Mushroom Clouds for Vitamin D?

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Values of serum 25-hydroxyvitamin D (25OHD) defined as insufficient or deficient are common in the general community, particularly among the elderly and people with chronic illnesses and reduced skin exposure to sunlight. Ultraviolet B exposure is essential for skin synthesis of vitamin D3 (cholecalciferol), the precursor to 25OHD3 and 1,25-dihydroxyvitamin D (calcitriol). Dietary sources of vitamin D include animal sources of cholecalciferol such as oily fish, and plant sterols that provide dietary vitamin D2 (ergocalciferol). Patients with CKD often fall within the populations at risk of vitamin D deficiency.1

After the establishment of a causal relationship of vitamin D deficiency to rickets, fortification of foods with vitamin D was initiated in some countries, with dramatic improvements on bone deformity in children. Subsequent observational studies have linked lower serum 25OHD values to increased risks of cardiovascular, malignant, endocrine, pulmonary, and autoimmune diseases, resulting in widespread testing of serum 25OHD levels and the prescription or self-initiation of vitamin D at doses that often exceed dietary reference values. This medicalization of vitamin D has also resulted in divergent health care messages on the risks of sun exposure, the usual source of vitamin D, as well as food fortification and supplementation.2 Even the terminology is loaded, with vitamin D deficiency and insufficiency reflecting cut points for disease associations rather than values at which interventions are proven to influence patient-level outcomes.3

Many tissues express both vitamin D receptors (VDRs) and cytochrome p450 27B1 (CYP27B1), the 1-α-hydroxylase enzyme that converts 25OHD to calcitriol, but in patients with CKD, renal calcitriol production may be reduced or absent. It has been proposed that vitamin D supplementation may, nevertheless, maintain sufficient 25OHD substrate for extrarenal calcitriol production, to allow the paracrine and autocrine actions of vitamin D and the modulation of vitamin D–responsive genes.3 In addition, serum 25OHD may act directly through the VDR if calcitriol levels are low. Bone is an obvious target tissue for extra-renal conversion of 25OHD to calcitriol, and in a cross-sectional study of patients on hemodialysis, 25OHD values <20 ng/ml (50 nmol/L) were associated with reduced bone turnover on histomorphometry, and values >40 ng/ml (100 nmol/L) were associated with increased bone turnover, independent of serum calcitriol and parathyroid hormone (PTH) values.4 Experimental support for extrarenal conversion comes from tissue culture of human osteoclasts.5 When incubated with physiologic 25OHD concentrations, these cells produce calcitriol and upregulate key osteoclast transcription factors and expression of the osteoblast coupling factor ephrin-b2. Low values of 25OHD have also been associated with muscle weakness and falls risk in patients on dialysis, independent of calcitriol values,6 but whether these abnormalities are a consequence of hypovitaminosis D or secondary to associated mineral disturbances is unclear, particularly because the identification of VDR in muscle has been questioned.7 Other associations of lower 25OHD levels include sudden cardiac death, cerebrovascular and all-cause mortality in patients on dialysis with diabetes,8 and a plethora of associations with morbidity and mortality in the general population. Therefore, given the plausible physiology and despite the potential for bias in these observational studies, the temptation to treat is difficult to resist. However, acolytes of vitamin D must, nevertheless, respect the science, and in a number of areas, evidence for and against a role for vitamin D in CKD has been accumulating.

The paper by Miskulin et al.9 published in this issue of the Journal of the American Society of Nephrology adds to this evolving evidence base and contrasts with an earlier cross-sectional study10 that reported a 2.8-fold increase in anemia prevalence for patients with CKD who were in the lowest versus the highest tertile of serum 25OHD values. This study by Miskulin et al.9 randomized 276 patients on hemodialysis with baseline 25OHD levels ≤30 ng/ml (12 nmol/L) to ergocalciferol or placebo for 6 months. Treatment was effective, with 25OHD values rising from 16.0±5.9 to 39.2±14.9 ng/ml (40±15 to 98±37 nmol/L) in the ergocalciferol arm, and there was no significant change for patients receiving placebo. Active vitamin D was used in 82% of patients, but doses were unchanged during the study. The study reports no significant differences between groups in the primary end point of epoetin requirements or in BP, change in serum PTH, phosphorus, calcium, inflammatory markers, or use of cinacalcet, calcitriol, or phosphate binders.9 These data9 and those of a similar but smaller randomized, controlled trial using cholecalciferol11 erode support for the use of nutritional vitamin D in the short-term management of anemia for patients on dialysis or patient-level outcomes assessed by functional or muscle
strength testing, BP control, differences in lipids, insulin resistance, inflammatory markers, vascular compliance as measured by pulse wave velocity, or quality of life. Although vitamin D is relatively inexpensive and adverse effects are infrequent, the additional pill burden and lack of proven efficacy suggest that, for patients with vitamin D values in the described range, relatively short–term treatment for those indications is unjustified.

