CE 1.5 Pharmacology and 2.0 ANCC Contact Hours

Prescribing Sunshine

Evidence for Vitamin D Supplements

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Suddenly, there seems to be great interest in vitamin D supplements. What is the evidence for vitamin D supplementation of the diet? I would also like Web resources to help me provide evidence-based recommendations for vitamin use.

Vitamin D promotes the absorption of calcium and phosphorus from the gastrointestinal tract. Extreme or prolonged vitamin D deficiency results in softening of bone, especially in children. Until the mid-20th century, rickets was a common part of the human condition. The addition of vitamin D to milk and cereals and multivitamins has made rickets rare in developed countries. However, for many areas of the world, vitamin D deficiency is common.[1]

Vitamin D deficiency is more than bone disease. This fat-soluble metabolite regulates cell activity, growth, and development. After activation in the kidney and liver, vitamin D binds to cell surfaces, and a multitude of intracellular pathways are activated that influence bone calcium homeostasis, immunity, and inflammation. The increasing number of genes being identified as affected by vitamin D suggests that vitamin D may play vast and significant roles in health. Emerging evidence also suggests that vitamin D deficiency may be linked to type 2 diabetes, cancer, heart disease, and depression.[2]

There are 2 forms of vitamin D: D_2 or ergocalciferol and D_3 or cholecalciferol, both of which can be obtained in fortified foods and some types of fish such as herring, mackerel, sardines, and tuna. However, nearly 90% of vitamin D is obtained through exposure to sunlight because endogenous production of D_3 relies on exposure to UV light.[3] Low production of D_3 can be a function of high latitude, dark skin pigment, protective clothing, and use of sunblock.[2,3]

Vitamin D deficiency is a worldwide health problem. While everyone seems to know the health benefits of vitamin D, defining what vitamin D deficiency is has not been so clear. Furthermore, the lack of randomized controlled clinical trials that demonstrate health benefits beyond bone health has encouraged the cynicism concerning the benefits of vitamin D supplementation.[3]

QUANTIFYING VITAMIN D

In the kidney, 25-hydroxyvitamin D [25(OH)D] changes into an active form of the vitamin, which helps control calcium and phosphate levels in the body. The 25(OH)D test (also called calcidiol or 25-hydroxycholecalciferol test) is the most accurate way to measure vitamin D levels. The reference range of vitamin D is measured as nanograms per milliliter. Many experts recommend a level between 20 and 40 ng/mL. Others recommend a level between 30 and 50 ng/mL. Reference value ranges may vary slightly among different laboratories.[4]

Considering the evidence that vitamin D supplementation has low toxicity potential at recommended doses, the US Endocrine Society recommends a serum 25(OH)D level of 30 ng/mL to reduce risks associated with insufficient vitamin D. In addition, the society suggests that for children and adults 25(OH)D levels can be defined as follows: deficiency (≤20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (30 ng/mL). A 25(OH)D level of 40 to 60 ng/mL may be the ideal in light of assay variability.[3,5,6]

Further research may provide stronger evidence of the potential significant benefits of vitamin D supplementation for patients with and at risk of chronic illness, cancer, autoimmune and infectious disease, allergy, type 2 diabetes, neurocognitive disease, and frailty.[3]

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VITAMIN D DEFICIENCY

Vitamin D deficiency is a commonly missed condition. Major risks are described in the Table.[4] Sunscreen with SPF 30 can reduce the ability of the skin to produce vitamin D by as much as 95% to 99%. Always indoors, extensive clothing coverage of skin, air pollution, hepatic and renal failure, winter season, lactose intolerance, food insecurity, and no vitamin use are additional risk factors. In addition, there may be specific genetic determinants of 25(OH)D levels.

Screening is appropriate for those at risk. However, at this time, there is no evidence to support screening at the population level. The most effective health strategy is to prevent vitamin D deficiency and insufficiency. Sensible sun exposure of the arms, legs, and abdomen is effective in production of necessary vitamin D. Facial exposure only to sunlight supplies very little vitamin D.[3] Considering the fact of very few negative studies as well as low toxicity potential of vitamin D supplementation at recommended doses, the US Endocrine Society recommends a serum 25(OH)D level of 30 ng/mL to reduce risks associated with insufficient vitamin D.[3]

Prescribing vitamin D is beyond the scope of this review. However, prescribing guidelines are available in text and on the Web.[6,7] Excess vitamin D is defined as hypervitaminosis.[4] Signs and symptoms of vitamin D intoxication include hypercalcemia, hypercalciuria, and hyperphosphatemia with serum 25(OH)D levels greater than 150 ng/mL.[3]

