J Nephrol (2016) 29:305–328
DOI 10.1007/s40620-016-0305-6

POSITION PAPERS AND GUIDELINES

Vitamin D in patients with chronic kidney disease: a position statement of the Working Group "Trace Elements and Mineral Metabolism" of the Italian Society of Nephrology

Luigi Francesco Morrone[1] · Pergiorgio Bolasco[2] · Corrado Camerini[3] · Giuseppe Cianciolo[4] · Adamasco Cupisti[5] · Andrea Galassi[6] · Sandro Mazzaferro[7] · Domenico Russo[8] · Luigi Russo[8] · Mario Cozzolino[9]

Received: 14 January 2016 / Accepted: 30 March 2016 / Published online: 9 April 2016

Abstract In the late 1970s, calcitriol was introduced into clinical practice for the management of secondary renal hyperparathyroidism in chronic kidney disease (CKD). Since then, the use of calcifediol or other native forms of vitamin D was largely ignored until the publication of the 2009 Kidney Disease Improving Global Outcomes (KDIGO) recommendations. The guidelines suggested that measurement of circulating levels of 25(OH)D (calcifediol) and its supplementation were to be performed on the same basis as for the general population. This indication was based on the fact that the precursors of active vitamin D had provided to CKD patients considerable benefits in survival, mainly due to their pleiotropic effects on the cardiovascular system. However, despite the long-term use of various classes of vitamin D in CKD, a clear definition is still lacking concerning the most appropriate time for initiation of therapy, the best compound to prescribe (active metabolites or analogs), the proper dosage, and the most suitable duration of therapy. The aim of this position statement is to provide and critically appraise the current plentiful evidence on vitamin D in different clinical settings related to CKD, particularly focusing on outcomes, monitoring and treatment-associated risks. However, it should be taken in account that position statements are meant to provide guidance; therefore, they are not to be considered prescriptive for all patients and, importantly, they cannot replace the judgment of clinicians.

Keywords Vitamin D · Chronic kidney disease · Dialysis · Kidney transplantation

✉ Luigi Francesco Morrone
lfmorrone@gmail.com

[1] Nephrology, Dialysis and Renal Transplantation Unit, University Hospital "Policlinico", Bari, Italy

[2] Territorial Unit of Nephrology and Dialysis-ASL 8 of Cagliari, Cagliari, Italy

[3] Operative Unit of Nephrology, AO Spedali Civili di Brescia and University of Brescia, Brescia, Italy

[4] Nephrology Dialysis and Renal Transplantation Unit, S. Orsola University Hospital, Bologna, Italy

[5] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[6] Renal Unit, AO Desio-Vimercate, Desio, Italy

[7] Department of Cardiovascular Respiratory Nephrologic Anesthetic and Geriatric Sciences, Sapienza University of Rome, Rome, Italy

[8] Department of Public Health, Unit of Nephrology and Hypertension, University of Naples Federico II, Naples, Italy

[9] Renal Division and Laboratory of Experimental Nephrology, Department of Health Sciences, San Paolo Hospital, University of Milan, Milan, Italy

Introduction

The native form of vitamin D is produced endogenously from cholesterol as vitamin D3 (cholecalciferol). In skin, 7-dehydrocholesterol is converted to pre-vitamin D3 by a narrow band of solar ultraviolet (UV) radiation (290–315 nm) and thereafter it is isomerized by the body's temperature to vitamin D3 [1]. On the other hand, vitamin D2 (ergocalciferol) is derived from the sterol ergosterol of plants and the main intake is through diet. However, only less than one-third of the native form of vitamin D originates from food as vitamin D2 or as vitamin D3 [2]. Of note, very few foods contain vitamin D (e.g. fatty fish, fish liver oil, mushrooms and egg yolk) and vitamin D status is generally maintained by exposure to sunlight [3].

If sunlight exposure is adequate, dietary supplementation of vitamin D can be unnecessary [4]. In contrast to

intermittent, short-term, high-dose solar UV-exposure, a more chronic and less intense exposure is recommended to obtain a sufficient vitamin D status without increasing the risk for skin cancer [5]. Indeed, vitamin D has been shown to inhibit proliferation and induce differentiation in melanoma cells [6]. But although some data suggest a protective role for vitamin D and/or analogs in the prevention and treatment of melanoma and other skin cancers, other data indicate a potential association between vitamin D levels and incidence of these neoplasms [7, 8]. Whether the beneficial effect of sunlight exposure in terms of dermal vitamin D production may overcome the risk of neoplastic skin lesions depends on several factors, including skin phototype and genetic susceptibility to the disease [7, 9]. In general, the question of how much sunlight we need to produce enough vitamin D without increasing the risk of skin cancer is still debated. However, there is no doubt regarding the fact that sunburn certainly causes melanoma and it must be avoided, also given that sunburn does not activate more vitamin D [10].

The dermal production of vitamin D is not an enzymatic process [11]. The D2 and D3 differ only in their structure and the differences do not affect the activation process. Both forms function as prohormones and when activated exhibit identical biological responses [12]. Conversely, the main steps in vitamin D metabolism, such as 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation are all enzymatic processes performed by cytochrome P450 mixed-function oxidases (CYPs). The liver is the major if not sole source of 25(OH)D production from native vitamin D. The native vitamin D2 and D3 are both 25-hydroxylated to 25(OH)D (calcidiol or calcifediol) by several 25-hydroxlases, such as CYP27A1 and CYP2R1 [11].

CYP2R1 25-hydroxylates both D2 and D3, unlike CYP27A1 which does not 25-hydroxylate vitamin D2. Thus, CYP2R1 appears to be the major 25-hydroxylase, but other enzymes may have different degrees of 25-hydroxylase activity, such as CYP3A4, CYP2J2/3, CYP2D11, CYP2C11 and CYP2D25 [13]. The hepatic 25-hydroxylation is induced by the availability of the substrate D2 and D3 and is not inhibited by the concentrations of its product 25(OH)D. Thus regulation of vitamin D 25-hydroxylation is not a major concern, and circulating levels of 25(OH)D are commonly considered useful markers of vitamin D status. Nevertheless, the kidney is essential for maintaining adequate serum 25(OH)D levels by means of the megalin-mediated uptake of 25(OH)D from the glomerular ultrafiltrate and its recycling into to the circulation [14].

The 25(OH)D uptaken from the glomerular ultrafiltrate may also be 1-α-hydroxylated in the kidney to produce the fully active form $1,25(OH)_2D$ (calcitriol). Unlike 25-hydroxylation, there is only one enzyme recognized to have 1α-hydroxylase activity, i.e. CYP27B1. Unlike the hepatic 25-hydroxylases, the renal 1-α-hydroxylase is substrate-independent but is tightly regulated by several factors. In the kidney the activity of CYP27B1 is primarily stimulated by parathyroid hormone (PTH) and suppressed by both fibroblast growth factor 23 (FGF23), and $1,25(OH)_2D$ itself [11]. The renal CYP27B1 activity can be secondarily suppressed by calcium via PTH as well as by phosphate via FGF23, although a direct effect of these ions on renal 1α-hydroxylation cannot be excluded. Of note, circulating 25(OH)D can also be 1-α-hydroxylated in extrarenal cells that express CYP27B1, such as keratinocytes and macrophages. Regulation of extrarenal CYP27B1 differs from the renal one: it is site-dependent, and involves several hormones and inflammatory molecules [15]. However the kidney is the major if not sole source of circulating $1,25(OH)_2D$ and its extrarenal percentage is negligible [11].

Both calcidiol and calcitriol are transported in the blood by the vitamin D binding protein (DBP) and are catabolized through a 24-hydroxylation process involving the 24-hydroxylase CYP24A1 [16]. Interestingly, the circulating calcitriol levels are in the picomolar range, while circulating calcidiol has a much higher concentration in the nanomolar range. DBP is produced primarily by the liver and represents the major carrier protein of 25(OH)D and its metabolites in the circulation. Most 25(OH)D and $1,25(OH)_2D$ circulates as bound to DBP (85–90 %) [17]. A smaller part circulates weakly bound to albumin, while less than 1 % circulates in its free form [18]. The DBP-bound vitamin D is relatively unavailable to target tissues, hence DBP levels or affinity could affect both vitamin D bioactivity and bone health [17]. The circulating DBP-bound vitamin D reaches the liver, kidney and other cellular activation sites and is stored in the adipose tissue. Finally, the bioactive vitamin D fraction exerts its biological functions in target tissues and is catabolized by 24-hydroxylase (CYP24A1) to inactive forms. The ubiquitous CYP24A1 represents a powerful catabolic enzyme provided with both 24-hydroxylase and 23-hydroxylase activities, hence being able to prevent the accumulation of toxic levels of $1,25(OH)_2D$ and 25(OH)D [19]. The regulation of CYP24A1 is reciprocal to that of CYP27B1, or at least this is so in the kidney [20]. The activity of CYP24A1 produces the biologically inactive calcitroic acid, but it is also able to induce few biologically active metabolites.

All genomic actions of biologically active vitamin D are mediated by the vitamin D receptor (VDR). Ubiquitously present in cells and tissues, the VDR exerts an extensive biological response, when activated by ligand-binding, via regulation of gene transcription and stimulation of intracellular signaling pathways [21]. The profile of VDR bioactivity and involved genes varies from cell to cell, but the active transcription unit is predominantly, although not exclusively, the VDR/RXR heterodimer [11]. The major

endocrine action of VDR is to regulate mineral and bone homeostasis in intestinal, renal and bone tissues. In fact, VDR activation leads to calcium and phosphate intestinal absorption as well as to renal calcium tubular reabsorption [22, 23]. Of note, vitamin D activity can directly regulate bone metabolism when insufficient calcium is acquired through diet or absorbed by the intestine, enhancing bone resorption and suppressing bone matrix mineralization [24, 25]. In addition, VDR activation suppresses PTH secretion by parathyroid glands and enhances FGF23 production by osteocytes [26, 27]. More recently, vitamin D has been shown to exert autocrine or paracrine activities in multiple cell functions including inhibition of cellular proliferation and stimulation of cell maturation which may involve skin, the immune system and colonic, breast and prostate cells [28].

Indeed vitamin D activity depends firstly on an adequate vitamin D status, as indicated by the circulating level of 25(OH)D. Reports outlining significant health risks associated with inadequate vitamin D status generate considerable interest in the scientific and medical communities. In chronic kidney disease (CKD) and other chronic disorders, vitamin D insufficiency (serum 25(OH)D <30 ng/ml) is very common and is associated with adverse outcomes [29], but intervention studies and randomized controlled trials (RCTs) in this field are still lacking. Plasma levels of 25(OH)D should be measured during the late summer and winter months because vitamin D levels show seasonal variation related to sun exposure [30]. Nevertheless, diverse forms of vitamin D have been used by nephrologists from many years in the prevention and treatment of renal hyperparathyroidism. In the last two decades, selective active vitamin D metabolites (paricalcitol, maxacalcitol) have been used to reduce circulating PTH with minor changes in calcium and phosphate concentrations compared to the non-selective calcitriol. However, there are many open questions regarding the optimal nutritional vitamin D to prescribe, and the most suitable dose and effectiveness of co-administration of nutritional vitamin with active vitamin D compounds. The latter issue is of clinical relevance in treating CKD patients who frequently have both hyperparathyroidism and 25(OH)D deficiency.

Vitamin D in non-dialysis CKD patients

Therapy with nutritional and active vitamin D in predialysis CKD patients pivots on four major issues: (1) how to deal with 25(OH)D deficiency, (2) when and how to treat secondary hyperparathyroidism and CKD mineral bone disorders (CKD-MBD), (3) potential efficacy of different formulations of vitamin D on proteinuria, left ventricular hypertrophy (LVH) and anemia, (4) existing evidence-based effects of vitamin D administration on clinical hard endpoints.

Although the correction of low 25(OH)D serum levels is encouraged by observational data linking 25(OH)D deficiency to unfavorable clinical outcomes and mortality risk in the general population and CKD patients [31–39], the optimal targets of 25(OH)D circulating levels and the best approach to obtain vitamin D replenishment remain unknown. Many international guidelines have provided heterogeneous definitions of 25(OH)D deficiency and insufficiency and they suggest different therapeutic strategies for 25(OH)D replenishment in the general population [40–42] and in CKD patients [43–47] (Table 1). Notably, the thresholds of a normal 25(OH)D range remain uncertain and are mainly based on epidemiological data derived from the general population. Furthermore, the normality of 25(OH)D levels should be in reference to the expected vitamin D actions as PTH secretion and bone health, at least. A deeper discussion about the normal 25(OH)D levels remains beyond the scope of the present position paper. Thus, in agreement with renal guidelines, it is the opinion of the Authors of this consensus statement that the achievement of 25(OH)D levels >30 ng/ml seems a reasonable target for the prevention and treatment of secondary hyperparathyroidism in CKD patients. Three nutritional forms are currently available for 25(OH)D replenishment: the two pro-drugs cholecalciferol and ergocalciferol (both requiring conversion by hepatic 25-α-hydroxylase to $25(OH)D_3$ or $25(OH)D_2$, respectively) and calcifediol (already available as $25(OH)D_3$). Many studies have indicated a potential superiority of cholecalciferol vs. ergocalciferol in increasing 25(OH)D levels [48–50]. Nonetheless, the levels of 25(OH)D are not always completely corrected; therefore alternative regimens with cholecalciferol and ergocalciferol supplementation have been proposed to reach the therapeutic levels of 25(OH)D as suggested by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [51–53]. More recently, calcifediol, in a modified-release formulation, resulted effective in increasing 25(OH)D levels in a dose-dependent manner among non-dialysis CKD patients compared to placebo [54]. Regardless of the preferred regime, in predialysis CKD patients treatment with cholecalciferol, ergocalciferol and calcifediol should be discontinued in the presence of 25(OH)D levels >100 ng/ml and/or with persistent serum calcium levels >10.5 mg/dl in the absence of active vitamin D administration. Attention should be paid in the presence of potentially increased 1-α-hydroxylase activity, as in transplanted patients and in those affected by sarcoidosis or B cell lymphoma, where 25(OH)D levels even lower than 100 ng/ml may result toxic. It is the Authors' opinion that nephrologists should adopt the

Table 1 Nutritional vitamin D in pre-dialysis CKD: guidelines

Guidelines	25(OH)D assessment	25(OH)D targets	Replenishment	Therapeutic indication
KDOQI 2003 [K/DOQI 2003 Am J Kidney Dis]	In the presence of PTH above the recommended range	≥30 ng/ml	6 months course of ergocalciferol at escalating doses according to basal levels 25(OH)D <5 ng/ml: 50,000 IU/week orally for 12 weeks then monthly or 500,000 IU as single IM dose 25(OH)D 5–15 ng/ml: 50,000 IU/week orally for 4 weeks then monthly 25(OH)D 15–50 ng/ml 50,000 IU/month orally	First line therapy against SHPT
KDIGO 2009 [KDIGO (2009) Kidney Int suppls]	At baseline and during further treatment in CKD 3–5D	As suggested for general population	–	First line therapy against SHPT
KDIGO 2012 [KDIGO CKD (2012). Kidney Int Suppl]	Do not assess 25(OH)D routinely in the absence of suspected deficiency	–	–	Not to be prescribed in the absence of deficiency to suppress PTH
ERBP 2010 [Goldsmith DJA (2010). Nephrol Dial Transplant]	At least once in CKD 3–4	25(OH)D levels >30 ng/ml as normal; replenish if 25(OH)D <12.5 ng/ml	–	Treat SHPT and offer potential Vitamin D pleiotropic effects
NICE 2014 [NICE guidance.nice.org.uk/cg182]	In all patients with CKD 4–5	≥20 ng/ml	–	Treat 25(OH)D deficiency and SHPT

CKD chronic kidney disease, *ERBP* European Renal Best Practice, *IU* international units, *KDIGO* Kidney Disease Improving Global Outcomes, KDOQI: Kidney Disease Outcome Quality Initiative, *NICE* National Institute of Clinical Excellence, *PTH* parathyroid hormone, *SHPT* secondary hyperparathyroidism

nutritional vitamin D scheme they are most confident with, avoiding overdosing.

