Vitamin D Deficiency, Its Role in Health and Disease, and Current Supplementation Recommendations

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Vitamin D deficiency has been identified as a common metabolic/endocrine abnormality. Despite known dietary sources of vitamin D and the role of sunlight in its production, much of the US population may have inadequate levels of serum 25-hydroxyvitamin D. Deficiency of vitamin D can be caused by a variety of health conditions, but studies on the effects of vitamin D supplements have had mixed results. This evidence-based clinical review discusses what is currently known about vitamin D and what areas need further research to clarify its role in health and disease.

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Owing to food fortification, diseases caused by severe vitamin D deficiency, such as rickets and osteomalacia, were virtually eradicated in the United States by the early 1900s. However, inadequate sun exposure and chronic disease continue to cause vitamin D deficiency in all age groups.[1] Vitamin D deficiency (<20 ng/mL) and insufficiency (20-30 ng/mL) affect almost 1 billion people worldwide.[1] Considered a hormone rather than a vitamin, vitamin D has receptors on virtually every cell in the human body.[2] In addition to bone metabolism, vitamin D has many roles in the body, including cell growth modulation, neuromuscular and immune function, and inflammation reduction.[3] It remains debatable, however, whether healthy levels of vitamin D can reduce the risk of nonskeletal diseases. The role of vitamin D in multiple sclerosis, autoimmune disorders, infections, respiratory disease, cardiometabolic disease, cancer, and fracture risk is still being studied. In light of how prevalent it is, knowing whom to test and when to treat patients for vitamin D deficiency is essential for primary care physicians.

As with many diseases, assessment and management of vitamin D deficiency should be consistent with osteopathic principles, including the relationship of nutrition and lifestyle changes with musculoskeletal health and the body's ability to regulate health when proper self-care is achieved.

Physiology

Vitamin D is produced when the skin is exposed to sunlight.[4] UV-B photons act on pro–vitamin D_3, a precursor in the cholesterol biosynthetic pathway, in the plasma membrane of epidermal cells to form pre–vitamin D_3.[1] Pre–vitamin D_3 is rapidly transformed into vitamin D_3 and transferred to the extracellular space where it binds to vitamin D–binding

protein.[1] From there it is transported to the liver, where it is hydroxylated into 25(OH)D.[5] Serum concentration of vitamin 25(OH)D is the best indicator of its status.[3]

Dietary sources of vitamin D include fatty fish (salmon, tuna, sardines, swordfish), cod liver oil, egg yolks, portabella mushrooms, beef liver, and fortified foods such as breakfast cereal, milk (dairy and nondairy), infant formula, cheese, and orange juice.[3,6] Fortified foods in the United States use synthetic vitamin D_2 (ergocalciferol) derived from irradiation of ergosterol found in plants, mold ergot, or plankton. Dietary vitamin D is absorbed in the small intestine, incorporated into chylomicrons, and then transported to the liver bound to vitamin D–binding protein.[5,7] From the liver, 25(OH)D travels to the kidney bound to vitamin D–binding protein.[5,7] The kidney further hydroxylates 25(OH)D to 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), the most active form.[4] Once in the active form, 1,25$(OH)_2$D (calcitriol) travels to the rest of the body and any cells with vitamin D receptors.[5] Vitamin 1,25$(OH)_2$D has a shorter half-life and is not as good of an indicator of vitamin D status in the absence of advanced renal disease.[3]

Risk Factors for Deficiency

Insufficient sunlight exposure, inadequate dietary sources, and malabsorption are common causes of deficient intake.

The amount of UV-B exposure for any individual varies based of the time of day, season, latitude, altitude, clothing, sunscreen use, skin pigmentation, and age.[8,9] Anyone residing in latitudes greater than 37° does not receive enough UV-B radiation to produce any vitamin D during winter months.[7] Age further complicates adequate sunlight exposure. An adult older than 70 years needs almost 3 times the duration of sun exposure to produce the same amount of vitamin D as a child.[1] A diet low in foods rich in vitamin D may also lead to deficiency. Infants are at risk of vitamin D deficiency if they are exclusively breastfed.[6]

KEY POINTS

- Routine screening should be done only for patients at risk for vitamin D deficiency.
- Patients with vitamin D deficiency should take vitamin D supplements to maintain bone health.
- Vitamin D_3 may be preferred over vitamin D_2.
- Replacement dose for adults should be 50,000 IU weekly or 6000 IU daily.
- There may be additional benefits of vitamin D supplementation, but further evidence is needed to support recommendations.

