

Vitamin D deficiency: Evolving concepts

Vitamin D has long been associated with rickets and bone health, but accumulating evidence shows that its role is much broader. Inadequate serum levels of this fat-soluble vitamin have been associated with a variety of conditions including: decreased bone mass and fractures; decreased muscle mass and increased propensity to falls; and increased risk of non-Hodgkin lymphomas, colon, ovarian, breast, prostate, and other cancers.¹⁻⁴

Unfortunately, vitamin D deficiency usually has no symptoms. Observational studies have shown the magnitude of this vitamin insufficiency in the general population and particularly among elderly individuals who are nursing home-bound, patients who have inadequate exposure to sunlight, or those living in the northern latitudes during the winter months.

Clinical trials have sought to establish the benefits—and optimal dosages—of vitamin D supplementation for calcium and bone metabolism, muscle and immunologic function, and chronic illness. These data are reviewed here to offer some perspective on the importance of vitamin D status in overall health.

Vitamin D status: Importance of measurement

On the basis of epidemiologic studies, certain populations appear to be at increased risk of vitamin D insufficiency.¹ Because vitamin D deficiency lacks obvious symptoms, it may be prudent to consider measuring serum 25(OH) vitamin D levels in at-risk individuals (TABLE 1). Although many of the available studies focus on elderly populations, recent epi-



demiologic reports have drawn attention to the prevalence of vitamin D insufficiency in reproductive-aged women and in infants and their mothers.^{5,6}

Most experts agree that measurement of 25(OH) vitamin D serum levels best reflects the vitamin D status of an individual. The most reliable techniques for measurement of 25(OH) vitamin D are radioimmunoassay, liquid chromatography, and tandem mass spectrometry.⁷ Commercial assays measure both 25(OH) vitamin D₂ and 25(OH) vitamin D₃.

With these types of assays, normal levels of 25(OH) vitamin D are in the range of 30 to 80 ng/mL (75 to 200 nmol/L). Concentrations below 12 to 20 ng/mL (30 to 50 nmol/L) are considered deficient. Levels above 150 ng/mL (374 nmol/L) are considered toxic (TABLE 2).

Common causes of low vitamin D levels

A number of factors lead to reduced vitamin D levels (TABLE 3). Exposure to the

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KEY POINT

Vitamin D doses between 700 and 800 IU/d (with calcium) increase hip bone density and reduce fracture risk; lower doses may have less effect.

TABLE 1

The At-Risk Elderly

Low 25(OH) vitamin D levels are particularly likely among

- Individuals older than 65 years
- Nursing home residents
- Individuals with nonvertebral or hip fractures
- Individuals with kidney disease
- Individuals with low bone mass or osteoporosis
- Individuals with a history of falls

TABLE 2

Vitamin D Status and 25(OH) Vitamin D Levels

| Deficiency | Preferred Range | Toxicity |
|------------|-----------------|-------------|
| <20 ng/mL | 30-80 ng/mL | >150 ng/mL |
| <50 nmol/L | 75-200 nmol/L | >374 nmol/L |

sun is an important factor affecting vitamin D levels (SIDEBAR). The use of sunscreens with a sun protection factor (SPF) of 8 or more blocks the beneficial effects of ultraviolet radiation on vitamin D production. Because sun-blocking agents are also common constituents in makeup and skin lotions, many women are not aware that these agents negate the positive impact of sun exposure. During the winter months, individuals who live in northern climates above 40° latitude can have insufficient sun exposure to produce sufficient amounts of vitamin D. In addition, elderly nursing home residents are at increased risk because they often do not participate in outdoor activities.

Major food sources of vitamin D include fortified breakfast cereals (100 IU/serving), fortified milk (98 IU/cup), and fortified margarine (60 IU/tbs). However, an analysis of milk samples from various commercial sources suggested that the actual vitamin D concentrations in milk can vary from less than 5% of the level on the label to more than 120%.⁸ Natural food sources such as cooked wild salmon provide 600 to 1000 IU of vitamin D per 3.5 oz, but farmed salmon has

considerably less.⁹ The dietary habits of most of the population—especially the elderly—are usually inadequate with respect to these food sources of vitamin D. Therefore, supplementation can be an important preventive strategy.

