

Vitamin D in Dialysis: Defining Deficiency and Rationale for Supplementation

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ABSTRACT

Vitamin D status is determined by the serum concentration of one of its metabolites, 25-hydroxy-D. Defining vitamin D deficiency based on its classical roles in gut calcium absorption and bone mineralization is problematic in dialysis patients and, until recently, was ignored in the nephrology literature. The newly recognized nonclassical functions of vitamin D include effects on the immune system, cardiovascular disease, and cancer. The nonclassical effects are likely to be equally relevant in the dialysis population, but suffer from a lack of strong evidence on which to base therapeutic targets. Past medical opinion in the nondialysis population warned that higher dose vitamin D supplementation may be toxic and was unnecessary.

This is because older supplementation recommendations were based on early twentieth century studies using cod-liver oil to treat rickets. The clinical resolution of rickets requires a relatively low dose of vitamin D. Current vitamin D guidelines generally target higher 25-hydroxy-D levels of 30 ng/ml, based on optimizing markers of bone health. This results in very high estimates of 50–100% for the prevalence of vitamin D deficiency in dialysis patients. This review examines the relevance of data on the classical and nonclassical effects of vitamin D in dialysis patients. An evidence-based dosing regimen for use in dialysis patients is suggested to safely and reliably achieve vitamin D sufficiency.

The nomenclature of vitamin D and its metabolites is confusing. Despite its name, Vitamin D is not a vitamin for most people, and has no activity at the vitamin D receptor (1). It is present naturally at only very low levels in most foods, except oily fish (2). Adding to the confusion is that a related metabolite 1,25(OH)₂D, also known as “active vitamin D,” is not present in appreciable quantities in any food. Unlike vitamin D itself, both 1,25(OH)₂D and its hundred-fold less potent precursor, 25(OH)D, are active at the vitamin D receptor (3). Unfortunately 1,25(OH)₂D is also sometimes termed “vitamin D,” particularly in nephrology literature. This review follows the KDIGO recommendations on nomenclature (4). “Vitamin D” refers to vitamin D that has no additional hydroxyl groups added, and includes both the D₂ (ergocalciferol) and D₃ (cholecalciferol) forms of the compound. Vitamin D₂ is derived from ergosterol (found in high concentrations in the mold, ergot), and its only major sources in humans are synthetic supplements. Vitamin D₃ behaves similarly to D₂ in the body, but is derived from cholesterol.

Most people derive the bulk of their vitamin D from the exposure of their skin to ultraviolet B (UVB) light, which is present in sunshine. The process starts with cholesterol in the skin, which is enzymatically converted to 7-dehydrocholesterol and then converted to an unstable compound, pre-vitamin D, by the action of UVB. Further exposure of pre-vitamin D to UVB results in its degradation (5), but if not degraded, it is converted to the more stable compound, “vitamin D”. Vitamin D enters the circulation bound to vitamin D-binding protein (DBP) (6) and is then rapidly 25-hydroxylated in the liver to form 25(OH)D. Vitamin D itself is therefore present at low concentrations in the blood and has a short circulating half-life (7). The 25(OH)D has a longer half-life, and is the metabolite taken up by the kidney and other tissues for conversion to the most active vitamin D metabolite—1,25(OH)₂D, which is named calcitriol (D₃) or ercalcitriol (D₂) (8,9).

Definition and Prevalence of Vitamin D Deficiency

The serum 25(OH)D level is widely accepted to determine a person's vitamin D status (10); however, the actual level that denotes deficiency remains controversial. Prior to the development of 25(OH)D assays in the late 1970s, deficiency was recognized as the clinical syndrome of rickets (in children) or osteomalacia (in adults). Both these diseases are conditions of inadequate

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bone mineralization, which is itself related to inadequate calcium absorption. Historically, 1 teaspoon of cod-liver oil, containing approximately 600 U vitamin D, was considered an adequate intake in children (11) based on its ability to cure rickets.