Although the targets of PTH serum levels as required to improve bone health and clinical hard endpoints have not been investigated in dedicated RCTs, vitamin D is suggested as a basic medication to prevent or treat secondary hyperparathyroidism in CKD (Table 1). Current data suggest a mild impact of nutritional vitamin D on non-severe secondary hyperparathyroidism in pre-dialysis CKD patients [51, 55–59], with a moderately stronger effect when administered at high doses against its mild phenotype [54, 60, 61]. An early replenishment of 25(OH)D levels could delay the onset and progression of secondary hyperparathyroidism [62, 63].

International guidelines provided discrepant suggestions about active vitamin D therapy for the treatment of secondary hyperparathyroidism (Table 2). A number of experimental and clinical data have proved the efficacy of active vitamin D administration in reducing PTH levels and improving bone histology [64, 65]. Selective vitamin D receptor activators (VDRA) should favor a stronger down-regulation of PTH synthesis with a lower impact on positive calcium-phosphate balance and a lower pro-calcifying effect on arterial walls. It can be speculated that the higher power elicited by paricalcitol in suppressing PTH levels may lead to further tapering of the maintenance doses, counteracting the risk of a positive calcium-phosphate balance. However, this consideration remains hypothetical, and it needs confirmation by ad hoc trials.

A potential superiority of selective VDRA, e.g. paricalcitol, with respect to non-selective VDRA such as calcitriol, alfacalcidol or doxercalciferol is still the subject of debate [66]. Despite encouraging experimental data, not all the available active vitamin D formulations have been tested in head-to-head RCTs on hard endpoints, PTH control, bone histology and vascular aging [67]. Furthermore, the neutral calcium-phosphate balance originally observed with the use of paricalcitol [68] has since been mitigated in several studies reporting a minimal but still existing increase of calcium and phosphate levels during paricalcitol administration [69–72]. The need to limit calcitriol administration for CKD patients at higher

Table 2 Active vitamin D in pre-dialysis CKD: guidelines

Guidelines	CKD stage	PTH target	Indication to start VDRA
KDOQI 2003	3	35–70 pg/ml	Start calcitriol, or alfacalcidol, or doxercalciferol in the presence of 25(OH)D levels <30 ng/ml and PTH levels above the suggested range
[K/DOQI 2003 Am J Kidney Dis]	4	70–110 pg/ml	
	5 d	150–130 pg/ml	
KDIGO 2009	3–5	Unknown	Start calcitriol or Vitamin D analogs to raise PTH levels above the normal range despite the correction of low 25(OH)D deficiency, hypocalcemia and hyperphosphatemia
[KDIGO (2009) Kidney Int suppls]		Maintaining PTH within the normal laboratory range is suggested	
KDIGO 2012	G3b–G5	Unknown	Start VDRA in the presence of PTH levels raising above the upper normal laboratory range only after ascertained absence of suspected or documented 25(OH)D deficiency, hyperphosphatemia and hypocalcemia
[KDIGO CKD (2012). Kidney Int Suppl]		Maintaining PTH within the normal laboratory range is suggested	
ERBP 2010	–	–	–
[Goldsmith DJA (2010). Nephrol Dial Transplant]			
NICE 2014	4–5	–	Start active vitamin D (alfacalcitol or calcitriol) in patients suffering from symptomatic CKD-MBD and GFR <30 ml/min despite an achieved 25(OH)D adequacy
[NICE guidance. nice.org.uk/cg182]			

CKD chronic kidney disease, *CKD-MBD* chronic kidney disease and mineral bone disorder, *ERBP* European Renal Best Practice, *KDIGO* Kidney Disease Improving Global Outcomes, *KDOQI* Kidney Disease Outcome Quality Initiative, *NICE* National Institute of Clinical Excellence, *PTH* parathyroid hormone

cardiovascular risk has been suggested by experienced authors [66].

Effects of different active vitamin D compounds on bone histology and risk of fractures has not been tested in head-to-head RCTs. Considerable symptomatic drawbacks of bone biopsies are even limiting the design of future ad hoc trials. Hence, current knowledge is limited to early studies in animal models regarding the more recent VDRA. Significant improvement of osteitis fibrosa together with a low risk of adynamic bone disease was observed among pre-dialysis CKD patients receiving calcitriol or alfacalcidol [64, 65]. Experimental data using paricalcitol showed better protective effects on bone health [73] and a lower risk of adynamic bone disease than calcitriol [74], doxercalciferol [75] and cinacalcet [76]. Notably, uncertainties about upper limits of PTH target levels are flanked by the lack of data on the lower PTH thresholds at risk for adynamic bone disease. Furthermore, the PTH serum level cannot be taken as an exhaustive and totally reliable biomarker of bone turn-over, thus limiting the intrinsic worth of a PTH-driven vitamin D schedule.

Based on the widespread genomic regulation elicited by VDR and its systemic expression, vitamin D has received growing interest as a treatment for several targets beyond PTH and bone health control, e.g. proteinuria, LVH and anemia. Proteinuria is an established biomarker of CKD severity as well as a strong direct pathogenetic factor of progression toward end-stage renal disease (ESRD), and worse survival [77]. Cholecalciferol at different dosages induced a mild but significant reduction of albuminuria among diabetic [78, 79] and non diabetic patients [57], although negative results were also reported [80]. About the impact of nutritional vitamin D on proteinuria reduction and calcium-phosphate balance there is still not concordance between different studies [57, 81]. The recent meta-analysis by de Borst et al. included 6 RCTs investigating the effect of active vitamin D on proteinuria [82]. Active vitamin D administration was associated with a significant 16 % reduction of proteinuria compared to 6 % reduction among controls with a more than 100-fold greater probability to reach a proteinuria reduction $\geq$15 % [82]. The analysis was not limited to diabetics [83, 84], but it included patients with immunoglobulin (Ig)A nephropathy [85] and patients with other renal disorders [86–88]. Sensitivity analysis did not reveal differences between vitamin D compounds, paricalcitol doses, sample size and length of follow-up. In contrast to encouraging data from animal models [89–91], the expected protective effects of VDRA on LVH in CKD patients were not confirmed in the PRIMO [88] and even in the further OPERA trial [92], which included patients with more severe LVH and hyperparathyroidism. An independent association between 25(OH)D levels and anemia was reported in CKD patients [93–96]. Down-regulation of hepcidine and PTH elicited by VDR activation represent the principal pathways linking anemia to vitamin D [97–99]. Although encouraging data

in humans suggest potential adjuvant effects of ergocalciferol, calcitriol and paricalcitol against renal anemia [96, 100, 101], further RCTs are required to investigate this specific issue.

The effects of vitamin D administration on survival, cardiovascular disease (CVD) and hospitalization rate in pre-dialysis CKD patients have not been investigated in dedicated RCTs. The recent meta-analysis by Mann et al. did not find a better survival in pre-dialysis CKD patients receiving either cholecalciferol or VDRA [102]. However, none of the included RCTs had either a study design or sufficient statistical power to test the effect of vitamin D on mortality [103]. Awaiting dedicated RCTs, the protective effect of active vitamin D on survival in pre-dialysis CKD patients remains only hypothetically reasonable.

Key messages

- Optimal 25(OH)D levels are still not well defined; achieving 25(OH)D levels >30 ng/ml seems a reasonable first-step intervention to avoid vitamin D deficiency and/or treat secondary hyperparathyroidism in CKD stages 3–5.
- The best therapeutic strategy to replenish 25(OH)D status is unknown.
- Nephrologists should follow the nutritional vitamin D administration scheme they are most confident with, exercising caution to avoid overdosing.
- Treatment with cholecalciferol, ergocalciferol and calcifediol should be discontinued in the presence of 25(OH)D levels >100 ng/ml and/or hypercalcemia in the absence of active vitamin D therapy. Attention should be paid in the presence of potentially increased 1-α-hydroxylase activity, as in transplanted patients and those affected by sarcoidosis or B-cell lymphoma, where 25(OH)D levels even lower than 100 ng/ml may result toxic.
- During nutritional vitamin D supplementation it is advisable to assess 25(OH)D levels twice a year, at the end of winter and at the end of summer, with potential extra tests in cases of persistent hypercalcemia and/or hyperphosphatemia.
- Active vitamin D therapy should be started in patients in CKD stages 3–5 with PTH above the normal range and normal levels of circulating 25(OH)D in the absence of hypercalcemia and/or hyperphosphatemia.
- Serum levels of calcium, phosphate and PTH should be monitored at least every 6–12 months in CKD stages 3–4 and at least every 3–6 months in CKD stage 5ND patients receiving VDRA, which should be discontinued in the case of persistent hypercalcemia and or hyperphosphatemia, or excessive reduction of PTH levels.
- Although several data encourage selective VDRA as the treatment of choice in patients at higher cardiovascular risk as in the presence of vascular calcifications or proteinuria, consistent evidence is still lacking in this regard.
- The potential additive effect of VDRA in reducing proteinuria among renal patients, on top of renin-angiotensin system inhibitors, warrants confirmation in further RCTs on the long run.
- Although nutritional and active forms of vitamin D may improve clinical hard endpoints in renal patients, consistent evidence is still lacking in this regard.

Vitamin D in CKD patients on dialysis

The International Osteoporosis Foundation guidelines [42] suggest levels of 25(OH)D >30 ng/ml as normal values in older adults. The KDOQI guidelines [43] suggest that levels of 25(OH)D >30 ng/ml should be regarded as normal limits for patients with non-dialysis CKD. Thus, 25(OH)D >30 ng/ml may be regarded as a suitable target also for patients on dialysis.

Several studies have evaluated the effects of vitamin D in the general population and in patients with CKD. In the latter population, the effects of either baseline serum concentrations of vitamin D or replenishment of insufficiency/deficiency on several outcomes have been studied. It is worth mentioning that outcomes were not always pertinent to mineral metabolism. For instance, there are data from observational studies that linked lower 25(OH)D levels to hypertension [31, 104–106] and to increased risk for cardiovascular events in both dialysis and non-dialysis patients [107, 108]. In addition, an association between vitamin D supplementation and reduced LV mass [109, 110] as well as a positive effect of vitamin D supplementation on the immune system [111] has been reported. Unfortunately, available data are conflicting and, therefore, they may cause uncertainty. Several additional factors can be held responsible for these discrepancies. For instance, there is no unanimous position on when to start treatment, on which vitamin D to prescribe, on dose to administer and on the route to prefer [112–115]. Furthermore, because most vitamin D comes from the sun and healthier people have more opportunities to spend time outdoors, studies in patients are particularly susceptible to confounding. Therefore the association between 25(OH)D levels with better outcome could be simply due to patients' lifestyle.

As said before, available studies are certainly interesting but still they do not offer us solid certainties on the use of vitamin D in patients on dialysis. Of note, consensus statements, according to the NIH, "synthesize new

information, largely from recent or ongoing medical research that has implications for re-evaluation of routine clinical practices. They do not give specific algorithms or guidelines for practice". In agreement with this important principle, we will try to analyze several studies and meta-analyses hoping to provide the best support for a reasoned clinical decision following the notion that both guidelines and consensus statements should inform but not dictate, guide but not enforce, support but not restrict.

As reported in Table 3, studies are listed on the basis of their design starting from observational studies to meta-analysis. Observational studies show great differences in duration of follow-up and number of enrolled patients; indeed, observation time varies from 90 days to 3 years and the number patients varies from a few tens to thousands. Further differences between studies are the aims to be assessed.

Studies on the role of baseline 25(OH)D concentration show an association between low serum levels with mortality. The association can be observed even in a short-term observation period. Indeed, Wolf et al. [116] investigated the relationship between baseline blood levels of 25(OH)D and $1,25(OH)_2D$ with outcomes in incident US hemodialysis patients. Among this cohort, 78 % of patients were considered moderately vitamin D deficient and 18 % severely vitamin D deficient. Baseline vitamin D levels were associated with 90-day mortality. Calcium, phosphorus, and PTH levels correlated poorly with 25(OH)D and $1,25(OH)_2D$ concentrations.

Drechsler et al. analyzed data from 762 patients in a prospective cohort study of incident dialysis patients in The Netherlands (NECOSAD study) [107]. The authors assessed the impact of 25(OH)D levels on short-term (6 months) and long-term (3 years) mortality. Patients were stratified as "severely vitamin D deficient" ($\leq$10.0 ng/ml), "moderately vitamin D deficient" ($> 10 \leq 30$ ng/ml) and "vitamin D sufficient" (>30 ng/ml). Mortality was higher in severely vitamin D deficient patients compared to the other groups. In particular, a strong association was evident between severe vitamin D deficiency and short-term cardiovascular mortality while no significant association was found between non-cardiovascular mortality and vitamin D status. Further, stratifying patients on the basis of PTH, the impact of 25(OH)D on clinical events was modified by PTH levels; low 25(OH)D levels were associated to outcomes only in patients with PTH above the median.

Similar results were found by Jean et al. who measured baseline 25(OH)D levels in 648 prevalent hemodialysis patients from the regional ARNOS French cohort [117]. A 42-month survival analysis was performed according to serum 25(OH)D level and calcitriol analog therapy. Baseline 25(OH)D levels above the median value (18 ng/ml) were associated with lower all-cause mortality (hazard ratio, HR, 0.73 [0.5–0.96], $p = 0.02$) after adjustment for age, gender, dialysis vintage, calcemia, phosphatemia, CVD, and diabetes. The association between low levels of vitamin D and mortality was evident also in the retrospective study carried out by Krause et al. [118]. Patients ($n = 6518$) from the German Renal Registry were matched with 73,919 recorded 25(OH)D measurements. All-cause mortality risk increased with decreasing vitamin D levels. For vitamin D insufficiency—25(OH)D levels ranging from 20 to <30 ng/ml—a moderate increase in risk was observed; for vitamin D deficiency—25(OH)D ranging from 12.5 to <20 ng/ml—the risk was much more pronounced; for severe vitamin D deficiency—25(OH)D <12.5 ng/ml—mortality risk was more than doubled. In addition to all-cause mortality risk, it was observed that the cardiac mortality risk increased among patients with vitamin D deficiency and that mortality risk for cancer was higher in patients with severe vitamin D deficiency [118].

Supplementation therapy appears to offer significant advantages. Untreated deficient patients were at increased risk for early mortality compared to patients with the highest 25(OH)D or $1,25(OH)_2D$ levels who received therapy with active vitamin D [116]. Interestingly, even not active forms of vitamin D showed significant positive effects on mortality. Low-dose oral alfacalcidol improved the survival rate in patients with and without 25(OH)D deficiency (HR 0.7 [0.5–0.92]; $p = 0.05$) [117]. In the prospective study of Bucharles et al., oral cholecalciferol was prescribed to 30 patients once a week during the first 12 weeks (50,000 IU) and at a lower dose during the last 12 weeks (20,000 IU) of the study; high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, and serum albumin were used as markers of inflammation [109]. Cholecalciferol supplementation resulted safe and effective in correcting hypovitaminosis D with a significant reduction of CRP, IL-6 and LVH with minor changes of markers of mineral metabolism. These data suggest that cholecalciferol supplementation may have a prominent anti-inflammatory action with concomitant improvement of cardiac dysfunction [109].

