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Vitamin D Replacement in Adults: Current Strategies in Clinical Management

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Vitamin D, a prohormone, is needed for proper calcium homeostasis and potentially a host of additional physiologic functions. With changes in diet and an age-related decline in dermal production of vitamin D, practitioners often encounter patients with varying degrees of vitamin D insufficiency or deficiency. It is imperative to recognize and treat vitamin D deficiency before it manifests with detrimental effects on the body. This review will provide background on the physiology of vitamin D, common causes of hypovitaminosis D and conclude by providing a practical guide to vitamin D replacement and monitoring in common clinical scenarios.

INTRODUCTION

Vitamin D plays a critical role in human health. Well recognized is the importance of vitamin D in the absorption of calcium and phosphate mineral and the subsequent actions on bone mineralization, bone strength, and fracture protection.¹ In recent years, increasing preclinical evidence supports a role for vitamin D in a multitude of extra-skeletal physiological functions while low vitamin D levels have been linked in observational studies to immune dysfunction, malignancies (e.g. breast, colon, prostate), skeletal muscle strength, cardiovascular, and glycemic regulation.^{2,3} Despite these associations, randomized controlled trials are either lacking or do not consistently find that vitamin D supplementation alters most of these non-skeletal outcomes.⁴⁻⁷ However, it is generally agreed that perturbations in vitamin D metabolism can have an important impact on human health and hence screening for, and adequately treating, vitamin D deficiency is important for general health purposes.⁸

There exist two primary sources of vitamin D in humans: dermal production of vitamin D₃ (cholecalciferol) and nutritional supplementation with either vitamin D₃ or vitamin D₂ (ergocalciferol). Shortfalls in dietary intake, reduction in ultraviolet

light exposure needed for dermal biosynthesis of vitamin D, age-related decline in dermal production of vitamin D, disorders altering the gastrointestinal absorption of fats, and conditions that accelerate the metabolism of vitamin D stores can all predispose an individual to vitamin D deficiency. It is not surprising that hypovitaminosis D can be present in a wide array of clinical scenarios.

Conversely, while wide-spread supplementation of milk, juices, cereal, and daily multivitamins and calcium preparations with vitamin D is part of a general health approach to prevent vitamin D deficiency, over-replacement with vitamin D can have adverse consequences. Excess absorption of calcium and phosphate can predispose to hypercalciuria and nephrolithiasis and much less commonly, calcium mineral deposition of soft tissues and organs such as the kidney, thereby adversely altering function. It is the purpose of this article to:

1. briefly review the physiology and regulation of vitamin D activity
2. identify common clinical conditions in adults in which an evaluation of vitamin D status is indicated

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3. review commercially available assays for vitamin D with their specific advantages and limitations,
4. propose a practical therapeutic plan for adults that includes monitoring and treatment goals that are generally acceptable for most patients with vitamin D deficiency.

Physiology of Calcium Homeostasis and the Role of Vitamin D

The central player in the regulation of calcium is parathyroid hormone (PTH). PTH synthesis and secretion are directly regulated by the extracellular calcium concentration via the Calcium-sensing receptor (CaSR) through an inhibitory mechanism. Activation of the CaSR results in a reduction in PTH. Conversely, hypocalcemia increases PTH. Target organs for PTH action include the bone and kidney. PTH increases bone turnover and osteoclast action to release calcium and phosphorus into the circulation. In terms of renal actions, PTH enhances resorption of filtered calcium thereby limiting renal losses of calcium. In addition, and relevant to this review, PTH drives conversion of stored 25-hydroxyvitamin D (calcidiol) into the active metabolite 1,25-dihydroxyvitamin D (calcitriol) via the actions of 1-alpha hydroxylase (CYP27B1). Calcitriol, in turn, enhances gastrointestinal absorption of calcium and phosphorus in the small bowel, though there may be a small contribution of calcidiol in this regard. In addition, and to a more modest degree, calcitriol favors bone mineralization and the deposition of calcium mineral into newly formed bone (osteoid). The increase in circulating calcium then feeds back at the level of the parathyroid gland to inhibit further PTH secretion.

Stored vitamin D, i.e. calcidiol, is the product of 25-hydroxylation by the hepatocytes. Both vitamin D₂ and D₃, regardless of their source, are fully and rapidly converted to calcidiol such that measurement of cholecalciferol or ergocalciferol is not practical. Calcidiol circulates attached to a vitamin D binding protein (high affinity, low capacity) and albumin (low affinity, high capacity), both products of hepatic biosynthesis. While the capacity to synthesize calcidiol from the parent compounds is generally well in excess of normal

physiologic needs, severe hepatic dysfunction and end-stage liver disease can be associated with vitamin D deficiency due to a decline in calcidiol production.

Due to the feedback regulation described above, vitamin D toxicity due to excess ingestion of calcidiol is unlikely. If calcidiol levels rise above the normal range, calcium feedback to the parathyroid glands inhibits parathyroid hormone release, via activation of the CaSR, which in turn reduces the conversion of calcidiol to calcitriol. In effect, thereby preventing further enhancement in calcium absorption. None-the-less, excess levels of vitamin D (> 80 ng/mL) can increase circulating calcium levels which results in hypercalcemia and hypercalciuria and a long-term risk of nephrolithiasis.