In keeping with the relatively low dose of vitamin D required to prevent rickets, the 25(OH)D level necessary to avoid osteomalacia in nondialysis patients is likely to be similarly low. In an uncontrolled trial of symptomatic, nondialysis patients with baseline levels below 8 ng/ml (20 nmol/l), supplementation to a mean 25(OH)D level over 14 ng/ml (34 nmol/l) largely eliminated musculoskeletal pain (a feature of osteomalacia) (12). Consistent with these data, a 25(OH)D level less than 11 ng/ml (27.5 nmol/l) is taken to define a deficiency state for the general population, by the American Committee for the Evaluation of Dietary Reference Intakes (10).

In the general population, there has been a move to alter the definition of vitamin D sufficiency, so that it is no longer simply a 25(OH)D level that avoids rickets. This has led to a progressive rise in the minimum recommended 25(OH)D level. There is evidence in the nondialysis population that 25(OH)D levels above 24–34 ng/ml (60–86 nmol/l) optimize bone density, falls prevention, calcium absorption, and PTH suppression (11,13–16). This has led to more recent guidelines, for those not on dialysis, defining vitamin D sufficiency as 25(OH)D levels over approximately 30 ng/ml (75 nmol/l) (17,18).

Applying a 30 ng/ml cut-off to hemodialysis patients yields estimates for the prevalence of deficiency that range from 50% to 98% (19–34) (Fig. 1). The calculated mean prevalence for these studies combined is 82% on a total sample size of 3722 patients. Deficiency appears to be both more severe and more common in peritoneal dialysis populations, with estimates of prevalence ranging from 86% to 100% (19,23,25,35–37) (see Fig. 2). The calculated mean prevalence across the 6 studies in peritoneal dialysis patients is 91% on a total sample size of 857 patients. These prevalence estimates are extraordinarily high, and substantially higher than estimates from NHANES III, a large cross-sectional study in the general US population. NHANES III analyzed nearly

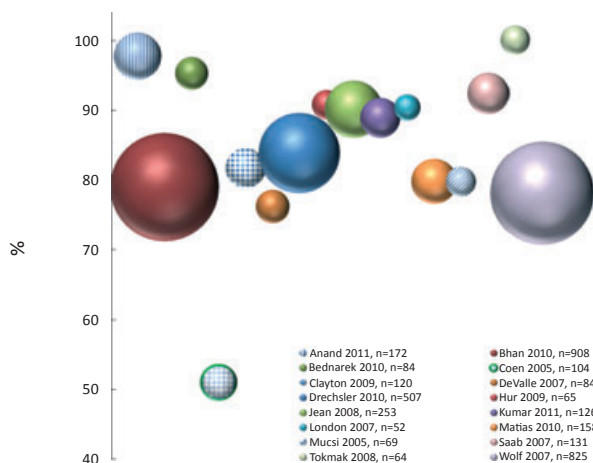


FIG. 1. Prevalence of vitamin D deficiency in hemodialysis.

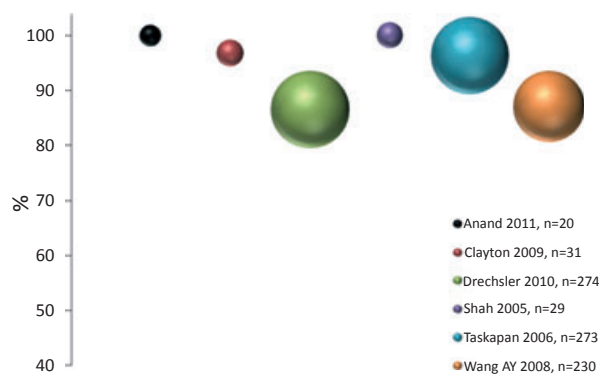


FIG. 2. Prevalence of vitamin D deficiency in PD patients.

14000 25(OH)D samples in those without CKD and found deficiency to be present in 54% (38). The Framingham Offspring Study, conducted in people living in north-eastern USA, found a much higher prevalence at 90% (39), whereas a similarly sized study in France (1569 subjects) found only 14% of subjects to be deficient (40). The differences between studies might be partly due to differences between populations in latitude and lifestyle; however, overall, there does appear to be a somewhat higher prevalence of deficiency in dialysis patients.