Daroux et al. [119] supplemented 39 patients with cholecalciferol or ergocalciferol (200,000 IU vitamin D per month) for 3 months and compared the usefulness of cholecalciferol and ergocalciferol in providing adequate vitamin D replenishment. Cholecalciferol resulted more effective than ergocalciferol in increasing 25(OH)D serum levels. In an open-label controlled trial performed by Del Valle et al. [113], ergocalciferol therapy was able to reach and maintain optimal serum 25(OH)D concentrations. In that study, 82 patients were supplemented with an initial oral ergocalciferol dose of 72,000 IU/week for 12 weeks and with a maintenance dose of 24,000 IU/week during the

Table 3 Studies on vitamin D deficiency and replenishment in dialysis patients

References	Study design (FU)	Patients or studies	Object of investigation	Main outcome (s)	Main results/conclusions
Wolf et al. [116]	Cross sectional, observational (90 days)	n.825 Incident hemodialysis patients	25(OH)D and 1,25$(OH)_2$D serum levels	Association between baseline vitamin D levels and 90-day mortality; interaction between vitamin D levels and subsequent active vitamin D therapy	Compared to patients with the highest 25(OH)D or 1,25$(OH)_2$D levels who received therapy, untreated deficient patients were at increased risk for early mortality
Drechsler et al. [107]	Observational, prospective (3 years)	n.762 Incident hemodialysis patients	25(OH)D serum levels	6-month and 3-year survival	Short-term mortality was associated with low levels of 25(OH)D in patients with PTH levels above the median
Jean et al. [117]	Cross sectional, observational (42 months)	n.648 Hemodialysis patients	25(OH)D serum levels and therapy with low-dose oral alfacalcidiol	42-month survival	Association between low levels of 25(OH)D and mortality. Better survival rate in patients treated with alfacalcidiol
Krause et al. [118]	Observational, retrospective	n.6518 Hemodialysis patients	25(OH)D serum levels	10-year survival	Association between low levels of 25(OH)D and all-cause mortality (cardiac disease, infectious disease and cancer)
Bucharles et al. [109]	Observational, prospective (24 weeks)	n.30 Hemodialysis patients	Vitamin D supplementation with initial high cholecalciferol dose (prescribed once a week in the first 12 weeks (50,000 IU) followed by lower dose in the last 12 weeks (20,000 IU)	Benefits and harms of vitamin D supplementation	Significant increase in serum 25(OH)D levels; significant reduction in high-sensitivity C-reactive protein and interleukin-6 levels
Daroux et al. [119]	Observational, prospective (3 months)	n.39 Hemodialysis patients	Vitamin D supplementation with cholecalciferol or ergocalciferol (200,000 IU vitamin D per month)	Direct comparison between cholecalciferol and ergocalciferol in providing adequate vitamin D replenishment	Cholecalciferol is more effective than ergocalciferol in providing increase of 25(OH)D serum levels
Del Valle et al. [113]	Observational, prospective (48 weeks)	n.82 Hemodialysis patients	Vitamin D supplementation with ergocalciferol 72,000 IU/week for 12 weeks followed by 24,000 IU/week as maintenance therapy for 36 weeks	Benefits and harms of a high-dose ergocalciferol dosage scheme	Serum 25(OH)D significantly increased and remained optimal. 84.8 % of patients reached values $\geq$30 ng/ml. PTH and alkaline phosphatase did not change compared to baseline. Bone alkaline phosphatase decreased
Marckmann et al. [60]	RCT (8 weeks)	n. 54 Hemodialysis and non-hemodialysis CKD patients	Vitamin D supplementation with cholecalciferol (40,000 IU weekly)	Biochemical effects of 25(OH)D replenishment	Significant improvement in 25(OH)D and 1,25$(OH)_2$ D levels and decline in PTH levels, but only in CKD-non D patients
Armas et al. [120]	RCT (15 weeks)	n. 42 Hemodialysis patients	Vitamin D supplementation with cholecalciferol 10,333 IU given weekly	Pharmacokinetic study of 25(OH)D response to cholecalciferol	Cholecalciferol (10,333 IU) given weekly induced a steady state in 25(OH)D levels (24 ng/ml)
Wasse et al. [121]	RCT (4 weeks)	n. 52 Hemodialysis patients	Vitamin D supplementation with cholecalciferol for 3 weeks (200,000 IU/wk)	Biochemical effects of 25(OH)D replenishment	90.5 % of subjects treated with cholecalciferol achieved normal serum 25(OH)D concentrations $\geq$30 ng/ml vs. 13.6 % of the placebo group

Table 3 continued

References	Study design (FU)	Patients or studies	Object of investigation	Main outcome (s)	Main results/conclusions
Delanaye et al. [122]	RCT (12 months)	n. 43 Hemodialysis patients	Vitamin D supplementation with cholecalciferol (25,000 IU every 2 weeks)	Benefits and harms of cholecalciferol therapy	Cholecalciferol increased serum 25(OH)D levels. PTH levels tended to decrease in the cholecalciferol group (significantly vs. placebo). The calcification score increased to the same extent in both groups
Hewitt et al. [123]	RCT (6 months)	n. 60 Hemodialysis patients	Vitamin D supplementation with cholecalciferol 50,000 IU, once weekly for 8 weeks and then monthly for 4 months	Effects on calcidiol and calcitriol serum levels, mineral metabolism and other clinical parameters	Cholecalciferol increased serum 25(OH)D and $1,25(OH)_2$ levels, but had no effect on muscle strength, functional capacity, PWV, or HRQOL
Massart et al. [124]	RCT (13 weeks)	n. 55 Hemodialysis patients	Vitamin D supplementation with cholecalciferol, 25,000 IU, per week	Percentage of patients with 25(OH)D levels $\geq$30 ng/ml at 13 weeks; percentage of patients with normal calcium, phosphorus, and PTH blood levels	Cholecalciferol increased serum 25(OH)D and $1,25(OH)_2$D levels, but did not significantly modify serum levels of PTH, calcium and phosphorus
Bhan et al. [125]	RCT (1 year)	n.105 Hemodialysis patients	Vitamin D supplementation with weekly dose of 50,000 IU ergocalciferol, followed by monthly 50,000 IU ergocalciferol compared to placebo)	Achievement of vitamin D sufficiency at the end of the 12-week treatment period. Survival was assessed for 1 year	At 12 weeks, sufficient vitamin D level was achieved in 91 % (weekly), 66 % (monthly), and 35 % (placebo) ($p < 0.001$). Lower all-cause mortality among ergocalciferol-treated participants was not statistically significant
Chonchol et al. [126]	Post-hoc analysis of RCT	n. 1340 Hemodialysis patients	25(OH)D and $1,25(OH)_2$D serum levels	Association between 25(OH)D, $1,25(OH)_2$D, and FGF23 serum levels and various clinical outcomes	Patients in the highest 25(OH)D quartile had the lowest risk of infectious events, cardiac events, and all-cause mortality. No significant associations of $1,25(OH)_2$D with clinical outcomes were observed
Miskulin et al. [127]	RCT (6 months)	n. 276 Hemodialysis patients	Vitamin D supplementation with ergocalciferol (patients with serum 25(OH)D $\leq$15 ng/ml received 50,000 IU weekly for 6 months, and those with 25(OH)D 16–30 ng/ml received 50,000 IU weekly for the first 3 months followed by 50,000 IU monthly for 3 months	Effects on epoetin utilization and other secondary outcomes	Ergocalciferol increased serum 25(OH)D levels in HD patients, but had no effect on epoetin utilization or secondary biochemical and clinical outcomes
Kandula et al. [51]	Meta-analysis	n. 22 studies (5 RCTs and 17 observational studies) enrolling 1593 patients (CKD-non D, HD, PD, TX)	Vitamin D supplementation with ergocalciferol or cholecalciferol	Benefits and harms of vitamin D supplementation	Significant improvement in 25(OH)D and associated decline in PTH levels

Table 3 continued

References	Study design (FU)	Patients or studies	Object of investigation	Main outcome (s)	Main results/conclusions
Zheng et al. [128]	Meta-analysis	n. 20 observational studies (17 in HD patients and 3 in CKD-non D patients) enrolling 49,1857 patients	Vitamin D treatment (calcitriol, paricalcitol, alfacalcidol, doxercalciferol)	Survival benefits of active vitamin D treatment	Vitamin D treatment was associated with decreased risk of all-cause and cardiovascular mortality. Paricalcitol had a survival advantage compared to calcitriol

RCT randomized controlled trial, *CKD* chronic kidney disease, *CKD-non D* non-hemodialysis chronic kidney disease, *HD* hemodialysis, *PD* peritoneal dialysis, *TX* kidney transplantation, *25(OH)D* 25-hydroxy vitamin D, *1,25(OH)2 D* 1,25-dihydroxyvitamin D, *PTH* parathyroid hormone, *PWV* pulse wave velocity, *HRQOL* health-related quality of life, *FU* follow-up, *IU* international units

following 36 weeks. Ergocalciferol supplementation was associated with a significant increase in plasma 25(OH)D levels at 12 weeks compared to baseline (42.5 ± 13.2 vs. 15.2 ± 5.4 ng/ml; $p < 0.01$) without changes in PTH, total alkaline phosphatase, bone alkaline phosphatase isoenzyme or serum phosphorus. Serum calcium significantly increased. This regimen with initial high doses was regarded as safe and adequate to obtain and maintain optimal serum 25(OH)D concentrations and prevent vitamin D insufficiency. Unfortunately there was no control group in the study.

RCTs have focused on supplementation therapy largely using cholecalciferol and assessing different outcomes. Marckmann et al. [60], in an 8-week randomized, placebo-controlled, double-blind parallel intervention study in 54 hemodialysis (HD) and non-HD CKD patients, analyzed plasma 25(OH)D, plasma $1,25(OH)_2D$, PTH, serum phosphate, ionized serum calcium and serum FGF23 [60]. Biomarkers related to CVD were investigated. The study evidenced that hypovitaminosis D was corrected with weekly ingestion of 40,000 IU D3 for 8 weeks. In non-HD patients, this replenishment was associated with increases in circulating $1,25(OH)_2D$, reduction of PTH and prevalence of hyperparathyroidism. Surprisingly, the authors were not able to demonstrate any effects of vitamin D3 supplementation in HD patients (except for a rise of FGF23). In contrast, Armas et al. [120] supplemented 42 patients with cholecalciferol (weekly dose of 10,333 IU) in order to assess the changes in serum levels of 25(OH)D. Cholecalciferol produced a steady state in serum levels of 25(OH)D (approximately 24 ng/ml). The efficacy of cholecalciferol in replenishing deficient/insufficient hemodialysis patients was documented by Wasse et al. in a prospective, double-blind, randomized controlled study that compared very high doses of oral cholecalciferol for 3 weeks (200,000 IU/week) with placebo in 52 HD patients [121]. Short-term, high-dose oral cholecalciferol treatment was effective in replenishing deficient/insufficient hemodialysis patients without toxic effects. In addition, mean serum $1,25(OH)_2D$ increased significantly in the cholecalciferol-treated group, whereas it decreased in the placebo group. There were no significant changes in hemoglobin, calcium, phosphorus, PTH, albumin and alkaline phosphatase between the study groups. The lack of toxicity of cholecalciferol was observed by Delanaye et al. [122] in 43 patients supplemented with cholecalciferol (25,000 IU every 2 weeks). In patients treated with cholecalciferol, serum 25(OH)D levels increased and PTH decreased compared to controls. The calcification scores, that was a further aim of the study, increased by the same extent in both groups.

The positive effects of cholecalciferol seem to be limited to replenishment of deficiency/insufficiency of

25(OH)D; cholecalciferol therapy seems unable to achieve better levels of PTH, calcium and phosphorus. Indeed, cholecalciferol (50,000 IU, once weekly for 8 weeks and then monthly for 4 months) increased serum 25(OH)D and $1,25(OH)_2D$ levels but had no effect on muscle strength, functional capacity, pulse wave velocity or health-related quality of life (HRQOL), as shown by Hewitt et al. in 60 patients [123]. Similarly, Massart et al. [124] reported that supplementation with cholecalciferol (25,000 IU/week) increased serum 25(OH)D and $1,25(OH)_2D$ levels, but did not significantly modify serum levels of PTH, calcium or phosphorus in 55 patients.

Ergocalciferol has a similar efficacy to cholecalciferol as replenishing therapy. Bhan et al. in 105 incident patients compared two dose-regimens of ergocalciferol (weekly or monthly) with placebo [125]. The primary endpoint was the achievement of vitamin D sufficiency (25(OH)D >32 ng/ml) at the end of the 12-week treatment period. The 1-year survival was assessed. Ergocalciferol increased 25(OH)D levels in incident HD patients without significant changes in blood calcium, phosphate, or PTH during a 12-week period. No differences were found in a host of adverse events, including hospitalizations, infectious events and cardiovascular events. When the two ergocalciferol arms were combined, the authors noted a trend toward reduction in all-cause mortality among ergocalciferol-treated participants compared to placebo-treated participants. Mortality was not a primary endpoint and the study was not powered to detect differences in mortality or other specific adverse events.

Chonchol et al., analyzing the data from HEMO study, examined the association between 25(OH)D, $1,25(OH)_2D$, and FGF23 serum levels and various clinical outcomes [126]. The HEMO study was a prospective, randomized, multicenter clinical trial in which 1846 HD patients were randomly assigned to either low-flux or high-flux membrane dialyzers. Therefore, the assessment of the effects of levels of 25(OH)D was not the primary endpoint. Higher serum 25(OH)D was associated with decreased risks of infectious events, cardiac events and all-cause deaths. In addition, high serum FGF23 levels were associated with infectious and cardiac events. Higher circulating 25(OH)D levels, when added as a time-dependent covariate, showed a graded relationship with a decreased risk of infectious and cardiac events and all-cause mortality that was independent of markers of inflammation.

Miskulin et al. [127] tested the efficacy of ergocalciferol on epoetin utilization and other secondary outcomes. Starting from the observation that nutritional vitamin D may enhance erythropoietin in the presence of 25(OH)D deficiency, the authors performed a double-blind, placebo-controlled RCT to assess the effects of supplementation with ergocalciferol on epoetin utilization and other secondary outcomes in 276 patients with serum 25(OH)D <30 ng/ml. Patients were randomized to 6 months of ergocalciferol or placebo. Serum 25(OH)D increased from 16.0 ± 5.9 ng/ml at baseline to 39.2 ± 14.9 ng/ml in the ergocalciferol arm but did not change (16.9 ± 6.4 vs. 17.5 ± 7.4 ng/ml, respectively) in the placebo arm. There was no significant change in epoetin dose over 6 months in the ergocalciferol or placebo arms (geometric mean rate 0.98 [95 % confidence interval (CI) 0.94–1.02] vs. 0.99 [0.95–1.03], respectively) and no difference across the arms ($p = 0.78$). No change occurred in serum calcium, phosphorus, intact PTH, or CRP levels, cinacalcet use, or phosphate binder or calcitriol dose in either study arm. Rates of all-cause and cardiovascular mortality as well as of infection-related hospitalizations did not differ between study arms. Therefore, 6 months of supplementation with ergocalciferol increased serum 25(OH)D levels in patients on hemodialysis with vitamin D insufficiency or deficiency, but it had no effect on epoetin utilization or secondary biochemical and clinical outcomes.

Confirmatory data on the usefulness of supplementation therapy are reported by a meta-analysis of 22 studies (17 observational and 5 RCTs) performed by Kandula et al. [51]. Selected studies evaluated the effects of vitamin D supplementation with either ergocalciferol or cholecalciferol in patients with non-dialysis-dependent CKD, dialysis-dependent CKD and in renal transplant recipients. Biochemical endpoints were: change in serum 25(OH)D, intact PTH, $1,25(OH)_2D$, calcium and phosphorous levels. Clinical endpoints were: cardiovascular events, outcomes related to bone disease, and all-cause mortality. There was a significant improvement in 25(OH)D levels and reduction of PTH levels. PTH reduction was more evident in dialysis patients. Incidence of hypercalcemia and hyperphosphatemia was irrelevant with vitamin D supplementation. Cardiovascular and skeletal effects of vitamin D supplementation were not endpoints of interest. Studies were of low to moderate quality. Zheng et al. [128] performed a meta-analysis from 20 studies (11 prospective cohorts, 6 historical cohorts and 3 retrospective cohorts) that compared several forms of vitamin D [128]. In aggregate, participants receiving vitamin D had lower mortality compared to those with no treatment (adjusted case mixed baseline model: HR 0.74 [95 % CI 0.67–0.82]; $p < 0.001$; time-dependent Cox model: HR 0.71 [0.57–0.89]; $p < 0.001$). On the basis of the active form of vitamin D, participants that received calcitriol (HR 0.63 [0.50–0.79]; $p < 0.001$) and paricalcitol (HR 0.43 [0.29–0.63]; $p < 0.001$) had a lower cardiovascular mortality. In detail, patients receiving paricalcitol had a survival advantage over those that received calcitriol (HR 0.95 [0.91–0.99]; $p < 0.001$).

The active forms of vitamin D have been successfully used for a long time to treat secondary

hyperparathyroidism in dialysis patients. More recently, selective VDRA have been widely used in clinical practice. The main characteristics of selective VDRA are their stronger effect in reducing serum concentration of PTH, lower impact on concentrations of calcium and phosphate, and reduced toxicity [129].

