Pediatr Nephrol
DOI 10.1007/s00467-010-1499-9

REVIEW

The virtues of vitamin D—but how much is too much?

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Received: 13 January 2010 / Revised: 6 February 2010 / Accepted: 16 February 2010

Abstract Vitamin D deficiency is common in healthy adults and children as well as in the chronic kidney disease (CKD) population. What was once a disease of malnourished children in the developing world has re-emerged and reached pandemic proportions. In parallel with this development, there is a growing awareness that vitamin D is not simply a 'calcaemic hormone' but plays an important role in the prevention of cardiovascular disease, infectious and autoimmune conditions, renoprotection, glycaemic control and prevention of some common cancers. Most tissues in the body have a vitamin D receptor and the enzymatic machinery to convert 'nutritional' 25-hydroxyvitamin D to the active form 1,25-dihydroxyvitamin D; it is estimated that 3% of the human genome is regulated by the vitamin D endocrine system. Although there are few well-conducted studies on the benefits of vitamin D therapy, an exuberant use of vitamin D is now seen in the general population and at all stages of CKD. There is emerging evidence that vitamin D may in fact have a therapeutic window, and at least from the effects on the cardiovascular system, more is not necessarily better. In this review, we discuss the role of nutritional vitamin D (ergocalciferol or cholecalciferol) supplementation in CKD patients, interpreting the clinical studies in the light of the vitamin D metabolic pathway and its pluripotent effects. While nutritional vitamin D compounds clearly have numerous beneficial effects, randomised controlled studies are required to determine the effectiveness and optimal dose at different stages of CKD, its concurrent use with activated vitamin D compounds and its safety profile.

Keywords Children · Cholecalciferol · Chronic kidney disease · Ergocalciferol · Vitamin D

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Introduction

Vitamin D deficiency is widely prevalent and often severe in chronic kidney disease patients. There is a growing awareness that vitamin D has far-reaching effects beyond its role in calcium (Ca) homeostasis, particularly in cardiovascular disease prevention. Both nutritional vitamin D supplements and activated vitamin D analogues are now widely used at all stages of chronic kidney disease (CKD). The sources, metabolism, potential causes for deficiency and clinical studies using nutritional vitamin D supplements are discussed below.

Sources of vitamin D

Vitamin D can be ingested orally or formed endogenously by the skin after exposure to sunlight (Fig. 1). Approximately 80–90% of an individual's vitamin D requirement is obtained through sunlight [1, 2]. Solar ultraviolet B (UV-B) radiation (wavelength 290–315 nm) converts 7-dehydrocholesterol in the epidermis to pre-vitamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process [3]. Cutaneous production of pre-vitamin D_3 depends on skin pigment, sunscreen use, clothing, time of day, season, latitude and altitude [1, 2]. In a light-skinned individual, full body exposure to sunlight for 10–15 min in the summer months will provide 10,000–20,000 IU of vitamin D within

Published online: 15 April 2010

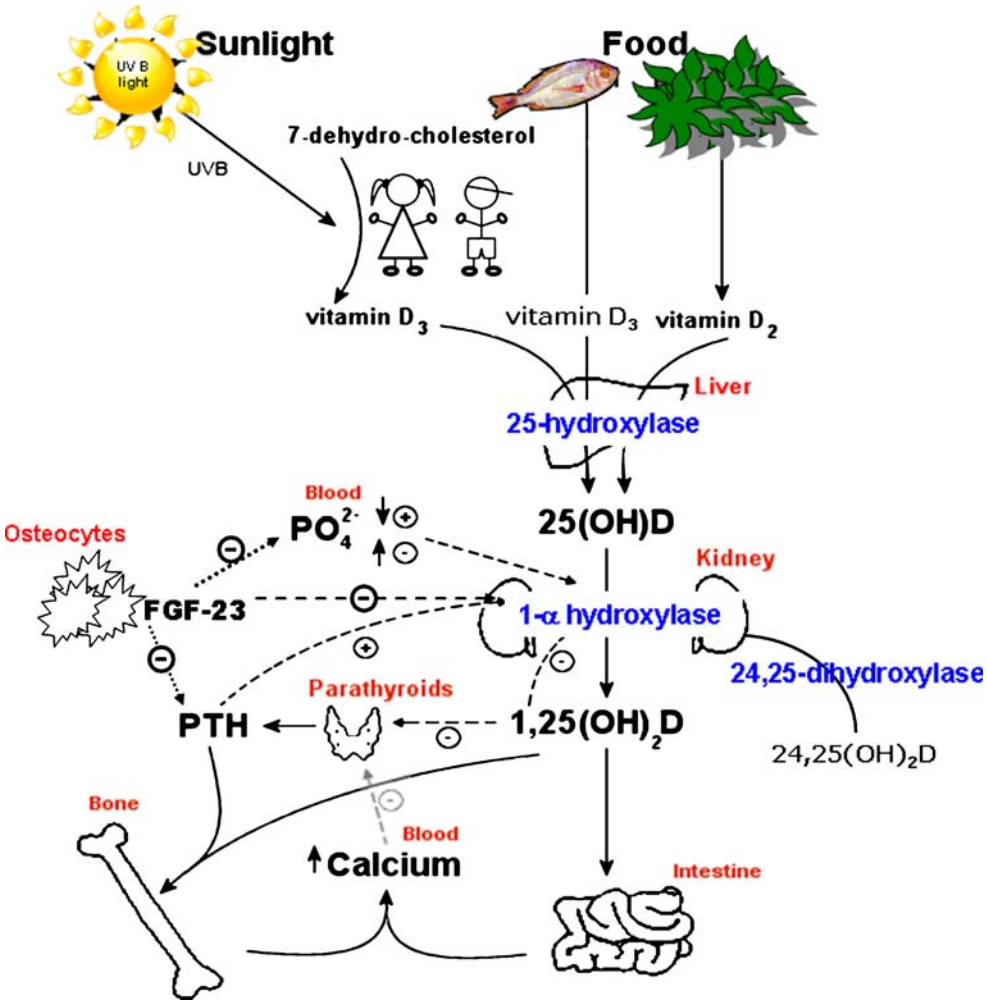

Fig. 1 Sources and metabolism of vitamin D. *PTH* Parathyroid hormone, *25(OH)D* 25-hydroxyvitamin D, *vitamin D_2* ergocalciferol, *vitamin D_3* cholecalciferol, *1,25(OH)$_2$D*, 1,25-dihydroxyvitamin D (calcitriol), *FGF-23* fibroblast growth factor 23, *UV-B* solar ultraviolet B radiation

24 h [4]. Vitamin D intake through sunlight exposure or the diet cannot lead to toxic levels. Prolonged exposure to sunlight causes the conversion of pre-vitamin D_3 to lumisterol and tachysterol that cannot bind to vitamin D binding protein (VDBP) and get sloughed off with natural turnover of skin [2, 5].