Low vitamin D, increased risk: Is the reverse true?

A number of clinical conditions have been associated with low levels of vitamin D, primarily on the basis of observational studies. These include osteoporosis, propensity among the elderly to fall, and various cancers.

Bone density and fractures

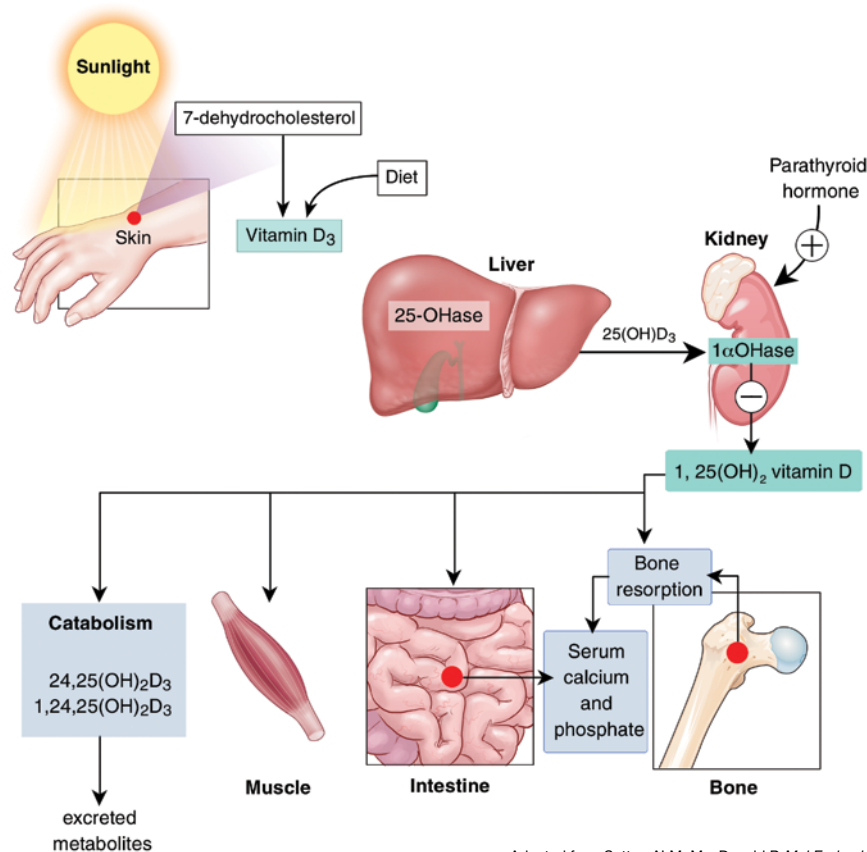
A large body of observational studies suggests that the risk of osteoporosis may be reduced with adequate intake of vitamin D and calcium. However, some of the clinical trials have had conflicting results, due perhaps to insufficient doses of vitamin D and calcium supplementation.

Lips et al randomized 2578 elderly participants to either vitamin D, 400 IU/d, or placebo with a calcium intake of 800 mg/d or more and found no impact on the rate of hip fractures (relative risk [RR], 1.21; 95% confidence interval [CI], 0.83-1.75).¹⁰ In a study of elderly French women (n = 3270; mean age, 84 years), Chapuy et al found that supplementation with 800 IU of vitamin D₃ and 1200 mg of calcium daily for 18 months reduced the overall risk of vertebral fractures by 32% and hip fractures by 43% relative to the placebo group.¹¹