Observational studies report improved cardiovascular and all-cause survival in hemodialysis patients receiving VDRA therapy compared to non-VDRA-treated patients [128, 130–133]. On the contrary, in the DOPPS cohort VDRA administration was not associated with improved survival in models that were more independent of unmeasured confounders as comorbidities [134]. Of note, selective VDRA such as paricalcitol resulted associated with lower mortality compared to calcitriol in some [128, 130, 131, 135] but not all studies [136]. Therefore, considering the inherent limitations of retrospective analyses, the benefit of VDRA treatment on survival in hemodialysis patients still remains to be confirmed by prospective RCTs.

Key messages

- Low levels of 25(OH)D are very frequent in the dialysis population. Insufficiency or deficiency of 25(OH)D may affect survival by directly influencing mineral metabolism. Better survival of patients treated with native or nutritional or active vitamin D over and above the effects on mineral metabolism indicates that vitamin D possesses pleiotropic protective actions. For this reason many interventional studies have evaluated the effectiveness of 25(OH)D replenishment with cholecalciferol, ergocalciferol, or calcidiol in correcting deranged mineral metabolism as well as in improving survival.
- Most of the available data come from observational studies which are characterized by significant differences in number of enrolled patients, administered doses of vitamin D sterols, duration of treatment and assessed outcomes. Therefore strong evidence supporting an association between vitamin D sterols and survival is lacking. Large RCTs addressing this issue need to be performed.
- Active forms of vitamin D are more effective than other forms in correcting secondary hyperparathyroidism despite the fact that they are not able to increase and/or normalize 25(OH)D levels. In contrast, native and nutritional vitamin D may increase $1,25(OH)_2D$ levels and reduce PTH levels. This finding may support the therapeutic strategy of dual administration of active and native/nutritional vitamin D, taking into account that a potential interaction may not be excluded. Beneficial effects of dual supplementation on survival have not been assessed as yet.
- Almost all studies indicate that supplementation does not markedly affect levels of calcium or phosphorus and does not accelerate the vascular calcification process. However, markers of mineral metabolism should be monitored during long-term treatment according to the presence of comorbidities and half-life of supplemented vitamin D. These suggestions should be taken into account particularly in dialysis patients treated with active forms of vitamin D.

Vitamin D in kidney transplant recipients

In kidney transplant recipients (KTRs) the impairment of vitamin D metabolism reflects allograft function, FGF23 and PTH levels, immunosuppressive therapy and environmental factors (nutritional deficiency, decreased sun exposure) [137, 138]. 25(OH)D deficiency and insufficiency are common in KTRs, with a prevalence of 30 and 81 %, respectively [139]. Even higher rates have been observed among black KTRs [140] and during the first year after transplantation [141]. In contrast, $1,25(OH)_2D$ is reported to reach normal levels within 3–6 months after transplantation [142, 143] following its higher renal synthesis along with the recovery of allograft function and following normal/high (or inappropriately high) PTH levels [139]. High FGF23 levels inhibit 1-α-hydroxylase and enhance 24-α-hydroxylase, leading to reduced $1,25(OH)_2D$ and 25(OH)D levels respectively. FGF23 levels decline 3 months after transplant but still remain higher than in CKD patients matched for estimated glomerular filtration rate (GFR) [144]. After 12 months, data are inconclusive: FGF23 levels seem to be appropriate for the CKD stage [145] or lower [146, 147]. The decrease of FGF23 levels within 1 year may account for the restored $1,25(OH)_2D$ levels within 3–6 months after transplantation [139, 148]. Immunosuppressive therapy may contribute to vitamin D derangement, although the scientific literature is still scanty in this regard. Steroids impair vitamin D metabolism activating the enzymes involved in vitamin D catabolism and increasing PTH and FGF23 levels [149]. In contrast, steroid sparing/withdrawal improves vitamin D metabolism [139]: in particular, cumulative prednisone dose was found to be inversely associated with $1,25(OH)_2D$ levels 2 years after transplantation and low $1,25(OH)_2D$ levels were inversely associated with the higher FGF23 concentrations induced by steroid therapy [150]. In agreement, Sanchez-Fructuoso et al. [146] showed that high levels of FGF23 are associated with higher cumulative doses of steroids and low levels of $1,25(OH)_2D$. Several discrepancies have been observed between the effects of calcineurin and mammalian target of rapamycin (mTOR) inhibitors on vitamin

D metabolism. Calcineurin inhibitors (CNI) have been recently associated with lower 25(OH)D levels [151]. This finding is in agreement with experimental studies showing vitamin D resistance induced by CNI through VDR downregulation. The loss of VDR removes feedback inhibition of vitamin D on 1-α-hydroxylase and increases the $1,25(OH)_2D$ level [152]. Rapamycin does not have any effect on vitamin D metabolism [153]. Substantial evidence has ascertained that the conversion of 25(OH)D to $1,25(OH)_2D$ via 1-α-hydroxylase in osteoblasts, osteocytes and osteoclasts regulates processes such as cell proliferation, mineralization as well as bone resorption [154]. Various studies have shown that bone loss is considerable during the first year after transplantation, with a rate of 14.5 % in the first 6 months, followed by a mild improvement after the second year post-transplant [155, 156], and recovers within the pre-transplant range only 8 years after transplantation [157]. Studies in late KTRs revealed a prevalence of osteoporosis ranging from 11 to 56 % and fractures ranging from 5 to 44 %; at any rate the risk of hip fracture, until 3 years after transplantation, is higher than in HD patients [158]. A few studies have reported histological patterns of post-transplant bone disease, describing a considerable prevalence of adynamic bone disease and of high bone turnover [159, 160]. Immunosuppressive drugs elicit a deep impact on bone loss. Steroids directly worsen bone formation by inducing: derangement of vitamin D metabolism, impaired osteoblastogenesis, increased apoptosis of osteoblasts and enhanced osteoclastogenesis through an increased receptor activator of nuclear factor kappa B ligand (RANKL)/osteoprotegerin (OPG) ratio [139]. Both cyclosporin and tacrolimus similarly promote bone loss via a direct osteoclast activation [153]. Conversely, sirolimus is taken as a bone-sparing immunosuppressive agent, due to its capability to inhibit osteoclast generation [153, 161].

KTRs show a 3.5–5 % annual risk of cardiovascular events. CVD is the leading cause of death in KTRs, also accounting for 42 % of total graft loss [162]. Vitamin D has sparked widespread interest following reports of its pleiotropic effects against CVD elicited by VDR activation [29]. A few observational studies have explored the correlations between the vitamin D system and CVD in KTRs. In a study carried out on 331 KTRs, low vitamin D levels were not associated with 3-year increased risk of CVD [163]. In contrast, in a cohort of 435 stable KTRs, Keyzer et al. [137] observed an association between 25(OH)D levels <12 ng/ml and all-cause mortality, CVD being the most frequent cause of death (53 %). Yilmaz et al. described an improvement of endothelium-dependent vasodilatation in association with increases of 25(OH)D levels and reduced FGF23 levels [164]. Recent observational studies have investigated the correlation between 25(OH)D and $1,25(OH)_2D$ deficiency and graft outcomes in KTRs. Reduced 25(OH)D levels where independently associated with lower GFR at 12-month follow-up and a higher risk for interstitial fibrosis and tubular atrophy [142]. Accordingly, a worse annual estimated GFR decline was observed in the presence of 25(OH)D levels <12 ng/ml [137]. Obi et al. noted that only in patients at less than 10 years after kidney transplant was 25(OH)D deficiency associated with a rapid decline in kidney function [165]. In contrast, no associations were observed in KTRs between $1,25(OH)_2D$ levels and GFR trends [137]. Increasing levels of proteinuria have been clearly associated with worsening graft survival [166]. More recently, vitamin D and its analogs resulted capable of reducing proteinuria in CKD patients [82] by endocrine suppression of the renin-angiotensin system.

No specific guidelines have been released to orient nutritional vitamin D replenishment in KTRs, leading to heterogeneous schedules of intervention to correct vitamin D deficiency in clinical studies. Although several authors reported a significant improvement of PTH and calcium levels in KTRs receiving nutritional vitamin D, the effects of ergocalciferol and cholecalciferol and calcifediol on BMD remains controversial [167–169]. Observational data by Stavroulopoulos et al. confirmed the high incidence of hypercalcemia following renal transplantation, that may vary in prevalence from 11–66 % depending on the time post-transplantation. This could affect which patients can be treated, because of concern that vitamin D treatment may worsen hypercalcemia [169]. Several studies have shown that calcitriol decreases PTH levels and improves BMD in KTRs with osteopenia or osteoporosis [170, 171], therefore becoming a well accepted preventive therapy against bone loss in KTRs [139, 172]. In contrast, Gonzalez et al. described how paricalcitol induced a 30 % reduction of PTH levels in 78 % out of 58 KTRs, although without data on the BMD trend in KTRs [173]. Amer et al. reported a greater PTH reduction and a lower prevalence of hyperparathyroidism (29–63 %) in KTRs receiving paricalcitol compared to controls, without any benefit on osteopenia [174]. In the RCT by Trillini et al., KTRs randomized to paricalcitol improved L3 and L4 vertebral BMD close with reduced serum levels of bone formation/reabsorption biomarkers. Furthermore, paricalcitol therapy was not associated with a higher risk of hypercalcemia [175].

Reports about vitamin D therapy to improve graft survival are still scanty. As regards the use of inactive vitamin D, in a retrospective analysis, cholecalciferol supplementation after kidney transplant did not modify the progression of GFR, the onset of interstitial fibrosis, tubular atrophy and proteinuria [176]. The ongoing VITALE study is comparing the effect of cholecalciferol at high or low

dose (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 [177]. Data on antiproteinuric effects of VDRA in KTRs look more promising. Paricalcitol at low doses (3 μg/week) was retrospectively associated with a significant reduction of proteinuria at 24 months [172]. Trillini et al. [175] performed a randomized, crossover study to compare the effect of 6-month treatment with paricalcitol (1 μg/day for 3 months and then uptitrated to 2 μg/day if tolerated) or non-paricalcitol therapy in KTRs with a long-term functioning graft. Compared with baseline, proteinuria showed a significant decrease at 6 months. Amer et al. randomized 100 incident KTRs to oral paricalcitol, 2 μg/day, for the first year post-transplant or no additional therapy [174]. They did not observe lower protein excretion among paricalcitol treated KTRs compared to controls at 1 year post-transplantation. However, moderate interstitial fibrosis was observed in 4/38 biopsies in the control group, but was absent in the paricalcitol group. Notably, neither of the previous two RCTs was designed to investigate the effect of paricalcitol on proteinuria as a primary outcome.

Key messages

- According to KDIGO, the Working Group suggests that vitamin D deficiency and insufficiency in kidney transplanted patients should be corrected using either cholecalciferol or ergocalciferol treatment as recommended for the general and CKD population given their positive effects on MBD.
- When faced with a reduced graft function, the Working Group suggests that the rationale for the use of VDRA is similar to that for CKD patients.
- The use of VDRA in the treatment of post-transplant hyperparathyroidism, whether ascertained in the early or long-term functioning kidney graft, should be contextualized to the calcium values. Treatment with VDRA improves BMD in kidney transplanted patients with estimated GFR <30 ml/min and secondary hyperparathyroidism without hypercalcemia.

Final suggestions

An important future challenge is the specific antiproteinuric effect of paricalcitol even if, in KTRs as well as in CKD patients, we do not know whether the reduction of proteinuria can be translated into a higher graft survival. Clinical results suggest a promising action of VDRA to reduce post-transplant proteinuria and hyperparathyroidism. Additional topics that need further studies are the interplay between vitamin D/VDRA and FGF23 and also the effect of immunosuppressive drugs on vitamin D metabolism.

Vitamin D in dialysis patients suffering from adynamic bone disease

Adynamic bone disease (ABD) and its intermediate forms, known as hypodynamic bone disease (HBD), together with osteoporosis, have long been ignored and underestimated, although present in the majority of menopausal female patients undergoing dialysis [178].

Osteoporosis is a common disease characterized by a systemic impairment of bone mass and microarchitecture that causes fragility fractures [179]. The World Health Organization defines osteoporosis based on bone density 2.5 standard deviations below the mean for young white adult women (t score) [180, 181]. In contrast, ABD is defined by the presence of markedly low bone turnover, reduced osteoblasts and osteoclasts and no accumulation of osteoid [182].

For many years, the definition of ABD has been based only on PTH <150 pg/ml. On the basis of this PTH cut-off, studies performed in the 1990s reported a prevalence of ABD ranging from 31.2 to 43 % in patients on continuous ambulatory peritoneal dialysis (CAPD) [183, 184] and 24 % in hemodialysis patients [185]. The percentage of 23–25 % of ABD in hemodialysis patients was confirmed by studies conducted in the years 2000 [186] and 2003 [187] in patients who underwent bone biopsy. More recently, low-turnover bone disease (LTBD) has been found in more than 60 % of Caucasian dialysis patients [188]. In our experience, the study of 155 hemodialysis patients in 2014 revealed a total of 24 % with PTH levels <150 pg/ml vs. 8 % with PTH >600 pg/ml. It is important to mention that more recent guidelines indicate that the histologic pattern of ABD is generally associated to low levels of PTH, below 2× the higher normal value of PTH (PMID 19644521). This makes questionable the definition of ABD that is based on PTH <150 pg/ml.

The identification of ABD using common markers for osteopathy is however problematic. PTH displays a relatively high sensitivity, but in the absence of suppressed PTH levels it is not sufficiently reliable to exclude LTBD. Barreto et al. reported in 2014, in 101 patients subjected to bone biopsy, that PTH levels <150 pg/ml were predictive of LTBD in 83 % of cases, but ABD was clearly seen to be present also in patients with PTH >300 pg/ml [189]. Bone alkaline phosphatase level appears to be a better marker in this respect, possibly reflecting the loss of specificity that is the result of large amounts of attenuated (oxidized and/or amino-terminal–truncated) forms of immunoreactive PTH

that persist in the uremic circulation [190]. Plasma concentrations of FGF23 may potentially reflect ongoing alterations in active bone mineralization since normal mineralization was observed in 90 % of patients with FGF23 levels above 2000 pg/ml [191]. Bone biopsy represents the most reliable diagnostic tool to use in ABD [186, 187], although this technique is little applied due to the lack of anatomic pathology labs trained in the preparation, staining and interpretation of the frustule, but also to the refusal of patients to undergo a considerably invasive procedure.

In the 1990s, several studies correlated ABD with the administration of toxic aluminum-based phosphor binders [192]. Generally, the ABD is associated with low PTH levels, although serum PTH may be raised in CKD patients, particularly when correlated with histological evidence of ABD resulting from accumulation of aluminum. Other causes underpinning the finding of PTH values <150 ρg/ml include calcium-based phosphobinders, calcium-rich diet, high dialysate concentrations of calcium, diabetes mellitus, malnutrition-inflammation, oxidative stress, peritoneal dialysis, old age, Caucasian race, methodological errors in determining PTH, nutritional supplements containing vitamin D, calcimimetics and inappropriate doses of effective vitamin D-based derivatives [193].

ABD is associated to increased OPG levels, decreased production and circulation of bone morphogenetic proteins, a peripheral effect of leptin and IL-6, inhibitory effect of osteocyte-secreted sclerostin, as well as the potential effect of (7–84 PTH) fragments that contrast the action of the intact PTH 1-84. The large number of findings correlating ABD with uremia-induced malnutrition and/or microinflammation should be further consolidated [194]. Lower PTH levels are associated with an increased risk of mortality and in ABD there is a higher incidence of vascular calcification and a greater fracture risk [182, 195, 196].

The latest report published by the COSMOS trial is particularly convincing: over a 3-year period it is establishing new ranges for decreased mortality risk in KDOQI and KDIGO guidelines, suggesting PTH values ranging between 168 and 674 ρg/ml; in 40.7 % of these patients PTH was <168 ρg/ml, thus indicating a higher risk of mortality [192].

The clinical picture in LBTD may be complicated in amenorrheic female patients in hemodialysis and owing to the well-known associated risk of bone fracture in elderly patients of both genders [197].