Malabsorption of vitamin D can result from disorders that affect the gastrointestinal tract, including Crohn disease, celiac disease, chronic active hepatitis, chronic kidney disease (CKD) with or without requiring dialysis, chronic pancreatitis, cystic fibrosis, diabetes mellitus, gastric bypass, and primary biliary cirrhosis.[1,10-15]

Advanced liver disease, CKD, and alcohol abuse are the most common causes of defective activation.[1] Increased catabolism of vitamin D can be caused by certain medications, such as anticonvulsants, glucocorticoids, antifungals such as ketoconazole, and highly active antiretroviral therapy.[1]

Vitamin D is fat soluble, and evidence exists that it becomes sequestered in adipose tissue.[16] Researchers measured serum 25(OH)D in 3890 third-generation participants of the Framingham Heart Study without cardiovascular disease and diabetes. They found decreased 25(OH)D levels with greater body mass index that could not be accounted for in variations in physical activity or diet. They also found an inverse relationship between 25(OH)D and subcutaneous and visceral adiposity even in lean individuals.[16] This area needs further research to clarify the relationship and mechanism.

Potential Risks of Vitamin D Deficiency

Some observational studies suggest an association between low levels of 25(OH)D and increased risk of

metabolic, neoplastic, and immune disorders, such as diabetes mellitus and multiple sclerosis. To date, however, no adequate randomized controlled trials have assessed whether vitamin D supplements reduce the risk of chronic diseases other than osteoporosis.[1]

Diagnosis

The 2013 US Preventive Services Task Force guidelines[17] and the 2011 Endocrine Society guidelines[18] recommend screening only those at risk for vitamin D deficiency. Serum 25(OH)D, the major circulating form of vitamin D, has a half-life of 2 to 3 weeks compared with $1,25(OH)_2D$, which has a circulating half-life of 4 hours.[18] In CKD and inherited disorders of 25(OH)D and phosphate metabolism, both 25(OH)D and $1,25(OH)_2D$ should be measured.[18] Multiple assays are available to measure 25(OH)D but with great variability in results. Therefore, treatment should target a goal above normal levels to ensure adequate levels of 25(OH)D.[18]

Vitamin D deficiency is generally recognized as a 25(OH)D level below 20 ng/mL.[1] Below this level, patients may be at an increased risk for muscle weakness, bone pain, and fragility fractures.[19] Vitamin D insufficiency has been defined as a serum 25(OH)D level of 21 to 29 ng/mL without overt clinical symptoms,[18,20] although definitions have been greatly debated. Intestinal absorption of dietary calcium and phosphorus is decreased with vitamin D deficiency, which causes an increase in parathyroid hormone levels.[18] Parathyroid hormone begins to plateau in adults with 25(OH)D levels between 30 and 40 ng/mL. This range is consistent with the threshold for hip and nonvertebral fracture prevention.[18]

Treatment

The Institute of Medicine recommends 600 IU of vitamin D per day to meet the needs of most people aged 1 to 70 years. Those older than 70 years may need 800 IU per day,[21] assuming minimal sun exposure. The Endocrine Society recommends 1500 to 2000 IU per day for adults and 1000 IU for children.[18] Vitamin D should be given with calcium to maintain bone health in those who are deficient.

Currently, there is no consensus as to which form of supplemental vitamin D is superior. However, one randomized, double blind, placebo-controlled study looked at supplementation with vitamin D_2 and vitamin D_3 in 85 healthy persons for 25 weeks starting at the end of summer. Researchers found that vitamin D_3 was more effective than vitamin D_2 in maintaining serum 25(OH)D levels during the fall and winter months.[22] They also found a relative decrease in serum $25(OH)D_3$ levels in the group that was given vitamin D_2 supplements.[22] A single 50,000-IU dose of D_2 or D_3 produced similar increases in total 25(OH)D, but D_3 had a longer half-life.[8]

