Should Vitamin D Screening be a Part of Primary Care?

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Introduction

Vitamin D is a steroid hormone that regulates transcription of over 900 genes and is involved in nearly every organ system in the human body.[1] Vitamin D insufficiency and deficiency are increasing in prevalence worldwide, yet are commonly unrecognized clinically, even though serum vitamin D levels can be measured, and vitamin D repletion is inexpensive and well tolerated.

Classic manifestations of vitamin D deficiency include symmetric low back pain, proximal muscle weakness, myalgias, and bone pain.[1] Most cases of deficiency or insufficiency in the modern era, however, are not accompanied by such dramatic symptoms. Nonetheless, vitamin D screening has become a routine part of the primary medical care of patients in many medical practices. In spite of the broad practice of screening for vitamin D deficiency or insufficiency, we are left with conflicting data on what constitutes a normal vitamin D level, and even more controversy surrounding whether vitamin D should be screened routinely.

What is a normal vitamin D level?

Vitamin D status is assessed by measuring the prohormone 25-hydroxyvitamin D, which is an indicator of supply rather than function, as it must be hydroxylated in the kidney to form the active metabolite 1,25-dihydroxy-vitamin D. 25-hydroxyvitamin D is the most stable and plentiful metabolite of vitamin D in human serum, though, with a half-life of about three weeks, making it a very attractive metabolite for screening purposes.

Precisely defining vitamin D deficiency or insufficiency on the basis of 25-hydroxy-vitamin D values is a matter of much debate, as a normal range cannot be defined based on population norms, as might be the case with other hormone levels. A *functional* definition of optimal vitamin D status is the 25-hydroxyvitamin D level that maximally suppresses parathyroid hormone (PTH) secretion, as the major stimulus for PTH secretion is a low level of serum ionized calcium.[2] An alternative, albeit less elegant, definition might be the level at which there appears to be protection against adverse skeletal outcomes such as fracture and falls,[3] indices of bone remodeling, decreased bone mineral density in cross-sectional studies, or fractures in observational studies.[4,5]

In the cross-sectional National Health and Nutrition Examination Survey (NHANES III) survey, serum 25-hydroxyvitamin D concentration was associated with bone mineral density in community-dwelling women and men aged at least 20 years and up.[6] A cause-and-effect relationship, however, was difficult to prove, given that low vitamin D intake and low bone density might simply reflect that healthier persons who exercise more (thus have greater bone density) may spend more time outside in the sun (thus have higher 25-hydroxyvitamin D levels).[7,8]

The Women's Health Initiative calcium and vitamin D supplementation trial revealed that hipbone mineral density was 1.06 percent higher in women receiving calcium and vitamin D than in women

receiving placebo after nine years, but the lumbar spine total bone mineral density in supplemented subjects did not differ significantly from those receiving placebo during this interval.[8,9] In the nested case-control study, the 25-hydroxyvitamin D baseline level was 46.0 +/- 22.6 nmol/L among participants who had hip fracture and 48.4 +/- 23.5 nmol/L among controls (p = 0.17). No statistically significant interactions were found between calcium with vitamin D supplementation and baseline 25-hydroxyvitamin D level with respect to either hip or total fractures.[8]

A cross-sectional, observational study conducted at 61 sites across North America showed that 52 percent of postmenopausal women receiving therapy for osteoporosis had 25-hydroxyvitamin D levels of less than 30 ng/ml.[4] As it stands, most experts define vitamin D deficiency as a serum 25-hydroxyvitamin D level of less than 20 ng/mL (50 nmol/L) and insufficiency as a serum 25-hydroxyvitamin D level of 20 to 30 ng/mL (50 to 75 nmol/L).[5,10]

Two rationales exist for setting the low end of the normal range for 25-hydroxyvitamin D at 30 ng/ml.[11] First, the serum level of parathyroid hormone (PTH) rises when the vitamin D level falls below 30 ng/ml. Second, active calcium absorption is optimal when the vitamin D level is 30 ng/ml.[12,13] However, an Institute of Medicine[14] report questions both of these tenets.[15]

More recently, vitamin D insufficiency has been used to describe low levels of serum 25-hydroxyvitamin D that may be associated with other (non-skeletal) disease outcomes.[9] Interpreting the import of a serum level of 25-hydroxyvitamin D in the insufficient range (i.e., 10-30 ng/ml) is challenging for at least three reasons. First, most reference laboratories have raised the lower boundary of normal range to 30 ng/ml.