Few foods naturally contain or are fortified with vitamin D. Vitamin D_2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D_3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Oily fish (such as eel, herring and salmon) are the richest natural source of vitamin D, but only contain 16–27 μg of vitamin D/100 gm per edible portion [6, 7] (1 μg= 40 IU). Unless consumed regularly, they will not provide adequate vitamin D levels. In some countries, foods are fortified (e.g. milk, butter, mayonnaise, vegetable oils, bread and cereals) with vitamin D. However, they contain <10 μg of vitamin D/100 gm edible portion [6, 7]. The European Union is currently supporting a strategy for optimal vitamin D fortification of food (OPTIFOFD project), particularly in terms of high-risk groups, including ethnic minorities [2].

Vitamin D metabolism

Ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) have a short circulating half-life of approximately ~ 24 h, but given their lipophilic nature remain in adipose tissue for approximately 2 months. To be biologically active they must be converted to 25-hydroxyvitamin D [25(OH)D]. A number of cytochrome P450 (CYP) enzymes, both mitochondrial and microsomal, are involved, among which CYP27A1 and CYP2R1 are the best known and studied [1, 8]. CYP27A1 and related enzymes are most abundantly present in the liver, but other organs are also capable of converting pre-vitamin D to 25(OH)D for local effects [9]. 25(OH)D_2 (calcidiol) and 25(OH)D_3 (ercalcidiol) behave in a similar manner and are subsequently referred to here only as 25(OH)D.

25(OH)D production is primarily substrate dependent, and, very importantly, there is no negative feedback control of this step. 25(OH)D is rapidly released from the liver into the blood stream where it circulates with a biological half-life of approximately 3 weeks [8, 10]. It is stored in adipose tissue and released into the circulation in an unregulated

manner that can continue for many months, depending only on the extent of its stores.

25(OH)D is further converted to the vitamin D hormone 1,25-dihydroxyvitamin D [1,25$(OH)_2$D, also called calcitriol] via a mitochondrial P450 enzyme, CYP27B1 [8]. The proximal renal tubule is the major site of 1-α hydroxylation of 25(OH)D, and circulating 1,25$(OH)_2$D levels are almost exclusively the result of renal production [1]. Over 30 different cell types, including immune cells, vascular smooth muscle cells, epithelia of many tissues, pancreatic β-cells, bone and parathyroid glands, express CYP27B1 (1-α hydroxylase) and have been shown to locally produce 1,25$(OH)_2$D [11, 12].

The renal synthesis of 1,25$(OH)_2$D is a tightly regulated step (Fig. 1), in keeping with its potent activity in Ca homeostasis. Dietary Ca can regulate the enzyme directly through changes in serum Ca and indirectly by altering parathyroid hormone (PTH) levels. High circulating Ca levels directly suppress renal 1-α hydroxylase activity, by acting directly on 1-α hydroxylase gene transcription and indirectly through PTH suppression via cAMP-mediated changes. The recently discovered phosphaturic hormone fibroblast growth factor 23 (FGF-23) is also involved in the negative feedback control of renal 1-α hydroxylase activity [13]. FGF-23 production is increased in the presence of high phosphate levels, and FGF-23 in turn will downregulate renal 1-α hydroxylase activity and thereby reduce both Ca and phosphorus (P) absorption [14]. Finally, 1,25$(OH)_2$D downregulates its own production by suppressing 1-α hydroxylase mRNA production, possibly mediated via the klotho gene product [15], and also promoting conversion to the inactive form 24,25$(OH)_2$D [1, 16].

Extra-renal 1-α hydroxylase activity is regulated by substrate availability and local factors, including cytokines and growth factors, that are not under Ca, PTH or FGF-23 control [12]. Extra-renal 1-α hydroxylase activity is not sufficient to maintain adequate circulatory levels of 1,25 $(OH)_2$D in advanced CKD or in anephric individuals [17].

The vitamin D receptor

The genomic actions of vitamin D are mediated via its nuclear receptor, the vitamin D receptor (VDR). The VDR is an ancient member of the superfamily of nuclear receptors of steroid hormones [16, 18] and has been conserved through many species. VDR functions as a heterodimer, usually with the retinoid X receptor (VDR-RXR). These heterodimeric complexes will interact with specific DNA sequences (called vitamin D response elements) within the promoter of target genes, leading to the activation or repression of gene transcription [18]. The genomic actions of VDR can be further modulated by post-translational modifications induced by various hormone systems or protein kinases acting on the cell surface [19]. In addition, vitamin D metabolites also elicit responses that are too rapid to involve changes in gene expression. These effects mainly involve Ca homeostasis and may be mediated by changes in cell-surface receptors [16, 18].

Polymorphisms of the chromosome 12 VDR gene have been described in humans and result in differences between racial and ethnic groups with resulting differences in bone density, propensity to hyperparathyroidism, resistance to vitamin D treatment and, possibly, also susceptibility to infections, cancer and autoimmune diseases [8].

The biological actions of vitamin D metabolites

In addition to its pivotal role in Ca homeostasis, it is now clear that vitamin D metabolites also have important non-calcaemic (also called 'non-classical') actions. The non-classical effects include actions on the heart and vasculature, regulation of the innate and adaptive immune systems, role in inflammatory and auto-immune diseases, release of insulin by pancreatic β cells, prevention of solid organ tumors and also a possible renoprotective effect [20, 21].