The largest randomized, controlled trial to evaluate use of vitamin D and calcium and the risk of fracture is the Women's Health Initiative (WHI), which recruited 36,282 postmenopausal women aged 50 to 79 years.¹² These women received either vitamin D, 400 IU/d, with 1000 mg of elemental calcium or placebo for approximately 7 years. In one subgroup of participants, hip bone density was increased by 1.06% in the treated group relative to placebo. Hip fractures were reduced in the women taking vitamin D/calcium (hazard ratio [HR], 0.88) but this was not significant because the 95% CI was broad (0.72-1.08). Clinical spine and total fractures also demonstrated a reduction in fracture rate in the treatment group that was not statistically significant. When the

SIDEBAR

Sun and Diet: Vitamin D Metabolism



Adapted from Sutton ALM, MacDonald P. *Mol Endocrinol.* 2003;17:777-791.

A major function of vitamin D is to regulate the absorption of calcium and phosphorus. Unlike most vitamins or cofactors, the production of vitamin D is negatively regulated. Exposure of the skin to ultraviolet B radiation drives the conversion of 7-dehydrocholesterol to vitamin D₃, which is classified as a secosteroid. Vitamin D is then sequentially hydroxylated by mitochondria in the liver to form 25(OH) vitamin D, its major circulating metabolite and a reservoir for vitamin D. In the circulation, 25(OH) vitamin D is specifically bound to the vitamin D binding protein. 25(OH) vitamin D is further hydroxylated in the kidney to form 1, 25(OH)₂ vitamin D, the biologically active metabolite.¹ This active metabolite can also be produced in situ by target tissues such as bone. The renal production of 1, 25(OH)₂ vitamin D is tightly regulated by levels of serum calcium, phosphorus, and parathyroid hormone (PTH). Levels of renal

1α-hydroxylase are decreased by high levels of 1, 25(OH)₂ vitamin D, whereas levels of 1α-hydroxylase are increased by PTH. Vitamin D metabolites are inactivated by further hydroxylation at the C-24 position and then are excreted.

Vitamin D can also be obtained from supplements or dietary intake of vitamin D-fortified milk, oily fish such as wild salmon, fortified cereals, margarine, and multivitamins. However, for most individuals, the ability to obtain vitamin D from dietary intake is quite limited.

Although circulating 25(OH) vitamin D is not biologically active, once 25(OH) vitamin D diffuses through the cell membrane, it is 1α-hydroxylated and can exert its biological action through vitamin D receptor (VDR)-mediated transcription. The process of in situ production of 1, 25(OH)₂ vitamin D allows each target tissue to regulate the downstream events mediated by the VDR. The domain structure of

the VDR and its isoforms is similar to other steroid hormone receptors, with zinc fingers, a hinge region, and a ligand-binding domain. VDR-mediated transcription requires steroid receptor coactivators.²

1, 25(OH)₂ vitamin D appears to be an important immunomodulator for monocytes and macrophages. Upon exposure to lipopolysaccharides, macrophages upregulate the VDR gene and synthesize cathelicidin, an antimicrobial polypeptide. This innate immune response appears to be attenuated when 25(OH) vitamin D levels are low.³ Other target tissues for vitamin D include bone, cartilage, intestine, brain, heart, skeletal muscle, and hair.

References

1. Van den Berg H. Bioavailability of vitamin D. *Eur J Clin Nutr.* 1997;51(suppl 1):S76-S79.
2. Sutton ALM, MacDonald P. Vitamin D: More than a "bone-a-fide" hormone. *Mol Endocrinol.* 2003;17:777-791.
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KEY POINT

The association of high vitamin D levels with lower risk of some cancers suggests that vitamin D does more than regulate calcium.