All adults found to be vitamin D deficient should be treated with either 50,000 IU of vitamin D_3 per week or 6000 IU per day for 8 weeks to achieve a serum 25(OH)D level of 30 ng/mL.[17] Treatment should be followed by a maintenance dose.[17] The Endocrine Society's guidelines[18] support this recommendation but add that a maintenance dose of 1000 IU per day may be needed to consistently raise serum 25(OH)D levels above 30 ng/mL in patients aged 1 to 18 years and as much as 1500 to 2000 IU per day in patients aged 19 to 50 years. It is unknown at this time whether these treatment recommendations are enough to provide all of the potential nonskeletal health benefits associated with vitamin D, specifically those that maximize muscle function.[18] In patients with malabsorption syndromes, with obesity, or taking medications that affect vitamin D metabolism, maintenance doses may need to be between 3000 and 6000 IU daily.[18]

The American Academy of Pediatrics recommends that all children receive 400 IU per day of vitamin D from their first few days of life through adolescence.[23] Vitamin D deficiency in children has been reported to be between 10% and 65% and, therefore, rickets continues to be reported in the United States.[23] Breastfed infants are at a higher risk of vitamin D deficiency because breast milk contains little to no vitamin D.[6]

Only 5% to 13% of breastfed children met a previous recommendation of 200 IU per day.[22] Children found to be deficient in vitamin D should be treated with either 50,000 IU per week or 2000 IU per day for 6 weeks to achieve serum 25(OH)D levels of 30 ng/mL.[17]

In a 2014 report, the American Geriatrics Society recommended vitamin D supplementation of 1000 IU per day or more plus calcium for all adults aged 65 years or older to reduce the risk of fracture and falls.[24] Further investigation contradicted the meta-analysis results showing reduction of falls with vitamin D supplements.[25] The Endocrine Society does not currently recommend supplements solely for fall prevention, prevention of cardiovascular disease or death, or improvement in quality of life.[17] For patients taking vitamin D supplements for deficiency, routine laboratory testing to monitor 25(OH)D levels is not recommended as long as the prescribed dose is within the recommended limits.[24] Further investigation contradicted the meta-analysis results and found that vitamin D supplements did not reduce falls.

Ongoing Research and Future Directions

Although research on vitamin D continues to accumulate, concrete recommendations beyond improving bone health have yet to be elucidated. In a 2014 umbrella review of observational and randomized controlled trials, the relationships between vitamin D and 137 outcomes were explored.[25] Researchers found only probable associations between vitamin D concentrations and birth weight, dental cavities in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with CKD requiring dialysis.[25] Evidence did not support the idea that vitamin D supplements alone increased bone mineral density or reduced the risk of fractures or falls among older people.[25]

Although vitamin D is thought to influence many disease processes, the evidence is currently insufficient to support supplementation to enhance extraskeletal benefits. The umbrella review[25] of vitamin D research revealed some evidence for decreased risk of colorectal cancer, nonvertebral fractures, cardiovascular disease prevalence, hypertension, ischemic stroke, high body mass index, metabolic syndrome, type 2 diabetes, small for gestational age–birth, and gestational diabetes mellitus; decreased balance sway, alkaline phosphatase concentrations in patients with CKD requiring dialysis, and parathyroid hormone concentrations in patients with CKD not requiring dialysis; and increased head circumference at birth, low density lipoprotein cholesterol levels, bone mineral density in the femoral neck, and muscle strength. However, the conclusion was that more evidence is needed.

Another 2014 review of vitamin D and all-cause mortality found an inverse association with circulating 25(OH)D.[26] This association was specifically evident for coronary artery disease, lymphoma, cancer of the upper digestive tract, and disorders of the respiratory tract.[26] These findings were supported by a 2015 study in which low 25(OH)D levels were associated with an increased risk of microvascular and macrovascular complications in persons with type 2 diabetes mellitus.[27] This finding remained statistically significant after multivariable adjustment.[27] Intervention with all forms of vitamin D, when given alone, did not reduce overall mortality significantly among older adults. However, when supplementation with vitamin D_3 alone was reviewed, all-cause mortality was reduced by 11%.[26]

Strong evidence for the range of health benefits and risks may come out of the Vitamin D and Omega 3 Trial.[28,29] This study is evaluating 26,000 adults aged 50 years and older who are receiving vitamin D supplements, omega-3 fatty acids, both, or placebo to determine the prospective risk of cancer and cardiovascular disease. These results are not expected until after 2020.

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