Vitamin D as a calcaemic hormone

Vitamin D metabolites are a potent negative regulator of PTH production. 1,25$(OH)_2$D binds with the vitamin D receptor complex on parathyroid cells and downregulates PTH gene expression, increases expression of VDRs and increases transcription of Ca sensing receptors (CaSR) [22]. Fascinatingly, a recent study has shown that even the parathyroid glands may function as a vitamin D autocrine system: they express 1-α hydroxylase (CYP27B1) and also 25-hydroxylase (CYP27A), allowing the gland to produce their own vitamin D to regulate PTH production [23]. This may explain why PTH levels correlate inversely with 25(OH) D levels in mild to moderate vitamin D deficiency with no changes in 1,25$(OH)_2$D levels [24]. Also, a prolonged deficiency of vitamin D metabolites leads to a need for higher serum Ca levels and vitamin D doses as there is a markedly reduced VDR and CaSR expression by the parathyroid cells [22]. Prophylactic administration of vitamin D analogues early in the course of renal decline will prevent the decrease in parathyroid VDR expression and dysregulation of the CaSR to prevent the secondary hyperparathyroidism [25] that is thought by many to be an unavoidable complication of CKD. Importantly, the presence of 1-α hydroxylase in the parathyroid gland also implies that non-1-hydroxylated analogues can be used to prevent and treat hyperparathyroidism, with the added advantage that their renal 1-α hydroxylation would be under negative feedback control, thereby preventing oversuppression of PTH.

1,25$(OH)_2$D enhances intestinal Ca absorption in the small intestine by interacting with the VDR-RXR complex to enhance the expression of the epithelial Ca channel [transient receptor potential cation channel, subfamily V, member 6 (TRPV6)] and calbindin 9 K, a Ca-binding protein [26, 27]. Without vitamin D, only 10–15% of dietary Ca and about 60% of P is absorbed. In the presence of 1,25$(OH)_2$D, the efficiency of intestinal Ca absorption increases to 30–40% and P absorption to approximately 80% [1, 28].

In bones, 1,25$(OH)_2$D is recognised by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-B ligand (RANKL) [1, 11, 29]. RANKL, the receptor for RANK on pre-osteoclasts, binds RANK, which induces pre-osteoclasts to become mature osteoclasts. Mature osteoclasts remove Ca and P from the bone so as to maintain their respective levels in the blood. Osteoblasts express both 25-hydroxylase as well as 1-α hydroxylase enzyme systems and can function as independent 1,25$(OH)_2$D-producing cells [30]. Several studies have shown that impaired mineralisation frequently complicates renal osteodystrophy in children, and there is an association between circulating 25(OH)D concentrations and bone health outcomes, such as established rickets, PTH levels and bone mineral density [31]. A recent Cochrane database review has not been able to demonstrate any significant difference in growth rate or bone histology with calcitriol or ergocalciferol use, supporting the observation that bone cells can independently produce 1,25$(OH)_2$D [32].

Non-calcaemic effects of vitamin D

Vitamin D metabolites play a role in preventing or regulating several conditions as far ranging as cardiovascular disease and diabetes to tuberculosis, rheumatoid arthritis, Crohn's disease, multiple sclerosis and breast and prostate cancers. Its role in cardiac and vascular disease is the most extensively studied and discussed below and shown in Table 1.

Vitamin D deficiency has been strongly correlated with left ventricular hypertrophy (LVH), hypertension and increased cardiovascular mortality [33–41]. In experimental animals, vitamin D has been shown to modulate the contractility of cardiomyocytes as well as their growth, differentiation, hypertrophy and collagen deposition [40, 42]. In humans, vitamin D receptor activator (VDRA) use is associated with an improvement in LV function, reduction of LVH [43] and reduction in the blood pressure (BP) [44, 45]. These effects may, in part, be mediated via a reduction in renin production [44, 45] and reduced endothelium-induced atrial natriuretic peptide levels [43].

Vascular smooth muscle cells (VSMCs) express the VDR and have functional 1-α hydroxylase and 25-hydroxylase enzyme systems so that all the vitamin D metabolites can be utilised by them in an autocrine/paracrine fashion [46]. VDRAs can have pro-calcific as well as protective effects on the vessels. They regulate the transcription of both pro-calcific (e.g. osteoblast differentiation factor runx2 and osteocalcin) [47, 48] and calcification inhibitory proteins (e.g. matrix gla-protein and osteopontin) [47] and dampen pro-inflammatory cytokines, such as interleukin (IL)-6, IL-1β and transforming growth factor alpha (TNF-α) [41, 49]. Calcitriol also increases VSMC proliferation through increased vascular endothelial growth factor (VEGF) production [50].

Low 25(OH)D and 1,25$(OH)_2$D levels have been associated with increased vascular stiffness and reduced distensibility in haemodialysis (HD) patients [51]. Both vitamin D deficiency and cardiovascular disease are prevalent in early CKD [52, 53], and low 25(OH)D levels have been found to be associated with an increased risk for developing coronary artery calcification in patients with pre-dialysis CKD [54]. In a clinical study involving children on dialysis, we found that both low and high levels of 1,25$(OH)_2$D were associated with an increased carotid intima media thickness and coronary calcification [55]. High 1,25$(OH)_2$D levels can clearly promote calcification through systemic effects on Ca–P regulation and also local VSMC effects, and low 1,25 $(OH)_2$D was shown to be associated with a raised inflammatory state and high PTH levels. Atherosclerosis is now well recognised to be an inflammatory condition, and a low vitamin D state may promote intimal calcification. Importantly, our study demonstrated that there is a narrow therapeutic window for vitamin D analogues on vascular health [55], and this result has been confirmed in various animal models and in in-vitro culture systems [28, 46].

In all of these disease states, 25(OH)D levels are low, but whether it is the direct effects of 25(OH)D on these cells or the effects of circulating 1,25$(OH)_2$D is not completely understood. There may be an advantage for local autocrine/paracrine production of 1,25$(OH)_2$D (as opposed to systemic administration of activated vitamin D), but further study is required to gain an understanding of the mechanism.