Second, the precision and accuracy of various vitamin D assays, especially in non-reference laboratories, remains problematic. High performance liquid chromatography is considered the gold standard method, but liquid chromatography-tandem mass spectrometry is currently among the most accurate measures of the separate contributions of both 25-hydroxyvitamin D2 and D3 to total 25-hydroxyvitamin D concentrations.[4] Different 25-hydroxy-vitamin D assays, though, yield markedly differing results; so different that whether an individual is found to have low or normal vitamin D status sometimes may be a function of the laboratory used. The chemiluminescent assay tends to give higher values of 25-hydroxyvitamin D. In a study in which a single serum sample showing adequate vitamin D status was sent to multiple laboratories, the level was correctly identified as adequate in one laboratory, but was considered insufficient in others, with differences of up to 17 ng/ml.[16] This discrepancy between labs and between assays has led to calls for measurement of 25-hydroxyvitamin D to be standardized.

Third, seasonal variation exists in both exposure to sunlight and in dietary intake of vitamin D, with levels typically highest during summer and lowest during winter.[5,17] A study of Asian adults in the United Kingdom showed that 82 percent had 25-hydroxyvitamin D levels less than 12 ng/ml during the summer season, with the proportion increasing to 94 percent during the winter months.[18] Vitamin D stored in body fat is released during winter, when vitamin D cannot be produced.

Previously, according to the World Health Organization (WHO), a 25-hydroxyvitamin D level below 10 ng/ml was classified as deficient and a level below 20 ng/ml was classified as insufficient.[13] However, with relatively recent changes in laboratory reference ranges, a normal level

now is defined by WHO as 30-76 ng/ml (75-190 nmol/L).[4,13,19]

The 2011 Dietary Reference Intake (DRI) for vitamin D based on bone health outcomes suggested that levels of 16 ng/ml meet the needs of approximately half the population and levels of at least 20 ng/ml meet the needs of 97.5% of the population (similar to the Required Dietary Allowance; RDA).[14] In 2010, the International Osteoporosis Foundation issued a statement on vitamin D status, based on observational data, recommending a target serum vitamin D level of 30 ng/ml in all elderly persons and vitamin D intakes as much as 2000 IU/day.[13]

Should we screen patients for vitamin D deficiency?

Given the conflicting but generally positive data outlined above, two arguments can be made in regards to vitamin D screening and/or treatment.

Patients routinely should be screened for vitamin D deficiency.

Patients should be screened for vitamin D deficiency for two reasons. First, screening detects potential vitamin D-associated disease states. Second, screening better determines the amount and duration of vitamin D supplementation needed to treat the disease state in question.

The serum 25-hydroxyvitamin D level is the best indicator for judging vitamin D status in patients with potential vitamin D-related disease states.[20] For example, severe deficiency (< 10 ng/mL) could be associated with osteomalacia or rickets, and moderate deficiency (10-25 ng/mL) may be associated with an increased risk of osteoporosis or secondary hyperpara-thyroidism.

Establishing the patient's untreated vitamin D level will give insight into the type of bone disease present, if any, and reduce the likelihood of causing harm through over-supplementation. Vitamin D toxicity causes hypercalcemia typically at serum levels over 120 ng/ml, and most often when it is consistently greater than 150-200ng/ml, although toxicity has been reported in patients with normal renal function and without primary hyper-parathyroidism at levels as low as 80 ng/mL.[9,13,21,22] The effects of toxicity (hypercalciuria, nephrocalcinosis, and calcium containing kidney stones) may take up to 6-9 months to abate after stopping vitamin D supplementation.

It commonly is assumed that the serum 25-hydroxyvitamin D level will increase by 1 nmol/L for every 57-100 IU of daily vitamin D intake taken as a loading dose, but this does not necessarily account for body weight and vitamin D metabolism.[13,23] Knowing the 25-hydroxyvitamin D level at baseline allows for a calculation of the amount of vitamin D supplementation needed to achieve a target vitamin D level, accounting for body weight:

Δ 25-hydroxyvitamin D = 0.025 x (dose IU/kg body weight)

therefore,

Loading Dose = 100 x (Desired Actual ng/mL of 25-hydroxyvitamin D) x Weight (kg)

This formula is not valid for cases of malabsorption, and its accuracy is unknown for patients over 125 kg. It also does not calculate the required maintenance dose.[23]

In addition to supplying information needed to calculate the required dose of vitamin D, knowledge of a baseline vitamin D level theoretically can help with timing of therapies. For example, administration of anti-resorptive therapy (e.g., bisphos-phonates, estrogen, raloxifene, or denosumab) to a vitamin D deficient patient

with osteomalacia may cause severe hypocalcemia.[24] Such a patient would need to normalize her vitamin D level before starting antiresorptive therapy.