Osteoporosis treatment is based on bisphosphonates. Use of this compound is strongly discouraged in patients with ABD [198]. Nephrologists have recently been authorized to prescribe denosumab which may represent a promising option for the treatment of osteoporosis in hemodialysis. However, the scarce number of cases reported in the literature has to date limited a more extensive use of this drug [199].

No comparison of therapeutic approaches used in the treatment of ABD can be made due to the lack of trials based on a similar number of patients, statistical methods and prospective design. Therefore, the therapeutic rationale is based on a single common denominator, i.e. suspension of vitamin D and derivatives or use of doses of 25(OH)D and $1,25(OH)_2D$ capable of eliciting a further reduction in PTH incretion [200]. It should however be taken into account that even low doses of intravenous calcitriol (0.5 μg/3 times weekly) may inhibit the parathyroid receptors [201]. On the other hand, vitamin D derivatives can be of potential benefit in CKD patients even in the presence of low PTH circulating levels. Results from the FARO survey suggest that VDRA treatment is associated with reduced overall mortality as well as factor-adjusted mortality risks among Italian dialysis patients, even when serum intact PTH levels are ≤150 pg/ml [202]. There is a lack in the literature of trials or reports on the use of cholecalciferol in ABD; likewise, no reports have been published with regard to daily oral administration of the drug. A feasible option may be to administer personalized daily oral doses of cholecalciferol based on the weight/-body mass index (BMI) of the patient and on the effect produced on plasma levels of calcifediol [203]. Cholecalciferol at low doses (e.g. from 25.000 to 50.000 UI/month in two administrations at intervals of 15 days) may be quite appropriate for most patients. Nevertheless, these doses should be personalized, administered with caution and strictly monitored to avoid total PTH blockade and/or vitamin D intoxication.

Final suggestions

Dialysis patients with ABD, in particular elderly malnourished patients, should receive an appropriately balanced intake of vitamin D in order to benefit from the fundamental pleiotropic action of this hormone. The administration of active forms of vitamin D may cause a further decrease of PTH levels. Therefore, cautious supplementation with native vitamin D could be a preferable approach; however, the efficacy and safety of this choice remains to be validated.

Vitamin D and vascular calcifications in CKD

The occurrence of vascular calcification is common, being found even in early stages of CKD [204–207]. Several promoters and inhibitors are involved in the pathogenesis of vascular calcification in CKD. The pathophysiologic role of many of them has been extensively ascertained by

experimental and clinical studies while the role of others is still debated [208, 209]. This is the case of vitamin D. To better evaluate the pathogenetic role of vitamin D on the process leading to extra-osseous calcification, it is important to separate studies that evaluated the association between circulating serum levels of vitamin D and vascular calcification from other studies that evaluated the effects of supplemental vitamin D on vascular calcification.

Low concentration of vitamin D increases PTH secretion, bone loss, core-binding factor alpha 1 (Cbfa1) and Type I collagen expression and decreases matrix Gla protein (MGP) and osteopontin (OP) expression [31, 210–214]. In addition, vitamin D is a strong inducer of FGF23 and Klotho, two important factors that maintain physiologic calcium and phosphate balance [215–218]. Finally, based on the presence of 1-α hydroxylase as well as vitamin D receptors in vascular smooth muscle cells (VSMC), it has been hypothesized that vitamin D may have direct effects on the vascular wall [138, 208, 219, 220].

All the above-mentioned vitamin D-regulated mechanisms may potentially promote vascular calcification. Nonetheless, data on the role of circulating levels of vitamin D on vascular calcification are not consistent. For instance, calcification of coronary arteries, measured by electron beam CT, correlated inversely with $1,25(OH)_2D$ in patients with familial hypercholesterolemia and coronary artery disease and in patients of the Framingham Study [221].

The association of vitamin D with calcification has been tested in CKD patients participating in the Multi-Ethnic Study of Atherosclerosis (MESA); this is the largest study on this issue [222]. After adjustment for many potential confounders (age, gender, race/ethnicity, site, season, physical activity, smoking, body mass index, blood pressure, diabetes, kidney function, CRP, and lipids), lower 25(OH)D concentration was associated with increased risk for developing incident CAC. The association of 25(OH)D with incident CAC was stronger among participants with lower estimated GFR. In the same population, low calcitriol concentrations were associated with increased risk for prevalent and incident CAC, but these associations did not reach statistical significance. Therefore, the authors concluded that lower 25(OH)D concentrations were associated with increased risk for incident CAC and that vitamin D deficiency likely accelerated the development of atherosclerosis.

Vascular calcification is regarded as a surrogate marker of atherosclerosis. The potential contribution of low levels of circulating vitamin D to atherosclerosis is confirmed by the observation that: (1) low 25(OH)D concentrations are associated with increased prevalence of peripheral artery disease, (2) 25(OH)D concentrations are inversely correlated with carotid intima-media thickness in patients with type 2 diabetes, (3) brachial artery flow-mediated dilation is lower in vitamin D-deficient and -insufficient vs. vitamin D-sufficient patients, with the lowest value observed in the vitamin D-deficient patients [223–225].

In contrast, in patients with CKD who had been examined with roentgenography and echocardiography, no relationship was observed with aortic calcification, while a significant inverse relation of vascular stiffness (measured by pulse-wave velocity) with both 25(OH)D and $1,25(OH)_2D$ was seen [226]. Similarly, serum concentrations of $1,25(OH)_2D$ had no significant correlation with levels of coronary calcification, assessed by calibrated CT analysis or coronary angiography [227].

In clinical practice, vitamin D is administered to reduce the circulating levels of PTH. However, in CKD patients it is difficult to determine the ideal level of PTH, on the one hand, and to achieve the ideal balance between PTH reduction and vitamin D-dependent increase of intestinal calcium and phosphate absorption, on the other. Indeed, increased serum phosphorus and calcium may stimulate the vascular calcification process. In addition, excessive vitamin D-dependent reduction of PTH levels causes adynamic bone disease that is associated with vascular calcification. Therefore, difficulties in achieving a stable balance between adaptive mechanisms and all factors regulating mineral metabolism do not allow to firmly establish the effect of supplemental vitamin D on vascular calcification. In addition, there are further factors that may add uncertainty and may be responsible for the conflicting data, such as differences in vitamin D compounds administered, in cumulative doses, and in experimental study models. Finally, endpoints such as lesser episodes of hypercalcemia and/or hypophosphatemia have been used as surrogate indexes indicating the absence of vascular calcification in some experimental and clinical studies with newer vitamin D analogs [228–234].

Experimental studies have established the relevance of dose, differential effects amongst vitamin D analogs and experimental model on the association between supplemental vitamin D and vascular calcification. In bovine vascular smooth muscle cells, $1,25(OH)_2D$ dose dependently increased calcification and alkaline phosphatase (ALP) activity and decreased secretion and gene expression of PTH. Furthermore, $1,25(OH)_2D$ dose dependently increased the expression of the osteopontin gene that contributes to the calcification process [235]. A high dose of cholecalciferol potentiated the calcification process in rats treated with warfarin [236]. In a mouse model of CKD-stimulated atherosclerotic cardiovascular mineralization at dosages sufficient to correct secondary hyperparathyroidism (equivalent to dosages that are used in clinical practice) calcitriol and paricalcitol were protective against aortic calcification, but higher dosages stimulated aortic

calcification [237]. In an in vivo model, doxercalciferol at 0.17 μg/kg raised serum calcium, phosphorus, the calcium-phosphorus product, and aortic calcification in uremic rats receiving a hyperphosphatemia-inducing diet. In contrast, paricalcitol at the same dose had no significant effect. In an ex vivo model, only aortic rings from doxercalciferol uremic rats exhibited a significant increase in Ca uptake. Serum from doxercalciferol-treated uremic rats induced Ca uptake into in vitro smooth muscle cells cultured in high phosphorus [238]. Furthermore, the effects of calcitriol and its analog paricalcitol on VSMC calcification were tested in vitro and in vivo. Cells and animals with 5–6ths nephrectomy were treated with both compounds. Calcitriol, but not paricalcitol, increased VSMC calcification in vitro and in vivo independently of calcium and phosphate levels [239]. Uremic rats were given vehicle, calcitriol, paricalcitol, or doxercalciferol three times a week for 1 month. Calcitriol and doxercalciferol significantly increased the aortic calcium content. Paricalcitol had no effect. A lower doxercalciferol dose increased the aortic calcium content while a higher dose of paricalcitol still had no effect [240]. In contrast, diffuse intimal and medial calcification of the aorta was produced in uremic rats that received low doses of oral calcitriol [241].

It is worth mentioning that few clinical studies have evaluated the per se effect of therapy with vitamin D analogs on vascular calcification; many studies have evaluated the beneficial effects of vitamin D analogs on survival of CKD patients taking in account other factors regulating mineral metabolism [130, 242].

Some studies have demonstrated an association between vitamin D therapy and vascular calcification. For instance, vitamin D therapy was a significant determinant of severity and rate of progression of vascular calcification in patients undergoing prolonged dialysis treatment [243]. Negative effects on calcification were also reported in young adult patients on dialysis; morphological alterations of the heart and arterial calcification were significantly correlated in a dose-dependent manner to the cumulative intake of active vitamin D preparations [244].

Other studies have failed to demonstrate an association between vitamin D therapy and vascular calcification. Indeed, when potential determinants of progressive vascular calcification were explored in 150 randomized CKD patients who underwent electron beam tomography at baseline and at follow-up (week 26 or 52), there was no association between vitamin D3 use and progression of calcification [245]. In patients on different stages of CKD (stage 3 to dialysis), aortic calcification (scored either with CT or X-ray) was not linked to supplementation with calcifediol or cholecalciferol but the increased risk of mortality was dependent on low 25(OH)D levels, suggesting that 25(OH)D may influence survival in CKD patients via additional pathways [246]. Calcitriol intake was not related to the presence of coronary artery calcification; the latter did correlate with higher serum phosphorus, calcium-phosphorus product and daily intake of calcium in pediatric patients with CKD [247]. Finally, calcification scores similarly progressed in hemodialysis patients treated for 12 months with cholecalciferol therapy (25 000 IU every 2 weeks) and in placebo patients [231]. In the treat-to-goal study it was difficult to ascribe the progression in calcification to vitamin D per se, since usage was higher in patients who experienced less calcification over time [248].

It is clinically relevant that the effects on vascular calcification may be diverse depending on the vitamin D compounds and dose administered. Indeed, both carotid intima-media thickness and calcification scores showed a U-shaped distribution across $1,25(OH)_2D$ levels; patients with both low and high $1,25(OH)_2D$ had significantly greater carotid intima-media thickness and calcification score than those with normal levels while 25(OH)D levels did not correlate with any vascular measure [249].

Final suggestions

It is still debated whether in vivo calcitriol and other vitamin D forms can directly induce vascular calcification or whether vascular calcification is due to other factors regulating the mineral metabolism. Indeed, available data do not firmly exclude a negative association between circulating levels of vitamin D as well as of supplemental therapy with the incidence, prevalence and progression of vascular calcification. In this regard, in clinical practice it is important that in reaching the target of serum vitamin D one consider also the serum levels of other factors regulating mineral metabolism.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Holick MF (2014) Sunlight, ultraviolet radiation, vitamin D and skin cancer: how much sunlight do we need? Adv Exp Med Biol 810:1–16
2. Holick MF (2007) Vitamin D deficiency. N Engl J Med 357:266–281. doi:10.1056/NEJMra070553
3. Macdonald HM (2013) Contributions of sunlight and diet to vitamin D status. Calcif Tissue Int 92:163–176. doi:10.1007/s00223-012-9634-1
4. Holick MF (2011) Vitamin D: a d-lightful solution for health. J Investig Med 59:872–880. doi:10.231/JIM.0b013e318214ea2d

5. Reichrath J, Reichrath S (2014) Sunlight, vitamin D and malignant melanoma: an update. Adv Exp Med Biol 810:390–405
6. Reichrath J, Rech M, Moeini M et al (2007) In vitro comparison of the vitamin D endocrine system in 1,25(OH)2D3-responsive and -resistant melanoma cells. Cancer Biol Ther 6:48–55
7. Reddy KK, Gilchrest BA (2014) The role of vitamin D in melanoma prevention: evidence and hyperbole. J Am Acad Dermatol 71:1004–1005. doi:10.1016/j.jaad.2014.08.013
8. Sertznig P, Seifert M, Tilgen W, Reichrath J (2010) Peroxisome proliferator-activated receptor (PPAR) and vitamin D receptor (VDR) signaling pathways in melanoma cells: promising new therapeutic targets? J Steroid Biochem Mol Biol 121:383–386. doi:10.1016/j.jsbmb.2010.03.003
9. Hou W, Wan X, Fan J (2015) Variants Fok1 and Bsm1 on VDR are associated with the melanoma risk: evidence from the published epidemiological studies. BMC Genet 16:14. doi:10.1186/s12863-015-0163-6
10. Field S, Davies J, Bishop DT, Newton-Bishop JA (2013) Vitamin D and melanoma. Dermatoendocrinol 5:121–129. doi:10.4161/derm.25244
11. Bikle DD (2014) Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 21:319–329. doi:10.1016/j.chembiol.2013.12.016
12. Jones G, Strugnell SA, DeLuca HF (1998) Current understanding of the molecular actions of vitamin D. Physiol Rev 78:1193–1231
13. Zhu J, DeLuca HF (2012) Vitamin D 25-hydroxylase—four decades of searching, are we there yet? Arch Biochem Biophys 523:30–36. doi:10.1016/j.abb.2012.01.013
14. Dusso AS (2011) Kidney disease and vitamin D levels: 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and VDR activation. Kidney Int Suppl 1:136–141. doi:10.1038/kisup.2011.30
15. Adams JS, Rafison B, Witzel S et al (2014) Regulation of the extrarenal CYP27B1-hydroxylase. J Steroid Biochem Mol Biol 144((Pt A)):22–27. doi:10.1016/j.jsbmb.2013.12.009
16. Christakos S, Ajibade DV, Dhawan P et al (2010) Vitamin D: metabolism. Endocrinol Metab Clin North Am 39:243–253. doi:10.1016/j.ecl.2010.02.002 **(table of contents)**
17. Bhan I (2014) Vitamin D binding protein and bone health. Int J Endocrinol 2014:561214. doi:10.1155/2014/561214
18. Bikle DD, Siiteri PK, Ryzen E, Haddad JG (1985) Serum protein binding of 1,25-dihydroxyvitamin D: a reevaluation by direct measurement of free metabolite levels. J Clin Endocrinol Metab 61:969–975. doi:10.1210/jcem-61-5-969
19. Jones G, Prosser DE, Kaufmann M (2012) 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch Biochem Biophys 523:9–18. doi:10.1016/j.abb.2011.11.003
20. Henry HL (2011) Regulation of vitamin D metabolism. Best Pract Res Clin Endocrinol Metab 25:531–541. doi:10.1016/j.beem.2011.05.003
21. Ryan JW, Anderson PH, Morris HA (2015) Pleiotropic activities of vitamin D receptors—adequate activation for multiple health outcomes. Clin Biochem Rev 36:53–61
22. Nicolaysen R (1937) Studies upon the mode of action of vitamin D: the influence of vitamin D on the absorption of calcium and phosphorus in the rat. Biochem J 31:122–129
23. Puschett JB, Moranz J, Kurnick WS (1972) Evidence for a direct action of cholecalciferol and 25-hydroxycholecalciferol on the renal transport of phosphate, sodium, and calcium. J Clin Invest 51:373–385. doi:10.1172/JCI106823
24. Lieben L, Masuyama R, Torrekens S et al (2012) Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. J Clin Invest 122:1803–1815. doi:10.1172/JCI45890
25. Lieben L, Carmeliet G (2013) Vitamin D signaling in osteocytes: effects on bone and mineral homeostasis. Bone 54:237–243. doi:10.1016/j.bone.2012.10.007
26. Chertow BS, Baker GR, Henry HL, Norman AW (1980) Effects of vitamin D metabolites on bovine parathyroid hormone release in vitro. Am J Physiol 238:E384–E388
27. Haussler MR, Whitfield GK, Kaneko I et al (2012) The role of vitamin D in the FGF23, klotho, and phosphate bone-kidney endocrine axis. Rev Endocr Metab Disord 13:57–69. doi:10.1007/s11154-011-9199-8
28. Morris HA (2014) Vitamin D activities for health outcomes. Ann Lab Med 34:181–186. doi:10.3343/alm.2014.34.3.181
29. Gonzalez-Parra E, Rojas-Rivera J, Tuñón J et al (2012) Vitamin D receptor activation and cardiovascular disease. Nephrol Dial Transplant 27(Suppl 4):iv17–iv21. doi:10.1093/ndt/gfs534
30. Elder GJ (2007) Vitamin D levels, bone turnover and bone mineral density show seasonal variation in patients with chronic kidney disease stage 5. Nephrol Carlton Vic 12:90–94. doi:10.1111/j.1440-1797.2006.00754.x
31. Forman JP, Giovannucci E, Holmes MD et al (2007) Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension 49:1063–1069. doi:10.1161/HYPERTENSIONAHA.107.087288
32. Wang L, Song Y, Manson JE et al (2012) Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 5:819–829. doi:10.1161/CIRCOUTCOMES.112.967604
33. Rizzoli R, Boonen S, Brandi M-L et al (2013) Vitamin D supplementation in elderly or postmenopausal women: a 2013 update of the 2008 recommendations from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Curr Med Res Opin 29:305–313. doi:10.1185/03007995.2013.766162
34. Forouhi NG, Luan J, Cooper A et al (2008) Baseline serum 25-hydroxy vitamin D is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. Diabetes 57:2619–2625. doi:10.2337/db08-0593
35. Ginde AA, Mansbach JM, Camargo CA (2009) Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 169:384–390. doi:10.1001/archinternmed.2008.560
36. Pilz S, Kienreich K, Tomaschitz A et al (2013) Vitamin D and cancer mortality: systematic review of prospective epidemiological studies. Anticancer Agents Med Chem 13:107–117
37. Schöttker B, Haug U, Schomburg L et al (2013) Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. Am J Clin Nutr 97:782–793. doi:10.3945/ajcn.112.047712
38. Ravani P, Malberti F, Tripepi G et al (2009) Vitamin D levels and patient outcome in chronic kidney disease. Kidney Int 75:88–95. doi:10.1038/ki.2008.501
39. Ureña-Torres P, Metzger M, Haymann JP et al (2011) Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD. Am J Kidney Dis 58:544–553. doi:10.1053/j.ajkd.2011.04.029
40. Ross AC, Manson JE, Abrams SA et al (2011) The 2011 Report on Dietary Reference Intakes for Calcium and Vitamin D from the Institute of Medicine: What Clinicians Need to Know. J Clin Endocrinol Metab 96:53–58. doi:10.1210/jc.2010-2704
41. Holick MF, Binkley NC, Bischoff-Ferrari HA et al (2011) Evaluation, treatment, and prevention of vitamin D deficiency:

an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930. doi:10.1210/jc.2011-0385
42. Dawson-Hughes B, Mithal A, Bonjour J-P et al (2010) IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 21:1151–1154. doi:10.1007/s00198-010-1285-3
43. Nkf K (2003) DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42:1–202
44. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group (2009) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. doi:10.1038/ki.2009.188
45. KDIGO CKD Work Group (2012) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 3:1–150
46. Goldsmith DJA, Covic A, Fouque D et al (2010) 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 25:3823–3831. doi:10.1093/ndt/gfq513
47. Chronic kidney disease in adults: assessment and management | Guidance and guidelines | NICE; https://www.nice.org.uk/guidance/cg182. Accessed 15 Dec 2015
48. Tripkovic L, Lambert H, Hart K et al (2012) Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 95:1357–1364. doi:10.3945/ajcn.111.031070
49. Houghton LA, Vieth R (2006) The case against ergocalciferol (vitamin D2) as a vitamin supplement. Am J Clin Nutr 84:694–697
50. Horst RL, Reinhardt TA, Ramberg CF et al (1986) 24-Hydroxylation of 1,25-dihydroxyergocalciferol. An unambiguous deactivation process. J Biol Chem 261:9250–9256
51. Kandula P, Dobre M, Schold JD et al (2011) Vitamin D supplementation in chronic kidney disease: a systematic review and meta-analysis of observational studies and randomized controlled trials. Clin J Am Soc Nephrol CJASN 6:50–62. doi:10.2215/CJN.03940510
52. Nigwekar SU, Bhan I, Thadhani R (2012) Ergocalciferol and cholecalciferol in CKD. Am J Kidney Dis 60:139–156. doi:10.1053/j.ajkd.2011.12.035
53. Chandra P, Binongo JNG, Ziegler TR et al (2008) Cholecalciferol (vitamin D3) therapy and vitamin D insufficiency in patients with chronic kidney disease: a randomized controlled pilot study. Endocr Pract 14:10–17. doi:10.4158/EP.14.1.10
54. Sprague SM, Silva AL, Al-Saghir F et al (2014) Modified-release calcifediol effectively controls secondary hyperparathyroidism associated with vitamin D insufficiency in chronic kidney disease. Am J Nephrol 40:535–545. doi:10.1159/000369939
55. Moe SM, Saifullah A, LaClair RE et al (2010) A randomized trial of cholecalciferol versus doxercalciferol for lowering parathyroid hormone in chronic kidney disease. Clin J Am Soc Nephrol CJASN 5:299–306. doi:10.2215/CJN.07131009
56. Kovesdy CP, Lu JL, Malakauskas SM et al (2012) Paricalcitol versus ergocalciferol for secondary hyperparathyroidism in CKD stages 3 and 4: a randomized controlled trial. Am J Kidney Dis 59:58–66. doi:10.1053/j.ajkd.2011.06.027
57. Molina P, Górriz JL, Molina MD et al (2014) The effect of cholecalciferol for lowering albuminuria in chronic kidney disease: a prospective controlled study. Nephrol Dial Transplant 29:97–109. doi:10.1093/ndt/gft360
58. Cupisti A, Vigo V, Baronti ME et al (2015) Vitamin D status and cholecalciferol supplementation in chronic kidney disease patients: an Italian cohort report. Int J Nephrol Renov Dis 8:151–157. doi:10.2147/IJNRD.S90968
59. Kooienga L, Fried L, Scragg R et al (2009) The effect of combined calcium and vitamin D3 supplementation on serum intact parathyroid hormone in moderate CKD. Am J Kidney Dis 53:408–416. doi:10.1053/j.ajkd.2008.09.020
60. Marckmann P, Agerskov H, Thineshkumar S et al (2012) Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. Nephrol Dial Transplant 27:3523–3531. doi:10.1093/ndt/gfs138
61. Alvarez JA, Law J, Coakley KE et al (2012) High-dose cholecalciferol reduces parathyroid hormone in patients with early chronic kidney disease: a pilot, randomized, double-blind, placebo-controlled trial. Am J Clin Nutr 96:672–679. doi:10.3945/ajcn.112.040642
62. Shroff R, Wan M, Gullett A et al (2012) Ergocalciferol supplementation in children with CKD delays the onset of secondary hyperparathyroidism: a randomized trial. Clin J Am Soc Nephrol CJASN 7:216–223. doi:10.2215/CJN.04760511
63. Jean G, Vanel T, Terrat J-C, Chazot C (2010) Prevention of secondary hyperparathyroidism in hemodialysis patients: the key role of native vitamin D supplementation. Hemodial Int 14:486–491. doi:10.1111/j.1542-4758.2010.00472.x
64. Nordal KP, Dahl E (1988) Low dose calcitriol versus placebo in patients with predialysis chronic renal failure. J Clin Endocrinol Metab 67:929–936. doi:10.1210/jcem-67-5-929
65. Hamdy NA, Kanis JA, Beneton MN et al (1995) Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. BMJ 310:358–363
66. Mazzaferro S, Goldsmith D, Larsson TE et al (2014) Vitamin D metabolites and/or analogs: which D for which patient? Curr Vasc Pharmacol 12:339–349
67. Galassi A, Bellasi A, Auricchio S et al (2013) Which vitamin D in CKD-MBD? The time of burning questions. BioMed Res Int 2013:864012. doi:10.1155/2013/864012
68. Coyne D, Acharya M, Qiu P et al (2006) Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. Am J Kidney Dis 47:263–276. doi:10.1053/j.ajkd.2005.10.007
69. Coyne DW, Goldberg S, Faber M et al (2014) A randomized multicenter trial of paricalcitol versus calcitriol for secondary hyperparathyroidism in stages 3–4 CKD. Clin J Am Soc Nephrol CJASN 9:1620–1626. doi:10.2215/CJN.10661013
70. Coyne DW, Andress DL, Amdahl MJ et al (2013) Effects of paricalcitol on calcium and phosphate metabolism and markers of bone health in patients with diabetic nephropathy: results of the VITAL study. Nephrol Dial Transplant 28:2260–2268. doi:10.1093/ndt/gft227
71. Martinez-Fernandez I, Saracho R (2015) Effects of paricalcitol on urinary calcium in patients with chronic kidney disease stages 2–4. Clin Nephrol 83:201–207. doi:10.5414/CN108306
72. Xu L, Wan X, Huang Z et al (2013) Impact of vitamin D on chronic kidney diseases in non-dialysis patients: a meta-analysis of randomized controlled trials. PLoS ONE 8:e61387. doi:10.1371/journal.pone.0061387
73. Slatopolsky E, Cozzolino M, Lu Y et al (2003) Efficacy of 19-Nor-1,25-(OH)2D2 in the prevention and treatment of hyperparathyroid bone disease in experimental uremia. Kidney Int 63:2020–2027. doi:10.1046/j.1523-1755.2003.00029.x
74. Balint E, Marshall CF, Sprague SM (2000) Effect of the vitamin D analogues paricalcitol and calcitriol on bone mineral in vitro. Am J Kidney Dis 36:789–796. doi:10.1053/ajkd.2000.17667
75. Nakane M, Fey TA, Dixon DB et al (2006) Differential effects of Vitamin D analogs on bone formation and resorption.

J Steroid Biochem Mol Biol 98:72–77. doi:10.1016/j.jsbmb.2005.07.007
76. Finch JL, Tokumoto M, Nakamura H et al (2010) Effect of paricalcitol and cinacalcet on serum phosphate, FGF-23, and bone in rats with chronic kidney disease. Am J Physiol Renal Physiol 298:F1315–F1322. doi:10.1152/ajprenal.00552.2009
77. Hallan SI, Matsushita K, Sang Y et al (2012) Age and association of kidney measures with mortality and end-stage renal disease. JAMA 308:2349–2360. doi:10.1001/jama.2012.16817
78. Kim MJ, Frankel AH, Donaldson M et al (2011) Oral cholecalciferol decreases albuminuria and urinary TGF-β1 in patients with type 2 diabetic nephropathy on established renin-angiotensin-aldosterone system inhibition. Kidney Int 80:851–860. doi:10.1038/ki.2011.224
79. Huang Y, Yu H, Lu J et al (2012) Oral supplementation with cholecalciferol 800 IU ameliorates albuminuria in Chinese type 2 diabetic patients with nephropathy. PLoS ONE 7:e50510. doi:10.1371/journal.pone.0050510
80. Ahmadi N, Mortazavi M, Iraj B, Askari G (2013) Whether vitamin D3 is effective in reducing proteinuria in type 2 diabetic patients? J Res Med Sci 18:374–377
81. Oksa A, Spustová V, Krivosíková Z et al (2008) Effects of long-term cholecalciferol supplementation on mineral metabolism and calciotropic hormones in chronic kidney disease. Kidney Blood Press Res 31:322–329. doi:10.1159/000157177
82. de Borst MH, Hajhosseiny R, Tamez H et al (2013) Active vitamin D treatment for reduction of residual proteinuria: a systematic review. J Am Soc Nephrol JASN 24:1863–1871. doi:10.1681/ASN.2013030203
83. de Zeeuw D, Agarwal R, Amdahl M et al (2010) Selective vitamin D receptor activation with paricalcitol for reduction of albuminuria in patients with type 2 diabetes (VITAL study): a randomised controlled trial. Lancet Lond Engl 376:1543–1551. doi:10.1016/S0140-6736(10)61032-X
84. Krairittichai U, Mahannopkul R, Bunnag S (2012) An open label, randomized controlled study of oral calcitriol for the treatment of proteinuria in patients with diabetic kidney disease. J Med Assoc Thai 95(Suppl 3):S41–S47
85. Liu L-J, Lv J-C, Shi S-F et al (2012) Oral calcitriol for reduction of proteinuria in patients with IgA nephropathy: a randomized controlled trial. Am J Kidney Dis 59:67–74. doi:10.1053/j.ajkd.2011.09.014
86. Agarwal R, Acharya M, Tian J et al (2005) Antiproteinuric effect of oral paricalcitol in chronic kidney disease. Kidney Int 68:2823–2828. doi:10.1111/j.1523-1755.2005.00755.x
87. Fishbane S, Chittineni H, Packman M et al (2009) Oral paricalcitol in the treatment of patients with CKD and proteinuria: a randomized trial. Am J Kidney Dis 54:647–652. doi:10.1053/j.ajkd.2009.04.036
88. Thadhani R, Appelbaum E, Pritchett Y et al (2012) Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA 307:674–684. doi:10.1001/jama.2012.120
89. Bae S, Yalamarti B, Ke Q et al (2011) Preventing progression of cardiac hypertrophy and development of heart failure by paricalcitol therapy in rats. Cardiovasc Res 91:632–639. doi:10.1093/cvr/cvr133
90. Wu J, Garami M, Cheng T, Gardner DG (1996) 1,25(OH)2 vitamin D3, and retinoic acid antagonize endothelin-stimulated hypertrophy of neonatal rat cardiac myocytes. J Clin Invest 97:1577–1588. doi:10.1172/JCI118582
91. Bodyak N, Ayus JC, Achinger S et al (2007) Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci USA 104:16810–16815. doi:10.1073/pnas.0611202104
92. Wang AY-M, Fang F, Chan J et al (2014) Effect of paricalcitol on left ventricular mass and function in CKD–the OPERA trial. J Am Soc Nephrol JASN 25:175–186. doi:10.1681/ASN.2013010103
93. Lac PT, Choi K, Liu I-A et al (2010) The effects of changing vitamin D levels on anemia in chronic kidney disease patients: a retrospective cohort review. Clin Nephrol 74:25–32
94. Kiss Z, Ambrus C, Almasi C et al (2011) Serum 25(OH)-cholecalciferol concentration is associated with hemoglobin level and erythropoietin resistance in patients on maintenance hemodialysis. Nephron Clin Pract 117:c373–c378. doi:10.1159/000321521
95. Kumar VA, Kujubu DA, Sim JJ et al (2011) Vitamin D supplementation and recombinant human erythropoietin utilization in vitamin D-deficient hemodialysis patients. J Nephrol 24:98–105
96. Rianthavorn P, Boonyapapong P (2013) Ergocalciferol decreases erythropoietin resistance in children with chronic kidney disease stage 5. Pediatr Nephrol Berl Ger 28:1261–1266. doi:10.1007/s00467-013-2431-x
97. Zughaier SM, Alvarez JA, Sloan JH et al (2014) The role of vitamin D in regulating the iron-hepcidin-ferroportin axis in monocytes. J Clin Transl Endocrinol 1:19–25. doi:10.1016/j.jcte.2014.01.003
98. Brancaccio D, Cozzolino M, Gallieni M (2004) Hyperparathyroidism and anemia in uremic subjects: a combined therapeutic approach. J Am Soc Nephrol JASN 15(Suppl 1):S21–S24
99. Nemeth E, Tuttle MS, Powelson J et al (2004) Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 306:2090–2093. doi:10.1126/science.1104742
100. Aucella F, Scalzulli RP, Gatta G et al (2003) Calcitriol increases burst-forming unit-erythroid proliferation in chronic renal failure. A synergistic effect with r-HuEpo. Nephron Clin Pract 95:c121–c127. doi:10.1093/ndt/14.5.1171
101. Riccio E, Sabbatini M, Bruzzese D et al (2015) Effect of paricalcitol vs calcitriol on hemoglobin levels in chronic kidney disease patients: a randomized trial. PLoS ONE 10:e0118174. doi:10.1371/journal.pone.0118174
102. Mann MC, Hobbs AJ, Hemmelgarn BR et al (2015) Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: a meta-analysis. Clin Kidney J 8:41–48. doi:10.1093/ckj/sfu122
103. Morrone LF, Cozzolino M (2015) The beneficial impact of vitamin D treatment in CKD patients: what's next? Clin Kidney J 8:38–40. doi:10.1093/ckj/sfu135
104. Almirall J, Vaqueiro M, Baré ML, Anton E (2010) Association of low serum 25-hydroxyvitamin D levels and high arterial blood pressure in the elderly. Nephrol Dial Transplant 25:503–509. doi:10.1093/ndt/gfp470
105. Argilés A, Lorho R, Servel M-F et al (2002) Blood pressure is correlated with vitamin D(3) serum levels in dialysis patients. Blood Purif 20:370–375. doi:10.1159/000063106
106. Krause R, Bühring M, Hopfenmüller W et al (1998) Ultraviolet B and blood pressure. Lancet Lond Engl 352:709–710. doi:10.1016/S0140-6736(05)60827-6
107. Drechsler C, Verduijn M, Pilz S et al (2011) Vitamin D status and clinical outcomes in incident dialysis patients: results from the NECOSAD study. Nephrol Dial Transplant 26:1024–1032. doi:10.1093/ndt/gfq606
108. Wang AY-M, Lam CW-K, Sanderson JE et al (2008) Serum 25-hydroxyvitamin D status and cardiovascular outcomes in chronic peritoneal dialysis patients: a 3-y prospective cohort study. Am J Clin Nutr 87:1631–1638
109. Bucharles S, Barberato SH, Stinghen AEM et al (2012) Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without