The molecular basis for differential actions of vitamin D metabolites

An understanding of the pharmacokinetic and pharmacodynamic factors that determine the differential effects of vitamin D metabolites on various tissues is important. The binding of vitamin D metabolites to VDBP affects their half-life and their rate of uptake by target cells [10, 56]. Thus, 25(OH)D, which has the strongest affinity to VDBP, has the longest half-life (approx. 3 weeks), whereas 1,25 $(OH)_2$D has a short circulating half-life (approx. 4–6 h) and is rapidly taken up by tissues [10, 19]. Only the free (unbound) vitamin D compound has biological activity. Secondly, various target cells may catabolise vitamin D

Table 1 Effects of vitamin D on cardiovascular disease

Potential inducers/inhibitors of cardiovascular disease[a]	Effect of vitamin D receptor activation	Effect of vitamin D treatment on cardiac/vascular function
Effect on cardiac function		
Renin [41, 42]	↓	
Atrial natriuretic peptide [40]	↓	Reduces cardiomyocyte hypertrophy and reduces LVH- Reduces BP
Cardiac troponin T [37]	↓	
Hyperparathyroidism [39]	↓	
FGF-23 [67]	↑ (? Direct effect or through ↑ PO_4 absorption)	Increased LVH and increased mortality
Indirect effects through anti-proteinuric effects, reduced insulin resistance, promoting adipocyte metabolism [10, 11, 16]		Indirect effects on reducing cardiovascular mortality
Effect on vascular calcification		
Hypercalcaemia [16, 43, 44]	↑	Promotes vascular calcification (Direct effect of ↑ serum Ca and by ↑ vascular smooth muscle cell Ca uptake)
Hyperphosphataemia [16, 43, 44]	↑	Promotes vascular calcification
Hyperparathyroidism [16, 43, 44]	↓	Inhibits calcification (direct effect and through prevention of hyperparathyroid bone disease)
Runx2 (cbfa-1) [10, 11, 44, 45]	↑	Promotes vascular calcification (promotes osteoblastic differentiation of vascular smooth muscle cell)
RANK-L/OPG [10, 11]	↑	Promotes vascular calcification
Osteocalcin [38, 46]	↑	Promotes vascular calcification
BMP-2 [10, 11, 18]	↓	Inhibits calcification
Matrix Gla-protein [10, 18, 44]	↑	Inhibits calcification (direct effect and through ↑ BMP-2)
Osteopontin [10, 18]	↑	Inhibits calcification
Inflammatory cytokines (IL-6, IL-1β and TGF-α) [38, 46]	↓	Inhibits calcification and inflammatory response to atheroma formation
Antithrombin and thrombomodulin [38, 46]	↑	Inhibits thrombogenesis and atheroma formation

TGF-α, Transforming growth factor alpha; IL, interleukin; RANK-L/OPG, receptor activator of nuclear factor κ-β ligand/osteoprotegerin; BMP-2, bone morphogenetic protein 2; cbfa-1, core binding factor alfa–1; FGF-23, fibroblast growth factor 23; BP, blood pressure; LVH, left ventricular hypertrophy

[a] Corresponding references are also given

metabolites in different ways, with the resulting catabolic products having different biological activity, resulting in cell-specific differences in VDRA activity.

The pharmacodynamic actions of VDRA are based on their ability to modulate VDR function by using different contact amino acid residues for binding and by inducing different structural conformations within the hormone–receptor complex [8]. This may prolong the half-life of the activated receptor, affect the DNA binding properties or promoter selectivity of the activated VDR and influence receptor interactions with tissue-specific co-factors. These factors determine the tissue-selectivity of vitamin D metabolites and may also explain how different vitamin D metabolites can induce differential gene expression profiles in the same cell [57, 58].

On a molar basis, $1,25(OH)_2D$ is the most potent vitamin D metabolite. Dose–response studies indicate a molar potency of $1,25(OH)_2D$ relative to 25(OH)D ranging from 125:1 to 400:1 in terms of increasing Ca absorption from the gut [56]. However, the serum levels of 25(OH)D are approximately 1:500 to 1:1000-fold higher than those of $1,25(OH)_2D$ (nanomolar vs. picomolar concentrations) [2]. The biological implications of differences in circulating levels, potency and half-life may imply that while 25(OH)D is more freely available for utilisation by several different tissues, $1,25(OH)_2D$ with its short circulating half-life and lower circulating levels is tightly regulated so as to keep Ca levels within a narrow range.

Assessing vitamin D status

The circulating level of 25(OH)D is the best marker of the vitamin D status of an individual for the following reasons:

(1) all pre-vitamin D metabolites from cutaneous synthesis and the diet are rapidly converted into 25(OH)D with no negative feedback to limit this conversion; (2) there is no significant storage in the liver; (3) 25(OH)D circulates in plasma with a half-life of approximately 3 weeks. In comparison, (1) conversion to $1,25(OH)_2D$ depends on the availability of its substrate 25(OH)D; (2) this conversion is a tightly regulated step with negative feedback control; $1,25(OH)_2D$ has a very short circulating half-life (approx. 4–6 h).

When 25(OH)D was first identified in the 1970s, its serum levels were defined as 'adequate' if they prevented rickets or osteomalacia [59]. Current definitions utilise biochemical and clinical parameters, but there is still no consensus on optimal serum levels. However, vitamin D deficiency is defined by most experts as a 25(OH)D level of <20 ng /ml [1, 60]: at this level, the body stores are already depleted and PTH levels are raised in an attempt to maintain normal Ca levels. In healthy subjects, 25(OH)D levels are inversely associated with PTH until 25(OH)D reaches 30–40 ng/ml [5, 60]. Furthermore, intestinal Ca transport increases by 45–65% when 25(OH)D levels are increased from approximately 20 to 32 ng/ml [61, 62], suggesting that 25(OH)D levels between 20 and 30 ng/ml can be considered to indicate a relative insufficiency of vitamin D. Circulating 25(OH)D levels between 40 and 80 ng/ml are now considered adequate as they are associated with normal Ca levels in the absence of hyperparathyroidism; healthy individuals living close to the equator with a constant UV-B exposure have 25(OH)D levels >40 ng/ml.

Table 2 shows the currently used terminology to describe the vitamin D status of patients based on 25(OH)D levels.