Classical Effects of Vitamin D in Dialysis Patients

The “classical” effects of vitamin D are those related to calcium/phosphate absorption and bone mineralization. Vitamin D receptor activation in the intestine leads to increased calcium absorption from food, whereas activation in bone can lead to mobilization of bone calcium (41–43). The net result is an increase in serum calcium. Following the commercial availability of 1,25(OH)₂D, the use of vitamin D was largely ignored in dialysis guidelines until the publication of the 2009 KDIGO recommendations (4). These suggest that 25(OH)D measurement, and vitamin D prescription should be on the same basis as for the general population. Unfortunately, there is no consensus on the optimal target level in the general population. However, achieving > 30 ng/ml (> 75 nmol/l) is recommended in the current International Osteoporosis Foundation guideline (17,18), and is the level selected in the 2003 KDIGO guidelines (17) for patients with nondialysis CKD. It therefore appears a reasonable consensus target for use in dialysis patients.

Early publications appeared to show that 25(OH)D had no effect on bone histology in dialysis patients (44), and to show that 1 α -hydroxylase activity was restricted to the kidney (45). However, there is now a small body of evidence indicating an effect of 25(OH)D on osteomalacia in dialysis patients (22,46–48). There is a larger body of evidence demonstrating that 1 α -hydroxylase activity is widespread in many organs and tissues (49–52). However, for PTH suppression in dialysis patients, which is probably the major clinical use of 1,25(OH)₂D,

the shorter half-life of 1,25(OH)₂D is a significant therapeutic advantage over vitamin D. The much shorter half-life of 1,25(OH)₂D substantially reduces the duration of inadvertent hypercalcemia, which can complicate high-dose treatment with both 1,25(OH)₂D and vitamin D (46).

Notably, the evidence for an effect of 25(OH)D on osteomalacia in dialysis patients was obtained from studies where most of the patients did not receive calcitriol therapy, despite relatively high serum PTH levels. The two larger, more recent, observational studies of 25(OH)D in dialysis patients show that a level below 15–16 ng/ml (37.5–40 nmol/l) is associated with radiologic or histologic osteomalacia (22,48). In these studies, there was no correlation between 25(OH)D and 1,25(OH)₂D levels, but in one of the studies, there was a weak negative correlation with PTH. Other data tend to support at least a weak correlation between 25(OH)D and 1,25(OH)₂D levels in dialysis patients (29,53–58), whereas the data are mixed with respect to PTH (24,27,29,31,34,37,59). It is therefore unclear whether the effect of 25(OH)D on osteomalacia in dialysis patients is mediated through slight changes in circulating 1,25(OH)₂D or through changes in PTH. It is possible, but unproven, that attaining a 15–16 ng/ml 25(OH)D level would reduce the need for active vitamin D analogs. In that case, adequate vitamin D prescription might lower the potential for toxicity related to PTH suppression by reducing the need for active analogs, which have greater hypercalcemic and hyperphosphatemic potential.

Nonclassical Effects of Vitamin D

Substantial, but largely observational, data have accumulated over the past 30 years that suggest actions of vitamin D that are unrelated to its classical effects on bone mineralization and calcium/phosphate absorption. These other actions are called the “nonclassical” effects of vitamin D. They include, in the nondialysis population, an impact on mortality (60,61), progression of CKD (62), cancer (63,64), vascular calcification (65), immunity/autoimmunity (66–70), and cardiovascular events (39).

Nonclassical effects are likely to be mediated by autocrine or paracrine stimulation of vitamin D receptors, following the local generation of 1,25(OH)₂D by extra-renal 1 α -hydroxylase (68). This implies that adequate circulating 25(OH)D, rather than 1,25(OH)₂D, is essential for expression of the nonclassical effects. There is experimental evidence to support this contention in some tissues, including lymphoid tissue and vascular smooth muscle (50,52). As extra-renal 1 α -hydroxylase activity is not obviously dependent on functional renal mass, the nonclassical effects of vitamin D are likely to be equally relevant in the dialysis population. There are (mostly) observational data in both dialysis and nondialysis patients that link lower 25(OH)D levels to hypertension (71–74) and increased cardiovascular events (25,35). In dialysis patients, there is also an association between vitamin D supplementation and reduced LV

mass (30,59) as well as an effect on the immune system (58). Unfortunately, because most vitamin D comes from the sun, and healthier people have more opportunity to spend time outdoors, observational studies are particularly prone to confounding. It may be that in some of these observational studies, the association of 25(OH)D levels with better health outcomes is merely a reflection that healthier patients spend more time outdoors, rather than the direct cause of their good health.

