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Opinion

The D-lemma: To Screen or Not to Screen for 25-Hydroxyvitamin D Concentrations

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Until recently, there has been little interest in the medical and pediatric communities regarding the vitamin D status of their patients. It had been assumed that everyone was vitamin D sufficient and that only those patients with fat-malabsorption syndromes were at risk *(1)*. African Americans were at risk because of their sunscreening skin pigment, but little attention was placed on their vitamin D status because African Americans were at less risk of fracture than Caucasians. The introduction of drugs to treat osteoporosis made physicians aware that vitamin D deficiency was a contributing factor for osteoporosis.

Vitamin D made in the skin or ingested from the diet is converted in the liver to 25-hydroxyvitamin D [25(OH)D][2] *(1, 2)*, the major circulating form of vitamin D used for evaluating the vitamin D status of patients. 25(OH)D is hydroxylated in the kidneys to form the biologically active metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] *(1, 2)*. Because most children and adults were assumed to be vitamin D sufficient when reference intervals for 25(OH)D were determined, values ranged from 10 μg/L (ng/mL) to 55 μg/L. Studies of adults that evaluated parathyroid hormone (PTH) with 25(OH)D revealed, however, that PTH concentrations began to plateau at 30–40 μg/L *(3)*. Healthy adults receiving vitamin D and calcium supplementation who had blood 25(OH)D concentrations between 11 μg/L and 19 μg/L demonstrated substantial decreases in their PTH concentrations, whereas adults with a 25(OH)D concentration between 20 μg/L and 25 μg/L had no significant change in PTH, suggesting that vitamin D deficiency should be defined as a 25(OH)D concentration <20 μg/L *(4)*. Postmenopausal women whose 25(OH)D concentration increased from approximately 20 μg/L to approximately 32 μg/L had a 65% increase in intestinal calcium absorption *(5)*. Thus, vitamin D deficiency was defined as a 25(OH)D concentration of <20 μg/L, but for maximizing the vitamin D effect on calcium metabolism, the recommendation was that a 25(OH)D concentration >30 μg/L was needed. The gap was bridged by defining vitamin D insufficiency as a 25(OH)D concentration of 21–29 μg/L *(1, 5)*.

In the 1980s came the first suggestion that a person's vitamin D status may be related to risk of developing and dying from colorectal cancer *(6)*. This seminal observation was quickly followed over the next 2 decades by a plethora of epidemiologic studies relating vitamin D deficiency with an increased risk for many deadly cancers *(1, 7, 8)*. These association studies were supported by a randomized controlled trial with postmenopausal women who received 1100 IU of vitamin D_3 plus 1500 mg of calcium per day for 4 years had a >60% reduction in the development of all cancers *(9)*. A multitude of retrospective studies that evaluated the long-term impact of ingesting vitamin D either during the first year of life or through adult life began to reveal intriguing associations between a higher intake of vitamin D or higher serum 25(OH)D concentrations and decreased risks for autoimmune diseases (including type I diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn disease), hypertension, heart disease, and stroke, as well as upper respiratory tract infections, wheezing disorders, asthma, and falling *(1, 10)*. The lay press's enthusiastic reporting of the potential health benefits of vitamin D has been the catalyst for patients requesting their physician to order a 25(OH)D test. The physician, reluctant to order a relatively expensive blood test, often finally relents and is shocked to find that the patient was right and was vitamin D deficient. This experience leads the physician to order 25(OH)D for all patients and then to discover that essentially all of the patients were vitamin D deficient or insufficient. Such experiences have led to the 25(OH)D assay being one of the most-ordered, if not the most-ordered, esoteric assay in the US. These anecdotal observations by physicians and pediatricians confirm what is well documented in the literature, which is that children and adults in the US are at high risk for vitamin D defi-

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[2] Nonstandard abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; PTH, parathyroid hormone; NHANES III, Third National Health and Nutrition Examination Survey.

ciency and insufficiency. Data from the Third National Health and Nutrition Examination Survey (NHANES III) not only has revealed that the prevalence of vitamin D deficiency and insufficiency is >50% among children and young, middle-aged, and older adults but also has made startling associations with increased risks for hypertension, type II diabetes, colorectal and breast cancers, myocardial infarction, strokes, peripheral vascular disease, and wheezing disorders *(1, 10–13)*. Retrospective and prospective studies have even linked vitamin D deficiency with an increased risk for preeclampsia and cesarean section *(1)*.

With the knowledge that most children and adults are vitamin D deficient or insufficient, and that this deficiency places them at high risk for chronic diseases, should everyone be tested for their blood 25(OH)D concentration, as we do for blood lipids, given that vitamin D status may play a more important role in health than almost any other biochemical marker? The skeptics have argued that most of the studies that have related vitamin D status with the risk of chronic disease have been epidemiologic association studies and that randomized controlled clinical trials are needed to prove the health benefits of vitamin D.

