, Amdahl M, Audhya P, et al: Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. *Lancet* 2010;376:1543–1551.
- 77 Agarwal R, Hynson JE, Hecht TJ, et al: Short-term vitamin D receptor activation increases serum creatinine due to increased production with no effect on the glomerular filtration rate. *Kidney Int* 2011;80:1073–1079.
- 78 Amer H, Griffin MD, Stegall MD, et al: Oral paricalcitol reduces the prevalence of post-transplant hyperparathyroidism: results of an open label randomized trial. *Am J Transplant* 2013;13:1576–1585.
- 79 KDIGO CKD Work Group: KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;3:1–150.
- 80 Anderson PH, Lam NN, Turner AG, et al: The pleiotropic effects of vitamin D in bone. *J Steroid Biochem Mol Biol* 2013;136:190–194.
- 81 Goldsmith DJ, Covic A, Fouque D, et al: Endorsement of the kidney disease improving global outcomes (KDIGO) chronic kidney disease-mineral and bone disorder (CKD-MBD) guidelines: a European renal best practice (ERBP) commentary statement. *Nephrol Dial Transplant* 2010;25:3823–3831.
- 82 NICE National Institute for Health and Care Excellence: Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care, 2014.
- 83 Wissing KM, Broeders N, Moreno-Reyes R, et al: A controlled study of vitamin D3 to prevent bone loss in renal-transplant patients receiving low doses of steroids. *Transplantation* 2005;79:108–115.
- 84 Sahin G, Yasar NS, Sirmagul B, Bal C, Yalcin AU: The effect of low-dose cholecalciferol and calcium treatment on posttransplant bone loss in renal transplant patients: a prospective study. *Ren Fail* 2008;30:992–999.
- 85 Courbebaisse M, Thervet E, Souberbielle JC, et al: Effects of vitamin D supplementation on the calcium-phosphate balance in renal transplant patients. *Kidney Int* 2009;75:646–651.
- 86 Steiner RW, Ziegler M, Halasz NA, et al: Effect of daily oral vitamin D and calcium therapy, hypophosphatemia, and endogenous 1–25 dihydroxycholecalciferol on parathyroid hormone and phosphate wasting in renal transplant recipients. *Transplantation* 1993;56:843–846.
- 87 Cueto-Manzano AM, Konel S, Freemont AJ, et al: Effect of 1,25-dihydroxyvitamin D3 and calcium carbonate on bone loss associated with long-term renal transplantation. *Am J Kidney Dis* 2000;35:227–236.
- 88 Torres A, García S, Gómez A, et al: Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. *Kidney Int* 2004;65:705–712.
- 89 Mainra R, Elder GJ: Individualized therapy to prevent bone mineral density loss after kidney and kidney-pancreas transplantation. *Clin J Am Soc Nephrol* 2010;5:117–124.