TABLE 3

Common Causes of Vitamin D Deficiency

Inadequate sun exposure

- Sunscreen use
- Pigmented skin
- Aging (older than 65 years)
- Winter season
- Northern latitudes above 40°

Decreased absorption

- Malabsorption syndromes
- Bowel bypass surgery
- Crohn disease
- Celiac disease
- Fat and cholesterol absorption inhibitors

Breastfeeding

Liver failure

Chronic renal disease

data were analyzed to include only those patients who were adherent to medication, hip fractures were significantly reduced (HR, 0.71; 95% CI, 0.52-0.97). The risk of kidney stones was increased in the vitamin D/calcium-supplemented group (HR 1.17; 95% CI, 1.02-1.34). This latter adverse effect may be related to the liberal use of additional calcium supplements by the WHI participants.

Bischoff-Ferrari et al conducted a meta-analysis of randomized clinical trials to estimate the effectiveness of vitamin D supplementation in the prevention of nonvertebral and hip fractures in an older population.¹³ Based on a pooled analysis, they concluded that oral doses of vitamin D, 400 IU/d, were not “sufficient for fracture prevention” (RR, 1.15; 95% CI, 0.88-1.50) while doses of vitamin D at 700 to 800 IU/d appeared to “reduce the risk of hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons” (RR, 0.77; 95% CI, 0.68-0.87). Taken together, these studies support the concept that vitamin D at doses between 700 and 800 IU/d with calcium supplementation effectively increase hip bone density and reduced fracture risk, whereas lower vitamin D doses may have less effect.

Muscle weakness and falls

Vitamin D appears to have a significant role in muscle function. Receptors for vitamin D have been localized to muscle tissue.¹⁴ In mouse gene knockout studies, absence of the vitamin D receptor causes significant developmental abnormalities in muscle that appear to be separate from hypocalcemic effects.¹⁵ Lastly, human observational studies indicate that vitamin D deficiency can be associated with proximal muscle weakness, significant myopathy,¹⁶ and an increase in falls.¹⁷

The link between vitamin D supplementation and the propensity to fall has been examined in a number of randomized trials. In a clinical trial of more than 3700 elderly participants randomized to receive either ergocalciferol, 2.5 mg, or placebo, Law et al found no impact of vitamin D supplementation on falls.¹⁸

In a smaller randomized clinical trial with 124 participants, supplementation with vitamin D at doses between 200 and 600 IU/d had little impact on falls, whereas the 800 IU/d dose was associated with a lower rate of falls.¹⁹ The Dawson-Hughes group conducted a 3-year randomized trial in 445 men and women older than 65 years.²⁰ Participants received either vitamin D, 700 IU, plus calcium citrate, 500 mg, or placebo. Treatment with vitamin D/calcium significantly reduced the odds of falling in women (odds ratio [OR], 0.54; 95% CI, 0.30-0.97) but not in men (OR, 0.93; 95% CI, 0.50-1.72). The reduction in number of falls was greatest in women who were less physically active (OR, 0.35; 95% CI, 0.15-0.81). In summary, recent studies suggest that vitamin D supplementation at doses between 700 and 800 IU/d in a vitamin D-deficient elderly population can significantly reduce the incidence of falls.

Colon cancer

Low intake of vitamin D and calcium has been associated with an increased risk of colorectal cancer. To evaluate this relationship, the WHI calcium and vitamin D randomized trial examined the effect of these 2 supplements on colorectal cancer as a designated secondary outcome.²¹ Baseline levels of 25(OH) vitamin D were inversely correlated with an increased risk of colorectal cancer. The overall incidence of colorectal cancer was similar between the treatment and placebo groups (HR, 1.08;

TABLE 4

Dietary Reference Intakes: Vitamin D

| Age | Average Intake (mcg/d) | Average Intake (IU/d) ^a | Upper Limit (mcg/d) | Upper Limit (IU/d) ^a |
|---------|------------------------|------------------------------------|---------------------|---------------------------------|
| 0-50 y | 5 | 200 | 50 ^b | 2000 ^b |
| 51-70 y | 10 | 400 | 50 | 2000 |
| >70 y | 15 | 600 | 50 | 2000 |

^a1 IU of vitamin D is defined as the biological equivalent of 0.025 mcg cholecalciferol in bioassays with rats.