Nonclassical Effects of Vitamin D: Determining the Optimal Level

There is no good quality evidence in either the dialysis or the nondialysis populations to guide therapy targeting nonclassical vitamin D effects. However, in normal infants, there are good quality longitudinal data that a Vitamin D dose over 2000 U/day is associated with the lowest risk of developing type 1 diabetes (66). What the equivalent adult dose would be is unknown, but 2000 U/day is at least double the dose found necessary in an adult meta-analysis, to raise 25(OH)D levels above 60 nmol/l (24 ng/ml) (14). Given the much smaller size of 1-year-old infants, there seems little doubt that 2000 U/day would achieve 25(OH)D levels well over 24 ng/ml. Whether such high 25(OH)D levels are optimal is uncertain, but perhaps they are more “normal” in the context of human development.

Determining what constitutes a “normal” 25(OH)D level is problematic. Unsupplemented humans derive all other vitamins entirely from food. This makes it reasonable to assume that a “normal” level for these vitamins is approximately the level seen in a healthy sample of the population. However, uniquely among the vitamins, humans obtain vitamin D predominantly from the sun and not from food. Current sun exposure patterns, at least for sedentary city dwellers, are very different from those pertaining to the past. For most of human prehistory, the majority of people probably worked outdoors hunting, gathering or farming food in a tropical environment. It is therefore reasonable to presume that a “normal” 25(OH)D level is closer to that seen in people who have an outdoor lifestyle, and is much higher than the levels seen in city dwellers, who spend much of the day indoors. In fact, individuals with an outdoor lifestyle have average 25(OH)D levels of approximately 53 ng/ml (133 nmol/l), with levels ranging as high as 111 ng/ml (278 nmol/l), without supplementation (75–77). Such levels are double those seen in a representative cross-section of the general US population (78) and are likely to be safe, as vitamin D toxicity has never been reported from sun exposure alone.

Vitamin D Toxicity

Fortunately, for most patients, vitamin D dosing is safe over a wide dosing range. This is probably because 24-hydroxylation degradation pathways are induced by 1,25(OH)₂D and FGF-23 (79–81). Hence, any rise in

free or total $1,25(\text{OH})_2\text{D}$ will lead to a protective acceleration in the rate of degradation for both $25(\text{OH})\text{D}$, and $1,25(\text{OH})_2\text{D}$. As at higher levels, $25(\text{OH})\text{D}$ appears to stimulate the vitamin D receptor (82), a higher $25(\text{OH})\text{D}$ level itself is also likely to lead to a protective acceleration in degradation. This would explain the trend toward a smaller relative increment in serum $25(\text{OH})\text{D}$ when higher vitamin D doses are given (83). FGF-23 levels tend to be very high in dialysis patients and are stimulated by a rise in $1,25(\text{OH})_2\text{D}$ levels, as well as by increases in phosphate (84,85). High FGF-23 levels are one explanation for the very high prevalence of low $25(\text{OH})\text{D}$ and $1,25(\text{OH})_2\text{D}$ levels in dialysis patients. If this explanation is correct, then it would suggest that higher than usual supplementation doses may be necessary to achieve any given $25(\text{OH})\text{D}$ target in dialysis patients.