The vitamin D deficiency/insufficiency epidemic is caused by the fact that few foods naturally contain or are fortified with vitamin D *(1, 12)*. For adults, 100 IU of vitamin D increases the blood 25(OH)D concentration by approximately 1 μg/L *(14, 15)*. In the winter, the mean 25(OH)D concentration is approximately 18–22 μg/L in Caucasian adults and approximately 15–18 μg/L in African American adults *(1, 14, 15)*. Thus, to raise blood concentrations into a sufficient range requires between 1500 and 2000 IU of vitamin D supplementation per day. Studies of children have suggested that 400 IU of vitamin D per day is inadequate to raise blood concentrations into the sufficient range. Young girls 10–17 years of age who received the equivalent of 2000 IU vitamin D per day for 1 year raised their blood concentrations into the sufficient range *(16)*.

With the recognition of widespread vitamin D deficiency/insufficiency in children and adults, there is no need to measure everybody's blood 25(OH)D. It would be much more cost-effective to implement a vitamin D supplementation program for all children and adults until there is higher fortification of vitamin D in more foods. What also needs to be appreciated is that sensible sun exposure in the spring, summer, and fall is also a good source for vitamin D *(1)*. The highest risk for vitamin D deficiency/insufficiency occurs in the winter, when little if any vitamin D can be produced in the skin if an individual lives at a latitude above Atlanta, Georgia (approximately 33° north latitude) *(1)*. People of color, especially African Americans, are at very high risk, owing to their avoidance of sun exposure and their decreased production of vitamin D due to their skin pigmentation *(1, 15)*. Obesity, which is also epidemic in children and adults, increases the risk of deficiency/insufficiency, partly because of the sequestration of the fat-soluble vitamin in body fat *(1, 11, 12)*. All of these high-risk groups, along with all children and adults, can maintain adequate serum 25(OH)D concentrations through vitamin D supplementation, ingestion of foods fortified with vitamin D, and sensible sun exposure *(1)*.

There are, however, patients who should be screened for vitamin D deficiency/insufficiency and monitored for their 25(OH)D concentration while being treated with vitamin D. Patients with inflammatory bowel disease, cystic fibrosis, and liver and kidney diseases; gastric-bypass patients; patients taking antiseizure medications, glucocorticoids, or AIDS medications are at high risk for vitamin D deficiency/insufficiency that will negatively affect their musculoskeletal health *(1, 10)*. Patients with primary hyperparathyroidism are often vitamin D deficient and benefit from vitamin D repletion *(1)*. Patients with chronic granulomatous disorders not only are at high risk for vitamin D deficiency because of the extrarenal production of $1,25(OH)_2D$ but also need to have their 25(OH)D concentration monitored so they do not experience the skeletal manifestations of vitamin D deficiency, which include osteomalacia, osteopenia, and osteoporosis. The blood concentrations of such patients also need to be monitored more frequently, because if the 25(OH)D concentration exceeds 30 μg/L, such patients are at increased risk for hypercalciuria and hypercalcemia *(1, 17)*.

It has been suggested that everyone should raise their blood 25(OH)D concentration to >40 μg/L or even 60 μg/L to obtain the maximum health benefits of vitamin D. These recommendations are based on the epidemiologic association data suggesting that children and adults who have the highest blood 25(OH)D concentrations are at the lowest risk for developing hypertension, increased blood sugar, and metabolic syndrome, among other chronic diseases *(1, 10, 11)*. A few intervention studies have suggested that increasing vitamin D intake will have a more positive health outcome, including reducing the risk for cancer *(9)*; however, until randomized controlled trials provide unequivocal evidence that higher blood 25(OH)D concentrations of 40 μg/L or greater are needed for maximum health, it would be premature at this time to monitor everyone's serum 25(OH)D concentration so that it is >40 μg/L.

Physicians often order both the 25(OH)D and $1,25(OH)_2D$ tests when evaluating the vitamin D status of their patients or mistakenly order only the

$1,25(OH)_2D$ assay. Although the $1,25(OH)_2D$ assay is of value for the differential diagnosis of hypercalcemic syndromes associated with chronic granulomatous disorders and inborn and acquired disorders of 25(OH)D metabolism, this assay is of no value in determining a patient's vitamin D status and should not be ordered for this purpose *(1)*. $1,25(OH)_2D$ concentrations are usually within reference intervals or increased in vitamin D–deficient/insufficient patients *(1)*.

Although the medical community has been greatly concerned about vitamin D intoxication, it is one of the rarest reported medical conditions and is usually not observed until >10 000 IU of vitamin D are ingested per day for >5 months *(1, 14)*. Blood 25(OH)D concentrations are usually >200 μg/L before manifestations of vitamin D intoxication, including hypercalcemia, hyperphosphatemia, and soft tissue calcification, are observed *(1)*. There is no downside to increasing everyone's vitamin D intake by increasing the consumption of foods that naturally contain or are fortified with vitamin D. Dietary sources are not adequate, however, to sustain vitamin D sufficiency in children and adults, and thus taking a vitamin D supplement and taking advantage of the beneficial effect of sun exposure will help guarantee vitamin D sufficiency for maximizing bone health and possibly for other health benefits. I recommend 400–1000 IU/day for infants, 1000–1500 IU/day for children 1–10 years of age, and 1500–2000 IU/day for teenagers and adults.

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