^bFor infants up to age 1 year, the upper limit is 25 mcg/d (1000 IU/d).

Institute of Medicine. Washington, DC: National Academy of Sciences; 1997.

95% CI, 0.86-1.34). These findings suggest that over a 7-year treatment period, vitamin D, 400 IU/d, and calcium supplementation had little impact on colorectal cancer in postmenopausal women.

Vitamin D supplementation at much higher levels might have an effect on colon cancer. Controversial findings from a population-based randomized trial showed that the incidence of cancer decreased with supplemental calcium plus vitamin D, 1100 IU/d. In a population of 1179 postmenopausal women older than 55 years, the adjusted RR of cancer for the calcium and vitamin D group was 0.232 (CI, 0.09-0.60). Vitamin D is not currently recommended for reducing cancer risk.²²

Autoimmune diseases

A number of observational studies suggest that vitamin D supplementation is associated with a lower risk of autoimmune diseases. In a Finnish birth cohort study of 10,821 children, supplementation with vitamin D at 2000 IU/d reduced the risk of type 1 diabetes by approximately 78%, whereas children who were at risk for rickets had a 3-fold higher risk for type 1 diabetes.²³ In a case-control study of 7 million US military personnel, high circulating levels of vitamin D were associated with a lower risk of multiple sclerosis.²⁴ Similar associations have also been described for vitamin D levels and rheumatoid arthritis.²⁵

Updated recommendations may be coming

The current nutritional recommendations for vitamin D were established in 1997 by the Food Nutrition Board of the Institute of Medicine (TABLE 4).²⁶ Unlike other nutrients, levels of 25(OH) vitamin D can vary by season, race, ethnicity, and age.

Significant new findings about vitamin D supplementation with improved functional measures have been published since that time. These studies suggest that the daily vitamin D intakes should be much higher than 400 IU/d. Daily intakes in the range of 800 to 1000 IU/d should be strongly considered.²⁷ Although there are concerns regarding vitamin D toxicity, side effects at intakes exceeding the current upper limit of 2000 IU/d have not been reported to date.²⁸ In 2 small clinical trials by Heaney et al and Barger-Lux et al, vitamin D at doses of 10,000 IU/d were administered for up to 20 weeks without observed changes in serum calcium levels or adverse side effects.^{29,30}

We anticipate that vitamin D requirements will soon be updated; until then, supplementing at the recommended dosages and ultraviolet light exposure are the standard ways of ensuring vitamin D sufficiency.

Summary

Vitamin D is endogenously produced, circulates bound to its own specific binding protein, and is converted in situ to the active form, 1, 25(OH)₂ vitamin D, in target tissues. Receptors for vitamin D are widely distributed, and these target tissues include macrophages, monocytes, bone, intestine, skeletal muscle, brain, and heart. Clinical studies of vitamin D supplementation at doses of 700 to 800 IU/d have shown beneficial effects on reducing hip and nonvertebral fractures and in improving muscle strength and reducing falls. There is also epidemiological evidence for reduction in colon, breast, and prostate cancers with higher vitamin D levels. Therefore, the potential role(s) of vitamin D are much broader than calcium regulation alone.

KEY POINT

Supplementation with vitamin D, 2000 IU/d, reduced the risk of type 1 diabetes by 78% among Finnish children.



Vitamin D deficiency appears to be more common than previously thought, especially in the elderly population. This condition is often unrecognized by clinicians; therefore, assessment of vitamin D status with serum measurements of 25(OH) vitamin D levels for a broader range of patients should be encouraged. Supplementation at a dose of 800 IU/d vitamin D appears to have a positive impact on reducing fractures and falls. Vitamin D toxicity is very uncommon, and there is a wide safety margin at these higher supplement doses.³¹ ■

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KEY POINT

No side effects have been reported for vitamin D intake that exceeds the current upper limit of 2000 IU/d.