The pandemic of vitamin D deficiency

With the use of the above definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency [1]! Children are particularly vulnerable as the growing skeleton has high Ca and P demands, and vitamin D deficiency may be most pronounced in infants of vitamin D-deficient mothers, particularly if exclusively breast-fed.

There is a marked seasonal variation in 25(OH)D levels, with significantly lower levels in winter due to UV-B radiation from sunlight being minimal at higher latitudes during this time (at 52°N, minimal UV-B between October to April; at 42°N, minimal UV-B between November and February; between 32°N and the equator, there is sufficient UV B exposure all year round). In healthy individuals in the northern hemisphere, maximum 25(OH)D levels are found in mid-August and correlate inversely with PTH levels, thus ensuring a tight regulation of serum Ca levels [63]. Of interest, skin creams even with sun protection factor (SPF) levels as low as 15 can block off 99% of UV-B light. Several studies have confirmed that ethnic groups living in northern countries are at greater risk as increased melanin pigmentation and cultural practices with dress code may limit sun exposure [64].

Vitamin D deficiency in CKD patients— epidemiology and causes

Virtually all studies in dialysis patients have reported vitamin D deficiency to the order of 50–90% [1, 51, 65, 66]. In a recent population-based study of >1,800 adults, vitamin D deficiency and the ensuing secondary hyperparathyroidism were seen to begin early in the course of renal decline and significantly before any abnormalities in Ca, P or PTH occurred [67]. Hyperparathyroidism was associated with low levels of $1,25(OH)_2D$ and was extremely common even at glomerular filtration rates (GFRs) higher than any previously reported: 13% of patients with eGFRs >80 ml/min/1.73 m^2 had $1,25(OH)_2D$ deficiency and 60% of patients with eGFRs <30 ml/min/1.73 m^2 were $1,25(OH)_2D$-deficient. Significant differences in PTH and $1,25(OH)_2D$ levels were seen across the deciles of estimated (e)GFRs and importantly, these were not associated with any change in serum Ca, P or 25(OH)D levels.

CKD patients can have low 25(OH)D levels for many reasons [65], including:

(1) They may be less active and have less sunlight exposure;
(2) The endogenous synthesis of vitamin D in the skin is reduced in CKD;

Table 2 Definitions of vitamin D status based on 25-hydroxyvitamin D [25(OH)D] levels

Vitamin D status	25(OH)D level (ng/ml)	Clinical and biochemical association
Severe deficiency	0–10	Rickets, osteomalacia, severe hyperparathyroidism, Ca malabsorption
Deficiency	10–20	Elevated PTH, reduced intestinal Ca absorption, reduced bone mineral density
Insufficiency	20–30	Low 25(OH)D levels, sometimes slightly raised PTH
Adequacy	40–80	No disturbance in vitamin D-dependent functions
Toxicity	>100	Hypercalcaemia

PTH, Parathyroid hormone

To convert nanograms/millilitre to nanomoles/litre, multiply by 2.5

(3) Ingestion of foods that are natural sources of vitamin D may be diminished;
(4) Proteinuria may be accompanied by high urinary losses of VDBP, leading to increased renal losses of all vitamin D metabolites [67, 68];
(5) 25(OH)D and VDBP may be lost in peritoneal dialysis fluid.

Of note, a low calcium diet can lead to a depletion of vitamin D stores as the resultant hyperparathyroidism will lead to a rapid degradation of 25(OH)D to inactive metabolites [69].

When the GFR falls to <50 ml/min/1.73 m^2, the kidney cannot convert 25(OH)D to 1,25$(OH)_2$D [27]. A number of factors have been proposed for reduced 1,25$(OH)_2$D production in advanced CKD patients [1, 11]:

(1) Reduced renal mass is accompanied by reduced availability of 1-α hydroxylase;
(2) Raised phosphate and FGF-23 downregulate renal 1-α hydroxylase [14];
(3) 1-α hydroxylase is suppressed in an acidic and uraemic milieu;
(4) There is reduced renal megalin expression—megalin endocytosis of the 25(OH)D–VDBP complex from the glomerular ultrafiltrate is the major mechanism for delivering 25(OH)D to the 1-α hydroxylase enzyme in the proximal tubules [70];
(5) There is reduced availability of the substrate 25(OH)D, and the 1-α hydroxylase enzyme is substrate dependent, particularly in CKD patients [24];
(6) Secondary hyperparathyroidism depletes body stores of vitamin D by promoting the enzyme 24,25-dihydroxy vitamin D to cause rapid degradation of 25(OH)D.

The low levels of 1,25$(OH)_2$D in CKD patients have even lower biological effects as the binding of VDR to the response element in the DNA is compromised in uraemia and may account for the resistance to vitamin D therapy that is seen in CKD patients [19].

Vitamin D deficiency in children with CKD

Studies in children report a similar prevalence of 50–92% vitamin D deficiency in the CKD population, with a graded association between CKD stage and 25(OH)D levels. In CKD stages 2–4, 25(OH)D deficiency (level <30 ng/ml) has been reported in 60–77% of children [71, 72]. Interestingly, even in a subtropical area with year-long sunshine, 25(OH)D deficiency was common, particularly in non-Caucasian children [72]. Also, vitamin D deficiency is more prevalent in overweight and obese patients, both among otherwise healthy children [73] and CKD patients [72]. This may be due to reduced outdoor activity and sunlight exposure as well as poor dietetic habits, but, in addition, excessive adipose tissue leads to sequestration of 25(OH)D in body fat compartments with reduced bioavailability.

Bone pain and fractures due to hyperparathyroidism are the commonest complaints of young adults with childhood onset CKD [74]. Hyperparathyroidism also results in poor growth [25]. Most importantly, an increased risk of cardiovascular morbidity and mortality is reported even in the early stages of CKD and in the childhood population, stressing the need for regular 25(OH)D measurements in pediatric CKD patients.