Clinical Presentation of Vitamin D Deficiency, Differential Diagnosis and Laboratory Testing in Adults

The majority of patients with vitamin D deficiency have few, if any signs or symptoms related to the condition. Over the long term, reductions in vitamin D can lead to a reduction in circulating calcium, secondary hyperparathyroidism, increased bone remodeling and mobilization of calcium from bone. Severe vitamin D deficiency can result in osteomalacia that is often asymptomatic, but in some can be associated with diffuse bone pain. In addition, enhanced bone fragility can present with fracture from a ground level fall. The associated laboratory studies include a reduced 25-hydroxyvitamin D, normal or low-normal calcium levels, elevated PTH and alkaline phosphatase levels and a reduced 24-hour urinary calcium excretion rate.

There remains some discussion on the proper diagnostic nomenclature for patients with hypovitaminosis D. The Endocrine Society's practice guidelines⁹ detail three categories:

1. Vitamin D sufficiency: 25-hydroxyvitamin D of > 30 ng/mL (75 nmol/L)
2. Vitamin D insufficiency: 25-hydroxyvitamin D between 21-29 ng/mL (51-74 nmol/L)
3. Vitamin D deficiency: 25-hydroxyvitamin D of < 20 ng/mL (<50 nmol/L)

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It is important to note that the biologic contributions of either vitamin D₂ or vitamin D₃ are similar and hence differentiation between the two forms is not important for diagnostic purposes. Of greater import, measurement of 1,25-dihydroxyvitamin D (calcitriol) is not included in the identification of vitamin D deficient patients. Calcitriol levels are maintained in the normal range even in the presence of severe calcidiol deficiency and will not reflect many patients' vitamin D balance.

A full discussion of the causes of vitamin D insufficiency and deficiency is beyond the scope of this manuscript. In overview, malabsorptive conditions predispose to deficiencies of all fat-soluble vitamins. Infectious etiologies (e.g. *C. Difficile*), inflammatory (e.g. ulcerative colitis) and iatrogenic (e.g. bariatric surgery) all can result in substantial reductions in vitamin D stores. In addition, with aging, dermal production of cholecalciferol declines and hence even reasonable UV light exposure may not be sufficient to maintain normal 25-hydroxyvitamin D levels.

It is also important to mention that there are acute causes of vitamin D deficiency. In

patients receiving care in an intensive care unit for severe illness, there is some data suggesting that 25-hydroxyvitamin D levels may abruptly drop below the reference range.^{10,11} That said, data supporting a benefit for urgent restoration of vitamin D levels is lacking. Hence, we neither check vitamin D levels, nor add vitamin D replacement in this patient population.

Measurement of Vitamin D

An immunoassay can use a variety of detection techniques and 2 methods for the measurement of 25-hydroxyvitamin D are chemiluminescence and radioactivity. Chemiluminescent immunoassays can be automated and allow for a faster turn-around time, with the downside being that it is unable to distinguish between 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and is reported only as a total 25-hydroxyvitamin D level. Radioactivity as a detection method is becoming less common but radioimmunoassays (RIA) are still available. In general, immunoassays tend to underestimate the concentration of 25-hydroxyvitamin D₂ due to a lower affinity of the antibody for this analyte compared to 25-hydroxyvitamin D₃. Liquid chromatography tandem mass spectrometry is a

Table 1. Comparison of Various Formulations of Vitamin D and Their Metabolites

Formulation	Available Strengths	Cost for 3 Month Supply	Advantages
Ergocalciferol (Vitamin D ₂)	400-50,000 IU	\$6-\$11	Affordable Available over the counter Can use daily, weekly or monthly dosing
Cholecalciferol (Vitamin D ₃)	400-50,000 IU	\$4-\$12	Affordable Available over the counter Can use daily, weekly or monthly dosing
Calcidiol (25-hydroxyvitamin D)	30mcg	\$3,000	Bypasses hepatic 25-hydroxylation Can be useful in malabsorption as it is more hydrophilic
Calcitriol (1,25-dihydroxyvitamin D)	0.25mcg, 0.5mcg	\$24-\$55	Active form of vitamin D Bypasses both hepatic and renal hydroxylation Can be useful in malabsorption as it is more hydrophilic

popular choice for measuring 25-hydroxyvitamin D, as it separates and measures 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ individually and has been established as the gold standard to which chemiluminescent and RIA assays are compared.

A study comparing measurements from different laboratories using either high-performance liquid chromatography (HPLC), RIA, or automated chemiluminescent assays for measurements of serum 25-hydroxyvitamin D demonstrated that the degree of variability of the results between methods and between laboratories, even when using the same method, confounded the diagnosis of vitamin D insufficiency.¹² Specifically, some chemiluminescent and RIA assays were found to underestimate the contribution of 25-hydroxyvitamin D₂ to total circulating 25-hydroxyvitamin D levels. Since ergocalciferol (vitamin D₂) is often used for treatment of hypovitaminosis D, the inability to measure 25-hydroxyvitamin D₂ could result in apparent laboratory failures in assessing therapeutic responses and/or lead to a misdiagnosis of vitamin D insufficiency or deficiency. Increases in unmeasured vitamin D could potentially result in dose escalation and subsequent dangerous consequences such as hypervitaminosis D. As a result, we suggest ascertaining the specific assay for 25-hydroxyvitamin D used by your own laboratory, not only during diagnosis (although measurement of only 25-hydroxyvitamin D₃ in that setting would be of little harm), but also when monitoring response to treatment.