hyperparathyroidism. J Ren Nutr 22:284–291. doi:10.1053/j.jrn.2011.07.001
110. Matias PJ, Jorge C, Ferreira C et al (2010) Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. Clin J Am Soc Nephrol CJASN 5:905–911. doi:10.2215/CJN.06510909
111. Stubbs JR, Idiculla A, Slusser J et al (2010) Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD. J Am Soc Nephrol JASN 21:353–361. doi:10.1681/ASN.2009040451
112. Goldsmith DJA, Cunningham J (2011) Mineral metabolism and vitamin D in chronic kidney disease–more questions than answers. Nat Rev Nephrol 7:341–346. doi:10.1038/nrneph.2011.53
113. Del Valle E, Negri AL, Fradinger E et al (2015) Weekly high-dose ergocalciferol to correct vitamin D deficiency/insufficiency in hemodialysis patients: a pilot trial. Hemodial Int 19:60–65. doi:10.1111/hdi.12209
114. Melamed ML, Thadhani RI (2012) Vitamin D therapy in chronic kidney disease and end stage renal disease. Clin J Am Soc Nephrol CJASN 7:358–365. doi:10.2215/CJN.04040411
115. Goldsmith DJA, Massy ZA, Brandenburg V (2014) The uses and abuses of Vitamin D compounds in chronic kidney disease-mineral bone disease (CKD-MBD). Semin Nephrol 34:660–668. doi:10.1016/j.semnephrol.2014.10.002
116. Wolf M, Shah A, Gutierrez O et al (2007) Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 72:1004–1013. doi:10.1038/sj.ki.5002451
117. Jean G, Lataillade D, Genet L et al (2011) Impact of hypovitaminosis D and alfacalcidol therapy on survival of hemodialysis patients: results from the French ARNOS study. Nephron Clin Pract 118:c204–c210. doi:10.1159/000321507
118. Krause R, Schober-Halstenberg H-J, Edenharter G et al (2012) Vitamin D status and mortality of German hemodialysis patients. Anticancer Res 32:391–395
119. Daroux M, Shenouda M, Bacri J-L et al (2013) Vitamin D2 versus vitamin D3 supplementation in hemodialysis patients: a comparative pilot study. J Nephrol 26:152–157. doi:10.5301/jn.5000123
120. Armas LAG, Andukuri R, Barger-Lux J et al (2012) 25-Hydroxyvitamin D response to cholecalciferol supplementation in hemodialysis. Clin J Am Soc Nephrol CJASN 7:1428–1434. doi:10.2215/CJN.12761211
121. Wasse H, Huang R, Long Q et al (2012) Efficacy and safety of a short course of very-high-dose cholecalciferol in hemodialysis. Am J Clin Nutr 95:522–528. doi:10.3945/ajcn.111.025502
122. Delanaye P, Weekers L, Warling X et al (2013) Cholecalciferol in haemodialysis patients: a randomized, double-blind, proof-of-concept and safety study. Nephrol Dial Transplant 28:1779–1786. doi:10.1093/ndt/gft001
123. Hewitt NA, O'Connor AA, O'Shaughnessy DV, Elder GJ (2013) Effects of cholecalciferol on functional, biochemical, vascular, and quality of life outcomes in hemodialysis patients. Clin J Am Soc Nephrol CJASN 8:1143–1149. doi:10.2215/CJN.02840312
124. Massart A, Debelle FD, Racapé J et al (2014) Biochemical parameters after cholecalciferol repletion in hemodialysis: results From the VitaDial randomized trial. Am J Kidney Dis 64:696–705. doi:10.1053/j.ajkd.2014.04.020
125. Bhan I, Dobens D, Tamez H et al (2015) Nutritional vitamin D supplementation in dialysis: a randomized trial. Clin J Am Soc Nephrol CJASN 10:611–619. doi:10.2215/CJN.06910714
126. Chonchol M, Greene T, Zhang Y et al (2015) Low Vitamin D and High Fibroblast Growth Factor 23 Serum Levels Associate with Infectious and Cardiac Deaths in the HEMO Study. J Am Soc Nephrol JASN. doi:10.1681/ASN.2014101009
127. Miskulin DC, Majchrzak K, Tighiouart H et al (2015) Ergocalciferol supplementation in hemodialysis patients with vitamin D deficiency: a randomized clinical trial. J Am Soc Nephrol JASN. doi:10.1681/ASN.2015040468
128. Zheng Z, Shi H, Jia J et al (2013) Vitamin D supplementation and mortality risk in chronic kidney disease: a meta-analysis of 20 observational studies. BMC Nephrol 14:199. doi:10.1186/1471-2369-14-199
129. Galassi A, Bellasi A, Auricchio S et al (2013) Which vitamin D in CKD-MBD? The time of burning questions. BioMed Res Int 2013:e864012. doi:10.1155/2013/864012
130. Teng M, Wolf M, Lowrie E et al (2003) Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 349:446–456. doi:10.1056/NEJMoa022536
131. Teng M, Wolf M, Ofsthun MN et al (2005) Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol JASN 16:1115–1125. doi:10.1681/ASN.2004070573
132. Messa P, Cozzolino M, Brancaccio D et al (2015) Effect of VDRA on survival in incident hemodialysis patients: results of the FARO-2 observational study. BMC Nephrol 16:11. doi:10.1186/s12882-015-0006-8
133. Kovesdy CP, Kalantar-Zadeh K (2008) Vitamin D receptor activation and survival in chronic kidney disease. Kidney Int 73:1355–1363. doi:10.1038/ki.2008.35
134. Tentori F, Albert JM, Young EW et al (2009) The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant 24:963–972. doi:10.1093/ndt/gfn592
135. Brancaccio D, Cozzolino M, Cannella G et al (2011) Secondary hyperparathyroidism in chronic dialysis patients: results of the Italian FARO survey on treatment and mortality. Blood Purif 32:124–132. doi:10.1159/000325454
136. Tentori F, Hunt WC, Stidley CA et al (2006) Mortality risk among hemodialysis patients receiving different vitamin D analogs. Kidney Int 70:1858–1865. doi:10.1038/sj.ki.5001868
137. Keyzer CA, Riphagen IJ, Joosten MM et al (2015) Associations of 25(OH) and 1,25(OH)2 vitamin D with long-term outcomes in stable renal transplant recipients. J Clin Endocrinol Metab 100:81–89. doi:10.1210/jc.2014-3012
138. Dusso AS, Brown AJ, Slatopolsky E (2005) Vitamin D. Am J Physiol Renal Physiol 289:F8–28. doi:10.1152/ajprenal.00336.2004
139. Alshayeb HM, Josephson MA, Sprague SM (2013) CKD-mineral and bone disorder management in kidney transplant recipients. Am J Kidney Dis 61:310–325. doi:10.1053/j.ajkd.2012.07.022
140. Tripathi SS, Gibney EM, Gehr TWB et al (2008) High prevalence of vitamin D deficiency in African American kidney transplant recipients. Transplantation 85:767–770. doi:10.1097/TP.0b013e3181613fb5
141. Querings K, Girndt M, Geisel J et al (2006) 25-Hydroxyvitamin D deficiency in renal transplant recipients. J Clin Endocrinol Metab 91:526–529. doi:10.1210/jc.2005-0547
142. Bienaimé F, Girard D, Anglicheau D et al (2013) Vitamin D status and outcomes after renal transplantation. J Am Soc Nephrol JASN 24:831–841. doi:10.1681/ASN.2012060614
143. Barros X, Fuster D, Rodríguez N et al (2015) Rapid calcitriol increase and persistent calcidiol insufficiency in the first 6 months after kidney transplantation. Nucl Med Commun 36:489–493. doi:10.1097/MNM.0000000000000265
144. Economidou D, Dovas S, Papagianni A et al (2009) FGF-23 levels before and after renal transplantation. J Transplant 2009:379082. doi:10.1155/2009/379082
145. Evenepoel P, Meijers BKI, de Jonge H et al (2008) Recovery of hyperphosphatoninism and renal phosphorus wasting one year

after successful renal transplantation. Clin J Am Soc Nephrol CJASN 3:1829–1836. doi:10.2215/CJN.01310308
146. Sánchez Fructuoso AI, Maestro ML, Pérez-Flores I et al (2012) Serum level of fibroblast growth factor 23 in maintenance renal transplant patients. Nephrol Dial Transplant 27:4227–4235. doi:10.1093/ndt/gfs409
147. Mazzaferro S, Pasquali M, Pugliese F et al (2012) Distinct impact of vitamin D insufficiency on calcitriol levels in chronic renal failure and renal transplant patients: a role for FGF23. J Nephrol 25:1108–1118. doi:10.5301/jn.5000102
148. Sánchez Fructuoso AI, Maestro ML, Calvo N et al (2012) Role of fibroblast growth factor 23 (FGF23) in the metabolism of phosphorus and calcium immediately after kidney transplantation. Transplant Proc 44:2551–2554. doi:10.1016/j.transproceed.2012.09.070
149. Akeno N, Matsunuma A, Maeda T et al (2000) Regulation of vitamin D-1alpha-hydroxylase and -24-hydroxylase expression by dexamethasone in mouse kidney. J Endocrinol 164:339–348
150. Neves CL, dos Reis LM, Batista DG et al (2013) Persistence of bone and mineral disorders 2 years after successful kidney transplantation. Transplantation 96:290–296. doi:10.1097/TP.0b013e3182985468
151. Filipov JJ, Zlatkov BK, Dimitrov EP, Svinarov D (2015) Relationship between vitamin D status and immunosuppressive therapy in kidney transplant recipients. Biotechnol Biotechnol Equip 29:331–335. doi:10.1080/13102818.2014.995415
152. Lee C-T, Ng H-Y, Lien Y-H et al (2011) Effects of cyclosporine, tacrolimus and rapamycin on renal calcium transport and vitamin D metabolism. Am J Nephrol 34:87–94. doi:10.1159/000328874
153. Westenfeld R, Schlieper G, Wöltje M et al (2011) Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis—implications for post-transplantation bone disease. Nephrol Dial Transplant 26:4115–4123. doi:10.1093/ndt/gfr214
154. Anderson PH, Lam NN, Turner AG et al (2013) The pleiotropic effects of vitamin D in bone. J Steroid Biochem Mol Biol 136:190–194. doi:10.1016/j.jsbmb.2012.08.008
155. Brandenburg VM, Politt D, Ketteler M et al (2004) Early rapid loss followed by long-term consolidation characterizes the development of lumbar bone mineral density after kidney transplantation. Transplantation 77:1566–1571
156. Kodras K, Haas M (2006) Effect of kidney transplantation on bone. Eur J Clin Invest 36(Suppl 2):63–75. doi:10.1111/j.1365-2362.2006.01662.x
157. Carlini RG, Rojas E, Weisinger JR et al (2000) Bone disease in patients with long-term renal transplantation and normal renal function. Am J Kidney Dis 36:160–166. doi:10.1053/ajkd.2000.8289
158. Ball AM, Gillen DL, Sherrard D et al (2002) Risk of hip fracture among dialysis and renal transplant recipients. JAMA 288:3014–3018
159. Brandenburg VM, Westenfeld R, Ketteler M (2004) The fate of bone after renal transplantation. J Nephrol 17:190–204
160. Borchhardt K, Sulzbacher I, Benesch T et al (2007) Low-turnover bone disease in hypercalcemic hyperparathyroidism after kidney transplantation. Am J Transplant 7:2515–2521. doi:10.1111/j.1600-6143.2007.01950.x
161. Campistol JM, Holt DW, Epstein S et al (2005) Bone metabolism in renal transplant patients treated with cyclosporine or sirolimus. Transpl Int 18:1028–1035. doi:10.1111/j.1432-2277.2005.00163.x
162. Kahwaji J, Bunnapradist S, Hsu J-W et al (2011) Cause of death with graft function among renal transplant recipients in an integrated healthcare system. Transplantation 91:225–230. doi:10.1097/TP.0b013e3181ff8754
163. Marcén R, Jimenez S, Fernández-Rodriguez A et al (2012) Are low levels of 25-hydroxyvitamin D a risk factor for cardiovascular diseases or malignancies in renal transplantation? Nephrol Dial Transplant 27(Suppl 4):iv47–iv52. doi:10.1093/ndt/gfs508
164. Yilmaz MI, Sonmez A, Saglam M et al (2013) Longitudinal analysis of vascular function and biomarkers of metabolic bone disorders before and after renal transplantation. Am J Nephrol 37:126–134. doi:10.1159/000346711
165. Obi Y, Hamano T, Ichimaru N et al (2014) Vitamin D deficiency predicts decline in kidney allograft function: a prospective cohort study. J Clin Endocrinol Metab 99:527–535. doi:10.1210/jc.2013-2421
166. Amer H, Cosio FG (2009) Significance and management of proteinuria in kidney transplant recipients. J Am Soc Nephrol JASN 20:2490–2492. doi:10.1681/ASN.2008091005
167. Wissing KM, Broeders N, Moreno-Reyes R et al (2005) A controlled study of vitamin D3 to prevent bone loss in renal-transplant patients receiving low doses of steroids. Transplantation 79:108–115
168. Courbebaisse M, Thervet E, Souberbielle JC et al (2009) Effects of vitamin D supplementation on the calcium-phosphate balance in renal transplant patients. Kidney Int 75:646–651. doi:10.1038/ki.2008.549
169. Stavroulopoulos A, Cassidy MJD, Porter CJ et al (2007) Vitamin D status in renal transplant recipients. Am J Transplant 7:2546–2552. doi:10.1111/j.1600-6143.2007.01978.x
170. Cueto-Manzano AM, Konel S, Freemont AJ et al (2000) Effect of 1,25-dihydroxyvitamin D3 and calcium carbonate on bone loss associated with long-term renal transplantation. Am J Kidney Dis 35:227–236
171. Torres A, García S, Gómez A et al (2004) Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. Kidney Int 65:705–712. doi:10.1111/j.1523-1755.2004.00432.x
172. Mainra R, Elder GJ (2010) Individualized therapy to prevent bone mineral density loss after kidney and kidney-pancreas transplantation. Clin J Am Soc Nephrol CJASN 5:117–124. doi:10.2215/CJN.03770609
173. Gonzalez E, Rojas-Rivera J, Polanco N et al (2013) Effects of oral paricalcitol on secondary hyperparathyroidism and proteinuria of kidney transplant patients. Transplantation 95:e49–e52. doi:10.1097/TP.0b013e3182855565
174. Amer H, Griffin MD, Stegall MD et al (2013) Oral paricalcitol reduces the prevalence of posttransplant hyperparathyroidism: results of an open label randomized trial. Am J Transplant 13:1576–1585. doi:10.1111/ajt.12227
175. Trillini M, Cortinovis M, Ruggenenti P et al (2015) Paricalcitol for secondary hyperparathyroidism in renal transplantation. J Am Soc Nephrol JASN 26:1205–1214. doi:10.1681/ASN.2013111185
176. Courbebaisse M, Xu-Dubois Y-C, Thervet E et al (2011) Cholecalciferol supplementation does not protect against renal allograft structural and functional deterioration: a retrospective study. Transplantation 91:207–212. doi:10.1097/TP.0b013e318200ba37
177. Courbebaisse M, Alberti C, Colas S et al (2014) VITamin D supplementation in renAL transplant recipients (VITALE): a prospective, multicentre, 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 15:430. doi:10.1186/1745-6215-15-430
178. Salam SN, Eastell R, Khwaja A (2014) Fragility fractures and osteoporosis in CKD: pathophysiology and diagnostic methods. Am J Kidney Dis 63:1049–1059. doi:10.1053/j.ajkd.2013.12.016