Doses of vitamin D up to 10,000 U/day generally result in serum $25(\text{OH})\text{D}$ levels remaining below approximately 88 ng/ml (220 nmol/l) (11). At this level, $25(\text{OH})\text{D}$ does not have a direct effect on gut calcium absorption (82) and hence should not, by itself, be capable of causing hypercalcemia. At levels over approximately 120 ng/ml (300 nmol/l), which are higher than that occurring without supplementation (75–77), $25(\text{OH})\text{D}$ does directly affect calcium absorption (82). When that occurs, direct toxicity from $25(\text{OH})\text{D}$ becomes more likely. Theoretically, toxicity could still occur at somewhat lower $25(\text{OH})\text{D}$ levels if they resulted in an increase in free or total $1,25(\text{OH})_2\text{D}$ levels. However, except perhaps in patients with specific comorbidities (86,87), neither total $1,25(\text{OH})_2\text{D}$ levels nor calcium absorption is noticeably affected at levels below 120 ng/ml (82). At these $25(\text{OH})\text{D}$ levels, an isolated increase in the free fraction of $1,25(\text{OH})_2\text{D}$ is unlikely to occur. Such changes have only been reported in the setting of massive vitamin D overdose, where much higher $25(\text{OH})\text{D}$ levels are seen (88).

Except in patients with autonomous 1α -hydroxylase activity, there are no compelling reports of vitamin D toxicity at $25(\text{OH})\text{D}$ at levels consistent with sun exposure alone (< 111 ng/ml), or at estimated vitamin D doses in the 10,000 U/day range. There is only one small case series (of 4 “toxic” patients) that has reported adverse effects (hypercalciuria and reduced bone density) at levels below 111 ng/ml (89). In that study, the toxicity reported was of dubious significance, as the time course for the resolution of toxicity had no obvious relationship with changes in serial serum $25(\text{OH})\text{D}$ levels. A case-control study also suggested possible toxicity, in the form of a possible increase in pancreatic cancer with higher $25(\text{OH})\text{D}$ levels (90). In this study, the absence of a dose-response relationship (cancer was more common at both low and high $25(\text{OH})\text{D}$ levels) suggests that the relationship may be spurious.

The risk of toxicity is, however, different in patients with autonomous 1α -hydroxylase activity as is seen in patients with granulomatous disease or lymphoma. Such patients may be unusually sensitive to vitamin D supplementation (86,87) with hypercalcemia resulting from even small vitamin D doses. This occurs because when 1α -hydroxylase activity is autonomous, $1,25(\text{OH})_2\text{D}$

production will be governed by the availability of $25(\text{OH})\text{D}$ substrate. In this situation, both $1,25(\text{OH})_2\text{D}$ production and $25(\text{OH})\text{D}$ metabolism will rise in proportion to the vitamin D dose. The net result may be hypercalcemia, but a much lower than expected increment in serum $25(\text{OH})\text{D}$. For such patients, it is possible that there is no completely safe dose of vitamin D.

Required Vitamin D Dose

The 2010 US Dietary guidelines recommended a daily intake for older American adults of 600–800 U for those with minimal sun exposure, and warn that the risks of adverse events increase at intakes over 4000 U/day (2). However, a study in non-CKD subjects estimated that the total vitamin D requirement (body store utilization plus oral and cutaneous inputs) to sustain a $25(\text{OH})\text{D}$ level of 28 ng/ml (70 nmol/l) is 3800 U/day (91). This suggests that, in the absence of sun exposure, 600–800 units/day is unlikely to maintain such levels.

There are conflicting estimates for the dose necessary to achieve a serum $25(\text{OH})\text{D}$ level over 30 ng/ml (75 nmol/l) in hemodialysis patients. Published data use a variety of dosing intervals; however, converting these doses to a dose/day equivalent shows that 2900 U/day cholecalciferol is often insufficient (33) to raise levels over 30 ng/ml, but that a dosage of 3300 U/day is usually sufficient (57). Other data suggest that a 1700 U/day dosage of ergocalciferol is almost always effective (32), or usually ineffective (28) at achieving the same $25(\text{OH})\text{D}$ levels. This variation in estimates is in keeping with the results of a large meta-analysis of studies performed in non-CKD patients, which demonstrates an inconsistent relationship between the prescribed vitamin D dose and the $25(\text{OH})\text{D}$ increment achieved (92). The inconsistent relationship is probably due mainly to many subjects obtaining significant, but varying amounts of vitamin D from the sun and to the effects of obesity. Obesity is both a risk factor for vitamin D deficiency and also reduces the $25(\text{OH})\text{D}$ increment achieved with sun exposure and oral supplementation (93,94). The reason for this reduced $25(\text{OH})\text{D}$ increment is unclear, but it may be due to increased storage of vitamin D in adipose tissue.