Effects of vitamin D deficiency on survival in CKD patients

The effects of vitamin D treatment on all-cause and cardiovascular mortality have been reported from several large epidemiological studies on HD patients and also from a meta-analysis of the general population [75]. All of these studies have consistently shown that HD patients receiving any activated vitamin D treatment have a survival advantage to the order of 20–25% as compared to vitamin D-naive patients [34–37, 39]. Although there are conflicting reports on this relationship, there is unlikely to be a significant difference in survival between different VDRAs (doxercalciferol vs. paricalcitriol) [36, 37]. Most importantly, vitamin D treatment was found to be able to mitigate the effects of high Ca, P and PTH on cardiovascular mortality: the survival advantage of vitamin D was seen across all quintiles of Ca, P and PTH levels [36], suggesting that vitamin D has important effects beyond its role in mineral metabolism. The improved survival of African Americans over whites on HD may be due to their more frequent use of activated vitamin D compounds [76]. Two recent studies have in fact shown that low 25(OH)D levels affected early all-cause mortality in incident dialysis patients [39, 77] and that the increased mortality was independent of vascular stiffness and calcification [77].

Importantly, all of these studies are non-randomised, and physician bias may have confounded the results. The methodological problems of pooling data from several centres and the conclusions reached by these studies have been highlighted by the DOPPS (Dialysis Outcomes and Practice Patterns Study) [78], and a recent meta-analysis has concluded that there is no proven benefit of vitamin D therapy in CKD patients [79]. These results suggest that well-designed randomised controlled studies are required and that it is still ethically justified to perform these studies.

Recommended intake of vitamin D

In healthy individuals

Recent recommendations from the American Academy of Pediatrics (AAP) state that all infants, children and

adolescents should have a minimum daily intake of 400 IU (=10 μg) of vitamin D beginning soon after birth [80]. Even though the AAP currently suggests a higher dose than it did in previous recommendations, this may still not be enough, particularly in the absence of regular and adequate sunlight exposure, to maintain adequate levels [2, 81].

There are currently no guidelines for the treatment of vitamin D deficiency in healthy adults. A vitamin D intake of 400 IU/day will only cause a modest increase in 25(OH)D levels by 2.8–4.8 ng/ml. To raise 25(OH)D levels from 20 to 32 ng/ml requires an additional intake of 1700 IU/day [56]. Treatment regimens vary widely, ranging from 600,000 IU of D_2 or D_3 as a single dose every 3 months (Stoss regimen), 2,000–4,000 IU daily for 3–6 months or 50,000 IU three times per week. All of these regimens have been shown to increase circulating 25(OH)D levels, but only the regimens using at least 600,000 IU ergocalciferol were able to achieve adequate 25(OH)D levels [82]. The total dose used and not the dosing frequency determined the 25(OH)D level achieved [82]. Only one study has looked at long-term treatment with ergocalciferol, reporting that 50,000 IU every other week (median study period 2 years) is safe and prevents recurrent vitamin D deficiency [83].

Vitamin D intoxication is observed when 25(OH)D serum levels are > 100 ng/ml [1]. This topic is discussed in detail in subsequent sections.

There is a significant economic benefit of improving the vitamin D status of the population: the costs of vitamin D supplementation and ancilliary costs of education and testing are approximately €10,000 million/year, but reducing the burden of diabetes, cardiovascular disease, cancer, infectious and autoimmune diseases may save up to €187,000 million/year [84].

In CKD patients

The doses of ergocalciferol or cholecalciferol required to correct vitamin D insufficiency and to maintain normal plasma levels have not been established in children with CKD. In the absence of robust evidence, a recent opinion-based guideline from the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) recommends that in children with CKD stages 3–5 and 5D serum 25(OH)D levels should be measured once a year, and if levels are <30 ng/ml, supplementation with ergocalciferol or cholecalciferol is suggested [85] (Table 3). Of note, the guidelines do not advocate supplementation only if the PTH levels are raised, recognising that vitamin D deficiency begins early and that vitamin D metabolites have far-reaching effects beyond the regulation of Ca–P–PTH regulation. The use of active vitamin D analogues is only recommended if PTH levels are raised in pre-dialysis CKD patients.

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines, which are more rigorously evidence-based, have only suggested the use of vitamin D analogues for the treatment of secondary hyperparathyroidism in pre-dialysis CKD stages 3–5, but the level of evidence for this is very weak and, therefore, no clear recommendations are given.

Of note, vitamins D_2 (ergocalciferol) and D_3 (cholecalciferol) are recommended interchangeably in most treatment regimens, and although there is some argument that the latter has a higher bioavailability than the former [86], the K/DOQI makes no distinction between the biopotencies of D_2 and D_3. Long-term comparative studies in humans are lacking.

Vitamin D supplementation—clinical studies in CKD patients

A number of small, mostly non-randomised and short-term studies using variable doses of ergocalciferol or cholecalciferol have been performed in adults [87–93] and children [71, 94] with pre-dialysis CKD; these are summarised in Table 4. It is clear that there is no consensus on the vitamin D preparation, its dose or frequency of treatment or its expected outcome measures. Only the calcaemic effects of the treatment are assessed, and no study has looked at glycaemic control, effect on infection rates, immune function or inflammatory measures or cardiovascular markers. Importantly, only biochemical measures are used as the primary end-point, with changes in PTH levels described by most studies [87–92], but no data on 'hard end-points' or survival are described. Sadly, the only two available pediatric studies do not provide sufficient clinical or biochemical information to shed further light on this subject [71, 94].

Although it is impossible to draw any definitive conclusions from these studies, they consistently show that a decrease in PTH is possible with ergocalciferol or cholecalciferol and that this is much more likely to occur in CKD stage 3 than in stage 4 [87–89, 92]. The K/DOQI stated that PTH target levels [95] are achieved in very few patients even in early stages of CKD. However, given the highly variable dosing regimens and the post-treatment 25 (OH)D levels achieved, it cannot be determined if the failure to achieve PTH control is a result of inadequate treatment. There is an urgent need for a dose-finding study that takes into account both the calcaemic and non-calcaemic effects of vitamin D.