Strategies for Vitamin D Replacement

While many preparations of vitamin D and its metabolites are available to restore normal circulating levels of vitamin D, cholecalciferol and ergocalciferol are used more frequently as they are less expensive and, in particular, cholecalciferol is readily available to most patients in over-the-counter formulations (Table 1). While the biological activities of the two forms of vitamin D are comparable, in our practice cholecalciferol is generally the preferred formulation for vitamin D supplementation as there is data to suggest that it is more effective than ergocalciferol at increasing total 25-hydroxyvitamin D levels.¹³⁻¹⁵ This observation may be due to a predictable decrease

in vitamin D₃ level seen in patients treated with ergocalciferol.¹⁶ We do not utilize calcitriol in most instances unless the patient manifests clinical signs of hypocalcemia, have hypoparathyroidism (and the associated deficit in renal 1-hydroxylation) or if they would be more likely to absorb calcitriol (e.g. following bariatric surgery).

In adult patients without malabsorption, but with vitamin D deficiency (25-hydroxyvitamin D of ≤ 20 ng/mL (<50 nmol/L)), we initially treat with 2,000-6,000 international units (IU) cholecalciferol daily or 50,000 IU of ergocalciferol (or cholecalciferol) weekly for 6-8 weeks.⁹ Once the course of therapy is complete, we repeat testing including a 25-hydroxyvitamin D level along with a measurement of serum calcium. In addition, in patients with secondary hyperparathyroidism prior to treatment, normalization of PTH levels can confirm adequacy of replacement, though we elect to do this infrequently to reduce cost and recognizing that changes in PTH levels can lag behind changes in vitamin D levels. Once replete, the vitamin D dose is reduced to a maintenance regimen generally of 2,000 IU/day cholecalciferol, or 50,000 IU of ergocalciferol (or cholecalciferol), every 14-30 days, and levels are again repeated in 2-3 months. We feel the majority of these patients are at a relatively high risk of repeat vitamin D deficiency in the future, and they are counseled that this is life-long therapy. Of note, in obese individuals, steady state levels may take a longer time to reach and hence we often delay repeat measurement for an additional 1-3 months.

Patients who have vitamin D insufficiency (25-hydroxyvitamin D between 21-29 ng/mL (51-74 nmol/L)) may be replaced with 400-2,000 IU cholecalciferol per day to achieve normal 25-hydroxyvitamin D levels. In general, we do not recommend high dose vitamin D without documentation of vitamin D deficiency as there are emerging data to suggest routine use of this type of supplementation in vitamin D replete individuals may not be beneficial.¹⁷

In patients with malabsorptive states, higher doses of vitamin D may be needed, even as high as 6,000 IU-10,000 IU daily of cholecalciferol or 50,000 IU twice weekly of ergocalciferol (or cholecalciferol) for short-term use.⁹ Once replete,

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these patients usually continue on slightly reduced or in some cases the same dose of vitamin D long term to avoid recurrence of vitamin D deficiency. We often follow vitamin D and calcium levels every 3-6 months going forward to ensure adequate replacement and less often once stable.

In addition, there are special patient populations that may benefit from treatment with metabolites of vitamin D. Patients with liver disease may have impairment of 25-hydroxylation of vitamin D and these patients may benefit from calcidiol (25-hydroxyvitamin D).^{18,19} Similarly, patients with severe renal disease or end-stage renal disease (ESRD, beyond stage 3) may have impairment in 1-hydroxylation of 25-hydroxyvitamin D and may benefit from calcitriol (1,25-dihydroxyvitamin D).²⁰ Vitamin D analogs are often used in the ESRD patient population to reduce the sequelae of severe secondary hyperparathyroidism and the decision whether to treat a low 25-hydroxyvitamin D level is complex. Indeed, in many instances, we do replace these patients with cholecalciferol or ergocalciferol, to potentially reduce the effects of secondary hyperparathyroidism, even while recognizing that calcium balance is not significantly altered as a result.

SUMMARY

Vitamin D has an important role in many physiological functions, most prominent and well established are its roles in calcium homeostasis and bone health and deficiency may be asymptomatic. Screening patients for vitamin D deficiency should be performed in individuals presenting with low bone mineral density. Cholecalciferol (D₃) is the preferred replacement supplement, inexpensive, and readily available over-the-counter. Monitoring the success of vitamin D replacement is key and needs to be tailored to the patient in light of the vitamin D preparation to ensure sufficiency and avoid toxicity. The treatment plans outlined within this manuscript should provide practitioners with safe and effective means to restore vitamin D levels to the normal range. ■

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