The minimum effective and maximum safe dose for vitamin D supplements is likely to be significantly affected by the amount of cutaneous vitamin D synthesis. However, it is difficult to estimate the amount of cutaneous synthesis in a given patient, as it requires knowledge of usual sun exposure duration, skin color, and the surface area of skin usually exposed (5). It may also be affected by age and CKD itself, with data to indicate that dialysis patients and the elderly have lower vitamin D generation for a given UV exposure (95,96). Other factors that determine what constitutes a safe and effective dose of vitamin D are the threshold level above which $25(\text{OH})\text{D}$ causes toxicity and whether the patient has excessive losses of vitamin D. Patients on peritoneal dialysis or those with heavy proteinuria appear to have increased losses (97–99), but quantifying this for an individual patient is not practical. Finally, it is unclear

whether supplemental vitamin D₂ or D₃ differentially affects the achieved steady-state 25(OH)D level. Some data suggest that D₂ has a more rapid metabolism and therefore a somewhat less potent effect on 25(OH)D levels (100); however, this is not a universal finding (101).

Recommendations for Testing and Therapy

The vitamin D dose necessary to achieve a 25(OH)D level of 30–120 ng/ml varies between patients, based mainly on the level of sun exposure. Fortunately, toxicity with vitamin D doses of less than 10,000 U/day is very unlikely in patients with any level of deficiency (11). Dosing with 50,000 U once per week is similar to the 3800–5000 U/day estimated to be necessary to achieve 25(OH)D levels > 30 ng/ml in 95% of the general US population (83). There is little to choose between dosing with ergocalciferol or cholecalciferol. Cholecalciferol is probably somewhat more potent at raising 25(OH)D levels, but as both forms of the vitamin are inexpensive, this is of no clinical importance, provided the assay used to assess levels has equal sensitivity to 25(OH)D₂ and 25(OH)D₃.

It is not clear whether patients routinely need to be retested for 25(OH)D after commencement of supplementation. However, if doses lower than 50,000 units/week are used, then retesting is necessary to ensure that adequate levels are achieved. For patients who are prescribed 50,000 units/week, a repeat level after 3–4 months does provide reassurance that the patient is being adequately and safely dosed. Caution should be exercised in patients who may have autonomous 1 α -hydroxylase activity. In such patients, vitamin D therapy should be introduced at much lower doses and the serum calcium monitored closely. Retesting patients who develop hypercalcemia, which might be related to dosing, is sensible, with therapy ceased if 25(OH)D levels approach 120 ng/ml (300 nmol/l). In patients who become hypercalcemic but do not have elevated 25(OH)D levels, measurement of 1,25(OH)₂D will enable autonomous 1 α -hydroxylase activity to be detected.

Summary

Recommendations regarding vitamin D in both nondialysis and dialysis patients are in evolution. There appears to be general, although not universal, acceptance that a 25(OH)D target over 30 ng/ml (75 nmol/l) is reasonable to optimize the classical effects on bone strength and falls prevention in the nondialysis population. The effect on bone health in dialysis patients is unclear, but supplementation is generally believed to be safe. There are almost no data to select an appropriate 25(OH)D target for optimizing the nonclassical effects of vitamin D, such as cardiovascular health, immune function, or cancer prevention. Consequently, at this point in time, it seems prudent to set the target level at > 30 ng/ml for this indication as well.

The upper bound to safe levels is not known with certainty; however, levels as high as 111 ng/ml are almost certainly both normal, in an evolutionary sense, and nontoxic. Based on limited experimental data, it is unlikely that levels below 120 ng/ml (300 nmol/l) in those without autonomous 1 α -hydroxylase activity are toxic (82). Certainly, there are no compelling data for clinical toxicity below this level, making it a reasonable, conservative upper bound to safe levels, and one that is unlikely to be exceeded even at doses as high as 10,000 U/day.

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