Despite the methodological difficulties associated with all of these studies, it is clear that ergocalciferol or cholecalciferol use in pre-dialysis CKD patients is safe and not associated with hypercalcaemia or hyperphospha-

Table 3 Recommended supplementation for vitamin D deficiency/insufficiency in children with CKD, used with permission from [85]

Serum 25(OH)D (ng/ml)	Definition	Ergocalciferol (D_2) or cholecalciferol (D_3) (oral dosing)	Duration (months)
<5	Severe vitamin D deficiency	8,000 IU daily (or 50,000 IU/week) for 4 weeks; then 4,000 IU daily (or 50,000 IU every alternate week) for 2 months	3
5–15	Mild vitamin D deficiency	4,000 IU daily for 12 weeks (or 50,000 IU every alternate week for 12 weeks)	3
16–30	Vitamin D insufficiency	2,000 IU daily (or 50,000 IU every 4 weeks)	3

CKD, Chronic kidney disease

taemia. However, the effects of long-term use at the doses used in these studies need to be carefully investigated.

Up to what CKD stage is ergocalciferol or cholecalciferol supplementation beneficial?

Independent of the use of activated vitamin D analogues for correcting $1,25(OH)_2D$ deficiency in advanced CKD, 25(OH)D deficiency is very likely to be present and severe. However, ergocalciferol or cholecalciferol monotherapy is unlikely to be effective when the GFR is <50 ml/min/1.73 m^2 as renal 1-α hydroxylase activity is then too low to maintain $1,25(OH)_2D$ production [87–89, 92]. In keeping with this observation, most clinical studies have shown that ergocalciferol or cholecalciferol use by patients at CKD stages 4 and 5 is ineffective, such that even though the 25(OH)D stores may be restored, $1,25(OH)_2D$ levels remain low, effective suppression of PTH is not achieved and histological deterioration of bone disease occurs [96, 97]. The isolated use of ergocalciferol or cholecalciferol is not recommended by K/DOQI or KDIGO in dialysis patients.

In two recent studies in adult HD patients with 25(OH)D deficiency, 100,000 IU of oral cholecalciferol was given monthly for 15 months without any other activated vitamin D analogue [98, 99]. While this treatment consistently resulted in increased serum 25(OH)D levels, the increase in $1,25(OH)_2D$ levels did not extend into the normal range in all patients: the median $1,25(OH)_2D$ level was 20 pmol/l. A modest suppression in PTH levels and alkaline phosphatase (ALK) was achieved. Approximately 50% of patients did not respond to cholecalciferol, and this was more likely to be the case in diabetic patients [99]. A similar study in anephric individuals confirmed that extra-renal 1-α hydroxylase may play a role [17], but all of these studies show that the non-1-α hydroxylated vitamin D analogues are unable to maintain adequate or sustained $1,25(OH)_2D$ levels.

However, even though ergocalciferol or cholecalciferol are unlikely to significantly improve $1,25(OH)_2D$ levels and secondary hyperparathyroidism, they have been shown to improve glycaemic control in diabetic patients on HD [100] and also to have an erythropoietin (EPO)-sparing effect [101], possibly as a result of improved PTH control.

Can we use ergocalciferol or cholecalciferol with activated vitamin D analogues?

In keeping with the above observations, in more advanced CKD, combined therapy with ergocalciferol or cholecalciferol and calcitriol may be necessary to enhance the cellular uptake of 25(OH)D [102]. $1,25(OH)_2D$ enhances megalin expression, and megalin endocytosis of the 25(OH)D–VDBP complex is required to deliver 25(OH)D to the 1-α hydroxylase in the proximal tubule [70]. In one observational study in HD patients, 50,000 IU ergocalciferol was used monthly along with paricalcitol [101] without any adverse hypercalcaemia or side-effects. The 25(OH)D level did show a significant increase, but the authors do not comment on PTH control or other bone markers.

A recent study looked at the survival of incident HD patients, of whom 80% had 25(OH)D deficiency. In those who received paricalcitol, 25(OH)D levels showed no correlation with survival, whereas in patients who did not receive any vitamin D metabolite, low 25(OH)D levels were associated with increased mortality [39]. These results raise the possibility that the VDBR on tissues can use activated VDRAs and that concomitant use of nutritional 25(OH)D is not essential. While it intuitively appears that the correction of 25(OH)D levels in patients with advanced CKD will play a beneficial role, the combined use of 25(OH)D and $1,25(OH)_2D$ requires further study to determine the dosage and potential toxic effects of combined therapy.

Toxicity

Despite all of the important effects of vitamin D, like most things, too much of a good thing can be bad for you. Given the reported beneficial effects of vitamin D in CKD, nephrologists widely prescribe it to the majority of their

Table 4 Key studies demonstrating the effects of ergocalciferol (D_2) or cholecalciferol (D_3) supplementation in adults and children with pre-dialysis CKD