Vitamin D supplementation may, nevertheless, be useful. For patients with CKD stages 2–4, treatment with cholecalciferol reduces PTH levels and may impede PTH values from rising.12,13 Cholecalciferol treatment is also reported to maintain or increase calcitriol levels,12,14 even for patients on dialysis,11 although the clinical benefit of this is unknown. Heavy proteinuria can result in substantial losses of vitamin D binding protein (DBP) and may contribute to vitamin D deficiency, whereas treatment with vitamin D may ameliorate podocyte injury and reduce proteinuria. In children with CKD, higher 25OHD levels are associated with reduced proteinuria and an attenuation of renal failure progression, independent of treatment with calcitriol.15 Similarly, in a recent 6-month prospective study of adults with CKD stages 3 and 4 and albuminuria, patients with lower serum 25OHD values and elevated serum PTH who were treated with cholecalciferol showed a 52% reduction in urinary albumin-to-creatinine ratios, independent of changes in weight, BP, or antihypertensive treatment.16 However, all interventions come at some cost. Although vitamin D treatment is generally safe, increased serum and urinary calcium levels have been reported, as having an increase of fibroblast growth factor 23 values in one study of patients with CKD12 but not in another study.13

A number of regimens have now been shown to increase 25OHD levels effectively in CKD stages 3–5 and 5D. Doses of 50,000 IU cholecalciferol or ergocalciferol, initially weekly and then, monthly achieve 25OHD levels ≥20 ng/ml (50 nmol/L) in most patients on dialysis.9,11 However, megadose treatments should be avoided; a randomized, controlled trial of 2256 elderly community–dwelling women reported that a single annual cholecalciferol dose of 500,000 IU led to increased falls and fractures,17 possibly by inhibiting bone mineralization, leading to osteomalacia, and affecting muscle strength. Lower–dose vitamin D that corresponds to the Institute of Medicine recommended daily allowance of 600 IU and is well below the suggested adult tolerable upper limit of 4000 IU daily,18 also seems effective in raising 25OHD levels and reducing levels of serum PTH values in earlier stages of CKD.

Vitamin D is a hormone that signals through multiple pathways, with effects that might be detected over years rather than weeks or months and that may depend on the intake of other nutrients. Although 25OHD deficiency might result in an earlier onset of illness, providing evidence–based serum targets may be unrealistic if we use a drug paradigm. We may also be overlooking environmental influences and subtleties of vitamin D metabolism, such as allelic variations that influence the affinity of vitamin D to DBP.19 It is even questionable whether total 25OHD is the best vitamin D to measure.20,21 Vitamin D bound to DBP is filtered and then reabsorbed in the proximal tubule, but free 25OHD is the biologically active moiety. Measuring free 25OHD may better inform our understanding of extraskeletal effects of vitamin D and of racial differences that affect the association of total 25OHD values to disease outcomes, including fracture risk and the sometimes paradoxical relationship of serum 25OHD to PTH and bone mineral density. For example, American women of African descent have lower 25OHD levels and higher bone mineral density than American women of European descent, but they also have lower DBP levels; therefore, their free 25OHD values do not differ.22

Although ongoing trials, such as the VITaminD and OmegA-3 Trial,23 may throw more light onto the vitamin D debate, on the basis of current data, it seems rational and justified to avoid very low levels of serum 25OHD. However, providing serum 25OHD values are within a range >12–20 ng/ml (30–50 nmol/L) and perhaps <40 ng/ml (100 nmol/L), there are few signals to suggest a risk to bone health. Certainly the data from Miskulin et al.9 suggest that we should have fewer expectations of short–term benefits from supplementation, but it remains possible that the benefits of maintaining adequate levels of this important hormone may emerge over time. Also, similar to the potential of extremely high fibroblast growth factor 23 values to assist in identifying patients at increased risk of mortality, and without assuming a role of vitamin D in causation, very low 25OHD levels should warn us of patients at increased risk for those conditions identified in observational studies. However, to influence their prognosis, our interventions will need to be more holistic than using vitamin D alone.

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DISCLOSURES

None.

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