Patients with suspected vitamin D deficiency should be treated empirically.

The serum 25-hydroxyitamin D level is an expensive test, and the cost is compounded when one considers that many patients deemed insufficient will undergo testing two or more times. No evidence-based consensus guidelines exist regarding screening for vitamin D deficiency/ insufficiency or for using serum markers for medical management of individual patients.[15] A more reasonable interpretation of current literature suggests that physicians should judge, based on an individual patient's risk of insufficiency or deficiency of vitamin D, whether measuring the 25-hydroxyvitamin D level will assist in diagnosing disease and/or significantly change medical management.

The National Health and Nutrition Examination Survey III data revealed that more than 90 percent of the pigmented population of the United States (Blacks, Hispanics, and Asians) now suffer from vitamin D insufficiency (defined as a 25-hydroxyvitamin D level less than 30 ng/ml), with nearly three-fourths of the white population in the United States also being vitamin D insufficient.[19,25] In general, males, children, leaner persons, and non-Hispanic whites have higher 25-hydroxyvitamin D concentrations than do females, adults, obese persons, non-Hispanic blacks, and Mexican-Americans.[26]

Conditions that cause very low levels (i.e., < 10 ng/ml) of 25-hydroxyvitamin D include use of anticonvulsant medications (e.g., phenobarbital, phenytoin) and long-term use of glucocorticoids, rifampin, cholestyramine,[5,27,28] poor dietary intake plus negligible sun exposure, or mal-absorption due to inflammatory bowel disease, gluten sensitive enteropathy, gastric surgery, biliary disease, or intestinal overgrowth.[10,13] These observations indicate that a person's risk for vitamin D deficiency could be established in many cases without an expensive laboratory study, and that the resulting financial resources could alternatively be put toward vitamin D replacement.

The very values defining vitamin D insufficiency are a moving target. 25-hydroxyvitamin D levels tend to be seasonal in the Midwest. Should a value of 30 ng/ml be sought all twelve months of the year, or should a winter level of 20 ng/ml be considered the "seasonal equivalent" of a summer value of 30 ng/ml? The long-term data do not exist to make such a distinction.

When laboratories across the US began using 30 ng/ml as their cut-off between sufficient and insufficient vitamin D blood levels, many physicians began instituting vitamin D supplementation in their patients. Since the Institute of Medicine's (IOM) decision to recognize a level of 20 ng/ml as meeting the requirements of 97.5% of the population, many of those same patients would now be considered replete without supplementation.[14]

Empiric supplementation of vitamin D appears safe, and the IOM raised its daily recommendations, stating most Americans and Canadians up to age 70 need no more than 600 IU/d and that older patients may need as much as 800 IU/d, along with diet and sunlight, to maintain health.[14] To illustrate the apparently wide therapeutic window of vitamin D though, the same report increased the upper limit of safe supplementation to 4,000 IU (100 mcg/day) for adults. Typical sun exposure of a person in a bathing suit of one minimal erythematic dose (which causes a slight pinkness to the skin) is equivalent to ingesting 20,000 IU of vitamin D.[29]

Summary

Low vitamin D status is increasing in prevalence worldwide. The role of screening for vitamin D deficiency in routine medical care though is still uncertain. Unresolved issues of vitamin D testing include definition of a normal serum level; prediction of a new serum vitamin D level as a function of dosage of vitamin D, given complex patient factors including age, endogenous production, season and geographic locale, ethnic background, diet, and underlying health conditions; and the fact that epidemiological studies appear to show different effective vitamin D levels for different disease states.

Large-scale randomized clinical trials and consensus cut-points for vitamin D level are needed to avoid both under- and over-treatment. Studies should be conducted with the goals of: 1) demonstrating a response to vitamin D supplementation as a function of vitamin D concentration with consideration of other patient variables, and 2) coming to agreement upon a 25-hydroxyvitamin D serum concentration goal to be aimed for through vitamin D supplementation for specific disease states.

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