Number	Author/year	CKD stage	Patients (*n*)	Supplementation used and dosage	Outcome measures			Toxicity
					Increase 25(OH)D >30 ng/ml	Increase 1,25 $(OH)_2D$ >30 pg/ml	Decrease PTH to KDOQI recommended levels	
Adult studies								
1.	DeVille et al. 2006 [89]	3–5	85	Ergocalciferol—800 IU/day to 100,000 IU/week for 3 months, based on initial 25(OH)D levels	Yes—in all CKD stages	Not mentioned	19% of CKD 3, 21% of CKD 4 and 0% in CKD 5 achieved KDOQI recommended levels	None
2.	Al-Aly et al. 2007 [87]	3–4	66	Ergocalciferol 50,000 IU/once/week for 12 weeks, then once/month for 6 months	Mean 25(OH)D levels <30 ng/ml after 6 months treatment	Not mentioned	Decreased PTH only in CKD 3 (although similar 25(OH)D levels in CKD 3 and 4)	None
3.	Zisman et al. 2007 [88]	3–4	52	Ergocalciferol—modified KDOQI regimen based on initial 25(OH)D levels	In 58% of CKD 3 and 68% CKD 4 patients	In 54% of CKD 3 and 20% CKD 4 patients	20% of CKD 3 achieved KDOQI recommended levels and associated with ↑ calcitriol. No decrease in PTH in CKD 4	In CKD 4 patients, four cases of hypercalcaemia, all self-resolving
4.	Dogan et al. 2008 [90]	3–4	40	Cholecalciferol—300,000 IU once monthly as single dose (1:1 randomisation, not blinded)	Increase but widely variable response	Not mentioned	PTH decreased by 30% in 45% of treated patients	None
5.	Oksa et al. 2008 [92]	2–4	87	Cholecalciferol—randomised to 5,000 or 20,000 IU/week	In 50% of patients, dose-related rise	Increased in CKD 2 and 3 only; wide variations in levels achieved	50% of CKD 3 and 41% of CKD 4 achieved KDOQI recommended levels	None
6.	Chandra et al. 2008 [91]	3–4	20	Cholecalciferol—50,000 IU/week for 12 weeks vs. placebo	Increase 25(OH)D in all, but widely variable response	No significant difference	No significant difference	None
7.	Rucker et al. 2009 [93]	3–5	128	Cholecalciferol—1,000 IU/day for 3 months (1:1 randomisation, not blinded)	37% patients achieved vitamin D >30 ng/ml	Not mentioned	Not mentioned	None
Pediatric studies								
8.	Menon et al. 2008 [71]	2–4 (age 10.6±5 years)	57	Ergocalciferol—modified KDOQI regimen based on initial 25(OH)D levels (*n*=22 treated)	Not mentioned	Not mentioned	Mean PTH after treatment decreased from 122 to 80 pmol/l (but wide variations)	None
9.	Belostotsky et al. 2008 [94]	Not stated Age 13.6 years	20	Ergocalciferol single dose 5–10 years 100,000 IU >10 years 150,000 IU	No patient achieved 25(OH)D >30 ng/ml	Not mentioned	Not mentioned	Not mentioned

K/DOQI, National Kidney Foundation's Kidney Disease Outcome Quality Initiative

CKD patients despite the absence of well-conducted studies to prove its benefits. Only a decade ago, the majority of adult CKD patients were seldom prescribed vitamin D, but now some would argue that withholding its use is unethical! Yet, as nephrologists, we have much to learn from our own exuberant prescribing of medication like EPO and higher dialysis doses as well as from the history of vitamin D usage [10, 41, 49, 103, 104].

When ergocalciferol supplements first became available in the 1920s, high doses were indiscriminately prescribed for rheumatoid arthritis, tuberculosis, Paget's disease and even chilblains; however, ergocalciferol has since been shown not to have any beneficial effect on any of these conditions [103]. Similarly, very high-dose ergocalciferol therapy (1000–2000 IU vitamin D_2/kg body weight) was used in infants to prevent rickets, leading to 25(OH)D levels > 250 ng/ml [104]. The chronic ingestion of over-fortified milk or contaminated food-sources has been reported [41, 105].

The effects of overdosage were described in the literature within a few years of this practice. Diagnosis was often delayed because the symptoms of hypercalcaemia can be non-specific, and patients usually present with nausea, vomiting, constipation, weight loss, polyuria and polydipsia, musculoskeletal pains, apathy and depression. Metastatic calcification, including tumoral calcinosis around joints and vascular calcification, has been reported even in non-CKD patients with vitamin D intoxication. Renal impairment secondary to hypercalcaemia has been reported. In all of these cases, hypercalcaemia resulted when the 25(OH)D levels were consistently >940–1250 ng/ml [10, 106], suggesting that there is a wide safety range and only chronic overdosage with nutritional vitamin D supplements will lead to toxic levels in people with intact renal function. Using a risk-assessment method to define a safe upper limit of intake, the Food and Nutrition Board advise that there is no risk of hypercalcaemia even at levels of 10,000 IU/day [107, 108].

The conversion of ergocalciferol to 25(OH)D by the liver is an unregulated step (no negative feedback) that is driven by the availability of its substrate. 25(OH)D is stored in fat cells where it can stay for many months until reabsorbed. It is thought that pharmacological concentrations of 25(OH)D can overcome its low affinity for its receptor and directly stimulate gene transcription [10, 109–111]. Also, high total vitamin D metabolite concentrations will displace $1,25(OH)_2D$ from its VDBP and increase its free, biologically active form [109, 112]. Although it is possible that an increased 25(OH)D level will increase the production of $1,25(OH)_2D$, this has not been shown in animal studies [10, 110, 111, 113]. In contrast to ergocalciferol or cholecalciferol, the activated forms of vitamin D will directly stimulate the vitamin D receptor with no feedback control, and the latter are far more likely to cause hypercalcaemia and hyperphosphataemia. There are anecdotal reports in the literature of patients requiring treatment for hypercalcaemia for 21 months after the withdrawal of vitamin D and of requiring steroids and pamidronate therapy to correct the hypercalcaemia [103, 114].

In CKD patients, high doses of vitamin D therapy have been repeatedly linked with vascular calcification in autopsy studies, pediatric and adult clinical studies, animal models and in in vitro cell cultures, and these have been described in the above sections. Admittedly, all of these studies have used activated vitamin D compounds, such as calcitriol, alfacalcidol or paricalcitol, but it needs to be recognised that vitamin D analogues have a narrow therapeutic window [28, 38, 46, 55] and, in particular, the recent trend in the use of ergocalciferol or cholecalciferol alongside an activated vitamin D analogue needs to be carefully studied.

Conclusions

Vitamin D deficiency is widely prevalent in adults and children and is present early in the course of CKD. It is an important modifiable risk factor, not only for the correction of secondary hyperparathyroidism, but also for its multiple cardioprotective, anti-inflammatory, immunomodulatory and renoprotective effects. The role of 25(OH)D in regulating many of the non-classical beneficial effects is increasingly recognised, and nutritional vitamin D supplements in the form of ergocalciferol and cholecalciferol are currently widely prescribed to all CKD patients. Yet, we do know that vitamin D has a therapeutic window and that an excess of vitamin D leads to vascular damage and calcification.

There is a need for well-designed randomised controlled studies to define the dosage of ergocalciferol or cholecalciferol required to achieve a therapeutic range for 25(OH)D in patients with pre-dialysis and dialysis-dependent CKD, particularly if there is a concurrent use of activated vitamin D analogues. The optimal 25(OH)D level would need to consider not simply that required for vitamin D's calcaemic role, but also for its non-calcaemic effects.

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