RISKS OF VITAMIN D THERAPY

Excess vitamin D can manifest as weakness, fatigue, headache, loss of appetite, nausea, vomiting, and dry mouth. Doses greater than 4000 U daily is *possibly unsafe* because of risk of creating high serum blood calcium levels. However, doses higher than this may be needed for short-term treatment for significant vitamin D deficiency. High-dose therapy should always be done under a prescriber's care. Evidence suggests high-dose vitamin D is *possibly unsafe* if used during pregnancy or while breast-feeding.[7]

Vitamin D may increase calcium levels and atherosclerosis in persons with serious kidney disease while trying to prevent renal osteodystrophy. Calcium levels should be monitored carefully in people with kidney disease. Vitamin D supplementation should be cautiously used in persons with sarcoidosis, histoplasmosis, lymphoma, or tuberculosis because therapy may promote formation of kidney stones. Patients with hyperparathyroidism should also be cautiously treated related to significant risk of hypercalcemia with therapy.[7]

Table. Risks of Vitamin D Deficiency[4]

• Lack of exposure to sunlight
• Lack of dietary vitamin D
• Liver and kidney diseases
• Poor food absorption
• Medication use: phenytoin, phenobarbital, and rifampin
• African American children (especially in the winter)
• Breast-fed–only infants
• Vegan

THE EVIDENCE FOR & AGAINST VITAMIN D SUPPLEMENTATION

In a meta-analysis of randomized controlled trials to October 2013 from MEDLINE and EMBASE/Excerpta Medica examining vitamin D supplementation compared with placebo or vitamin D in addition to another compound such as calcium and observational studies of vitamin D levels, clinical outcomes were evaluated. Excluded from analysis were dietary observational studies and UV light exposure studies with vitamin D levels as an outcome. Clinical outcomes included cardiovascular disease, mortality, and outcomes related to pregnancy and bone health. Findings revealed that vitamin D supplementation reduced risk of low birth weight. As for cardiovascular disease and mortality, vitamin D outcomes did not differ from placebo or no vitamin D. Results were mixed in support of vitamin D supplementation in the reduction of nonvertebral fractures in older persons.[1]

Effects of vitamin D therapy on quality of life were examined via meta-analysis of primary research articles for persons receiving treatment or supplementation from 1950 to May 2014. Articles on topical treatment or vitamin D replacement and vitamin D supplementation via a multivitamin were excluded. Only 15 articles met the inclusion criteria for review. Average vitamin D supplementation was 400 IU/d for a mean of 7.1 years, and sample sizes ranged from 28 to 33 067 persons. The majority of studies had a control group. Populations included healthy Asian females and elderly women. Patient groups included persons with chronic pain, Crohn disease, heart failure, sickle cell disease, bone trauma, kidney disease, chronic obstructive pulmonary disease, and osteoporosis. Analysis revealed that vitamin D was not associated with significant changes in quality of life except for specific clinical groups on short-term therapy.[2]

Vitamin D effects on fetal development and gene regulation may explain why reports regarding vitamin D therapy have such a wide range of reported benefits. Low vitamin D during pregnancy appears associated with increased childhood susceptibility to type 1 diabetes, as well as multiple sclerosis and schizophrenia in later life through specific target organ effects and/or epigenetic modification.[8]

Emerging evidence also suggests that there may be a relationship between vitamin D and estrogen metabolism. With the decline of estrogen during menopause, increased bone turnover and decreased bone mineral density increase

the risk of fracture. Increased body fat concomitant with decreases in lean body mass during menopause increases the risk of vitamin D deficiency. Dietary restrictions adopted to lose weight further reduce calcium and increase fracture risk. Risk may be offset by vitamin D supplementation to increase calcium reabsorption.[9]

Considering that menopause and vitamin D deficiency share risk factors beyond bone health for cardiovascular, metabolic, affective, and cognitive disease, as well as the rising risk of cancer with age, perhaps vitamin D status should be assessed in all perimenopausal and postmenopausal women to improve health. What is needed are large randomized controlled trials to assess the effects of vitamin D supplementation for perimenopausal and postmenopausal women.[9]

Finally, what about vitamin D effects on cardiovascular health? Vitamin D deficiency appears to result in endothelial dysfunction. Vitamin D stabilizes endothelium, modulates activation, and is a significant part of cell repair. More research is needed to confirm or refute the benefits of vitamin D on cardiovascular mortality and to determine the optimal serum 25(OH)D levels needed for endothelial function.[10]

THE FUTURE FOR VITAMIN D

The lack of evidence for the beneficial effects of long-term vitamin D supplementation on quality of life may be a function of poorly designed studies. Lack of control for sunlight exposure and dietary intake of vitamin D makes comparison of study outcomes difficult. What is needed are well-designed studies of both healthy population and population with no disease before conclusions can be drawn regarding the benefits of vitamin D therapy.[2]

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