179. Rachner TD, Khosla S, Hofbauer LC (2011) Osteoporosis: now and the future. Lancet Lond Engl 377:1276–1287. doi:10.1016/S0140-6736(10)62349-5
180. Genant HK, Cooper C, Poor G et al (1999) Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. Osteoporos Int 10:259–264
181. Moorthi RN, Moe SM (2013) Recent advances in the noninvasive diagnosis of renal osteodystrophy. Kidney Int 84:886–894. doi:10.1038/ki.2013.254
182. Coen G (2005) Adynamic bone disease: an update and overview. J Nephrol 18:117–122
183. Hutchison AJ, Whitehouse RW, Freemont AJ et al (1994) Histological, radiological, and biochemical features of the adynamic bone lesion in continuous ambulatory peritoneal dialysis patients. Am J Nephrol 14:19–29
184. Couttenye MM, D'Haese PC, Deng JT et al (1997) High prevalence of adynamic bone disease diagnosed by biochemical markers in a wide sample of the European CAPD population. Nephrol Dial Transplant 12:2144–2150
185. Belbrik S, Marie A, Boudailliez B et al (1990) Prevalence of histological types of bone disease in a hemodialysis center limiting the oral intake of aluminum hydroxide. Néphrologie 11:83–90
186. Gerakis A, Hadjidakis D, Kokkinakis E et al (2000) Correlation of bone mineral density with the histological findings of renal osteodystrophy in patients on hemodialysis. J Nephrol 13:437–443
187. Torres PU, Bover J, Mazzaferro S et al (2014) When, how, and why a bone biopsy should be performed in patients with chronic kidney disease. Semin Nephrol 34:612–625. doi:10.1016/j.semnephrol.2014.09.004
188. Malluche HH, Mawad HW, Monier-Faugere M-C (2011) Renal osteodystrophy in the first decade of the new millennium: analysis of 630 bone biopsies in black and white patients. J Bone Miner Res 26:1368–1376. doi:10.1002/jbmr.309
189. Barreto FC, Barreto DV, Moysés RMA et al (2008) K/DOQI-recommended intact PTH levels do not prevent low-turnover bone disease in hemodialysis patients. Kidney Int 73:771–777. doi:10.1038/sj.ki.5002769
190. Sardiwal S, Magnusson P, Goldsmith DJA, Lamb EJ (2013) Bone alkaline phosphatase in CKD-mineral bone disorder. Am J Kidney Dis 62:810–822. doi:10.1053/j.ajkd.2013.02.366
191. Lima F, El-Husseini A, Monier-Faugere M-C et al (2014) FGF-23 serum levels and bone histomorphometric results in adult patients with chronic kidney disease on dialysis. Clin Nephrol 82:287–295. doi:10.5414/CN108407
192. Ballanti P, Wedard BM, Bonucci E (1996) Frequency of adynamic bone disease and aluminum storage in Italian uraemic patients—retrospective analysis of 1429 iliac crest biopsies. Nephrol Dial Transplant 11:663–667
193. Palcu P, Dion N, Ste-Marie L-G et al (2015) Teriparatide and bone turnover and formation in a hemodialysis patient with low-turnover bone disease: a case report. Am J Kidney Dis 65:933–936. doi:10.1053/j.ajkd.2015.01.025
194. Dukkipati R, Kovesdy CP, Colman S et al (2010) Association of relatively low serum parathyroid hormone with malnutrition-inflammation complex and survival in maintenance hemodialysis patients. J Ren Nutr 20:243–254. doi:10.1053/j.jrn.2009.10.006
195. Morrone LF, Mazzaferro S, Russo D et al (2009) Interaction between parathyroid hormone and the Charlson comorbidity index on survival of incident haemodialysis patients. Nephrol Dial Transplant 24:2859–2865. doi:10.1093/ndt/gfp170
196. Fernández-Martín JL, Martínez-Camblor P, Dionisi MP et al (2015) Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrol Dial Transplant 30:1542–1551. doi:10.1093/ndt/gfv099
197. Mathew AT, Hazzan A, Jhaveri KD et al (2014) Increasing hip fractures in patients receiving hemodialysis and peritoneal dialysis. Am J Nephrol 40:451–457. doi:10.1159/000369039
198. Liu W-C, Yen J-F, Lang C-L et al (2013) Bisphophonates in CKD patients with low bone mineral density. ScientificWorldJournal 2013:837573. doi:10.1155/2013/837573
199. Hiramatsu R, Ubara Y, Sawa N et al (2015) Denosumab for low bone mass in hemodialysis patients: a noncontrolled trial. Am J Kidney Dis 66:175–177. doi:10.1053/j.ajkd.2015.03.012
200. Uhlig K, Berns JS, Kestenbaum B et al (2010) KDOQI US commentary on the 2009 KDIGO clinical practice guideline for the diagnosis, evaluation, and treatment of CKD-mineral and bone disorder (CKD-MBD). Am J Kidney Dis 55:773–799. doi:10.1053/j.ajkd.2010.02.340
201. Bolasco P, Altieri P (1994) Pulses di calcitriolo endovena nel trattamento dell'iperparatiroidismo secondario nei pazienti in emodialisi cronica: esperienza a lungo termine. G Ital Nefrol 11:377–382
202. Cozzolino M, Brancaccio D, Cannella G et al (2012) VDRA therapy is associated with improved survival in dialysis patients with serum intact PTH $\leq$150 pg/ml: results of the Italian FARO Survey. Nephrol Dial Transplant 27:3588–3594. doi:10.1093/ndt/gfs108
203. Jansen RB, Svendsen OL (2014) The effect of oral loading doses of cholecalciferol on the serum concentration of 25-OH-vitamin-D. Int J Vitam Nutr Res 84:45–54. doi:10.1024/0300-9831/a000192
204. Russo D, Corrao S, Battaglia Y et al (2011) Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney Int 80:112–118. doi:10.1038/ki.2011.69
205. Russo D, Bellasi A, Pota A et al (2015) Effects of phosphorus-restricted diet and phosphate-binding therapy on outcomes in patients with chronic kidney disease. J Nephrol 28:73–80. doi:10.1007/s40620-014-0071-2
206. Di Lullo L, Gorini A, Bellasi A et al (2015) Fibroblast growth factor 23 and parathyroid hormone predict extent of aortic valve calcifications in patients with mild to moderate chronic kidney disease. Clin Kidney J 8:732–736. doi:10.1093/ckj/sfv073
207. Russo D, Morrone LF, Errichiello C et al (2014) Impact of BMI on cardiovascular events, renal function, and coronary artery calcification. Blood Purif 38:1–6. doi:10.1159/000362862
208. Andress DL (2006) Vitamin D in chronic kidney disease: a systemic role for selective vitamin D receptor activation. Kidney Int 69:33–43. doi:10.1038/sj.ki.5000045
209. Schlieper G, Schurgers L, Brandenburg V et al (2015) Vascular calcification in chronic kidney disease: an update. Nephrol Dial Transplant. doi:10.1093/ndt/gfv111
210. Wang TJ, Pencina MJ, Booth SL et al (2008) Vitamin D deficiency and risk of cardiovascular disease. Circulation 117:503–511. doi:10.1161/CIRCULATIONAHA.107.706127
211. Scragg R, Sowers M, Bell C, Health Third National, Survey Nutrition Examination (2004) Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 27:2813–2818
212. Ford ES, Ajani UA, McGuire LC, Liu S (2005) Concentrations of serum vitamin D and the metabolic syndrome among US adults. Diabetes Care 28:1228–1230
213. Martins D, Wolf M, Pan D et al (2007) Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 167:1159–1165. doi:10.1001/archinte.167.11.1159
214. Li YC, Kong J, Wei M et al (2002) 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 110:229–238. doi:10.1172/JCI15219

215. Schlieper G, Hess K, Floege J, Marx N (2015) The vulnerable patient with chronic kidney disease. Nephrol Dial Transplant. doi:10.1093/ndt/gfv041
216. Shimada T, Yamazaki Y, Takahashi M et al (2005) Vitamin D receptor-independent FGF23 actions in regulating phosphate and vitamin D metabolism. Am J Physiol Renal Physiol 289:F1088–F1095. doi:10.1152/ajprenal.00474.2004
217. Razzaque MS (2011) The dualistic role of vitamin D in vascular calcifications. Kidney Int 79:708–714. doi:10.1038/ki.2010.432
218. Nakatani T, Ohnishi M, Razzaque MS (2009) Inactivation of klotho function induces hyperphosphatemia even in presence of high serum fibroblast growth factor 23 levels in a genetically engineered hypophosphatemic (Hyp) mouse model. FASEB J 23:3702–3711. doi:10.1096/fj.08-123992
219. Somjen D, Weisman Y, Kohen F et al (2005) 25-Hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation 111:1666–1671. doi:10.1161/01.CIR.0000160353.27927.70
220. Merke J, Hofmann W, Goldschmidt D, Ritz E (1987) Demonstration of 1,25(OH)2 vitamin D3 receptors and actions in vascular smooth muscle cells in vitro. Calcif Tissue Int 41:112–114
221. Watson KE, Abrolat ML, Malone LL et al (1997) Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 96:1755–1760
222. de Boer IH, Kestenbaum B, Shoben AB et al (2009) 25-Hydroxyvitamin D levels inversely associate with risk for developing coronary artery calcification. J Am Soc Nephrol JASN 20:1805–1812. doi:10.1681/ASN.2008111157
223. Melamed ML, Muntner P, Michos ED et al (2008) Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. Arterioscler Thromb Vasc Biol 28:1179–1185. doi:10.1161/ATVBAHA.108.165886
224. Targher G, Bertolini L, Padovani R et al (2006) Serum 25-hydroxyvitamin D3 concentrations and carotid artery intima-media thickness among type 2 diabetic patients. Clin Endocrinol (Oxf) 65:593–597. doi:10.1111/j.1365-2265.2006.02633.x
225. Zhang Q-Y, Jiang C-M, Sun C et al (2015) Hypovitaminosis D is associated with endothelial dysfunction in patients with non-dialysis chronic kidney disease. J Nephrol 28:471–476. doi:10.1007/s40620-014-0167-8
226. London GM, Guérin AP, Verbeke FH et al (2007) Mineral metabolism and arterial functions in end-stage renal disease: potential role of 25-hydroxyvitamin D deficiency. J Am Soc Nephrol JASN 18:613–620. doi:10.1681/ASN.2006060573
227. Arad Y, Spadaro LA, Roth M et al (1998) Serum concentration of calcium, 1,25 vitamin D and parathyroid hormone are not correlated with coronary calcifications. An electron beam computed tomography study. Coron Artery Dis 9:513–518
228. Valdivielso JM, Ayus JC (2008) Role of vitamin D receptor activators on cardiovascular risk. Kidney Int Suppl. doi:10.1038/ki.2008.545
229. Takahashi F, Finch JL, Denda M et al (1997) A new analog of 1,25-(OH)2D3, 19-NOR-1,25-(OH)2D2, suppresses serum PTH and parathyroid gland growth in uremic rats without elevation of intestinal vitamin D receptor content. Am J Kidney Dis 30:105–112
230. Kalantar-Zadeh K, Kovesdy CP (2009) Clinical outcomes with active versus nutritional vitamin D compounds in chronic kidney disease. Clin J Am Soc Nephrol CJASN 4:1529–1539. doi:10.2215/CJN.02140309
231. Llach F, Yudd M (2001) Paricalcitol in dialysis patients with calcitriol-resistant secondary hyperparathyroidism. Am J Kidney Dis 38:S45–S50
232. Martin KJ, González EA, Gellens M et al (1998) 19-Nor-1-alpha-25-dihydroxyvitamin D2 (Paricalcitol) safely and effectively reduces the levels of intact parathyroid hormone in patients on hemodialysis. J Am Soc Nephrol JASN 9:1427–1432
233. Sprague SM, Lerma E, McCormmick D et al (2001) Suppression of parathyroid hormone secretion in hemodialysis patients: comparison of paricalcitol with calcitriol. Am J Kidney Dis 38:S51–S56
234. Cunningham J, Zehnder D (2011) New vitamin D analogs and changing therapeutic paradigms. Kidney Int 79:702–707. doi:10.1038/ki.2010.387
235. Jono S, Nishizawa Y, Shioi A, Morii H (1998) 1,25-Dihydroxyvitamin D3 increases in vitro vascular calcification by modulating secretion of endogenous parathyroid hormone-related peptide. Circulation 98:1302–1306
236. Price PA, Faus SA, Williamson MK (2000) Warfarin-induced artery calcification is accelerated by growth and vitamin D. Arterioscler Thromb Vasc Biol 20:317–327
237. Mathew S, Lund RJ, Chaudhary LR et al (2008) Vitamin D receptor activators can protect against vascular calcification. J Am Soc Nephrol JASN 19:1509–1519. doi:10.1681/ASN.2007080902
238. Wu-Wong JR, Noonan W, Ma J et al (2006) Role of phosphorus and vitamin D analogs in the pathogenesis of vascular calcification. J Pharmacol Exp Ther 318:90–98. doi:10.1124/jpet.106.101261
239. Cardús A, Panizo S, Parisi E et al (2007) Differential effects of vitamin D analogs on vascular calcification. J Bone Miner Res 22:860–866. doi:10.1359/jbmr.070305
240. Mizobuchi M, Finch JL, Martin DR, Slatopolsky E (2007) Differential effects of vitamin D receptor activators on vascular calcification in uremic rats. Kidney Int 72:709–715. doi:10.1038/sj.ki.5002406
241. Haffner D, Hocher B, Müller D et al (2005) Systemic cardiovascular disease in uremic rats induced by 1,25(OH)2D3. J Hypertens 23:1067–1075
242. Shoji T, Shinohara K, Kimoto E et al (2004) Lower risk for cardiovascular mortality in oral 1alpha-hydroxy vitamin D3 users in a haemodialysis population. Nephrol Dial Transplant 19:179–184
243. Goldsmith DJ, Covic A, Sambrook PA, Ackrill P (1997) Vascular calcification in long-term haemodialysis patients in a single unit: a retrospective analysis. Nephron 77:37–43
244. Briese S, Wiesner S, Will JC et al (2006) Arterial and cardiac disease in young adults with childhood-onset end-stage renal disease-impact of calcium and vitamin D therapy. Nephrol Dial Transplant 21:1906–1914. doi:10.1093/ndt/gfl098
245. Chertow GM, Raggi P, Chasan-Taber S et al (2004) Determinants of progressive vascular calcification in haemodialysis patients. Nephrol Dial Transplant 19:1489–1496. doi:10.1093/ndt/gfh125
246. Barreto DV, Barreto FC, Liabeuf S et al (2009) Vitamin D affects survival independently of vascular calcification in chronic kidney disease. Clin J Am Soc Nephrol CJASN 4:1128–1135. doi:10.2215/CJN.00260109
247. Goodman WG, Goldin J, Kuizon BD et al (2000) Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342:1478–1483. doi:10.1056/NEJM200005183422003
248. Chertow GM, Burke SK, Raggi P, Treat to Goal Working Group (2002) Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 62:245–252. doi:10.1046/j.1523-1755.2002.00434.x
249. Shroff R, Egerton M, Bridel M et al (2008) A bimodal association of vitamin D levels and vascular disease in children on dialysis. J Am Soc Nephrol JASN 19:1239–1246. doi:10.1681/ASN.2007090993