Vitamin D (Calciferol)

Scientific names of various forms: cholecalciferol (D3), ergocalciferol (D2), 25-hydroxyvitamin D (calcidiol; calcifediol), 25-hydroxycholecalciferol, 1,25-dihydroxycholecalciferol (calcitriol).

Vitamin D isn’t actually a vitamin; it’s a steroid pre-hormone. Vitamin D3 (cholecalciferol) is synthesized in the skin of humans from 7-dehydrocholesterol after ultraviolet B (UVB) exposure. The endogenous production of vitamin D3 (cholecalciferol) is determined by the amount of UVB radiation on the skin as well as the availability of 7-dehydrocholesterol in the skin. (1)

Cholecalciferol can be stored in the liver and fat tissues for long periods of time, and converted to the active hormone by the liver and kidneys when needed. Whereas vitamin D3 (cholecalciferol) has an average lifetime in the body of approximately 2 months, 25(OH)D (calcidiol) has a lifetime of 15 days, and calcitriol (1,25-(OH)2 D3) has a lifetime measured in hours. Most circulating 25-hydroxyvitamin D originates from exposure to sunlight; however, use of sunscreen, living in colder, seasonal climates, dark skin pigmentation, aging, obesity, and many other factors restrict this process, making reliance on dietary sources and supplementation necessary to supply the needed precursor to 25-hydroxyvitamin D. (1,2).

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Unfortunately, we can get some, but very minimal, vitamin D from diet. It is a fat-soluble vitamin which is absorbed with other dietary fats in the small intestine. Vitamin D can accumulate in the body because it can be stored in the liver and fat tissues for long periods of time. Very few foods are naturally rich in vitamin D although sources include some fatty fish like wild caught salmon, (but not in farm raised salmon), fish liver oils, egg yolk, mushrooms, butter and liver. The only regularly vitamin D fortified foods in the U.S. are fluid milk and cereals, although some orange juice and soy/nut milks may also be fortified. Because of the potential for toxicity if it is chronically consumed at very high doses, in Canada and the United States, the addition of vitamin D to foods is very carefully regulated. In spite of fortification, it remains very difficult to meet nutritional need for vitamin D from diet alone. Research suggests that current US fortification practices are not effective in preventing hypovitaminosis D (vitamin D insufficiency) particularly among vulnerable populations during the winter (3).

Vitamin D deficiency is more common than previously realized and especially so for newborns, people of color and older adults. Other risk factors for insufficiency include obesity, impaired renal function, liver disease, inflammatory bowel disease and fat malabsorption. Vitamin D deficiency not only causes osteomalacia, and may precipitate and exacerbate osteoporosis, it also causes generalized muscle weakness, muscle aches (e.g., back pain) and bone pain. (1)

Vitamin D receptors are common in most tissues in the body, and the new revelation that many tissues produce 1,25-dihydroxyvitamin D suggests a new important role for this hormone in helping to maintain good health throughout life. (4)

**USES**

Vitamin D is important in maintaining overall good health. It helps develop and maintain bones and teeth. It’s an important immune system modulator. Orally, vitamin D is used for preventing rickets, osteomalacia, osteoporosis, muscle weakness, supporting healthy immune function and cardiovascular function.

Vitamin D is also used for preventing and treating bone disorders in people with familial hypophosphatemia, hypophosphatemia associated with Fanconi syndrome, and hypocalcemia associated with postoperative or idiopathic hypoparathyroidism or pseudohypoparathyroidism, corticosteroid-induced osteoporosis, osteomalacia, anticonvulsant-induced osteomalacia, hepatic osteodystrophy and osteogenesis imperfecta.

Other uses include treatment of plaque-type psoriasis, actinic keratosis, lupus vulgaris, vitiligo, scleroderma, and periodontal disease.

Vitamin D is also used orally to treat myopathies associated with vitamin D deficiency or statin-induced myopathy, and to maintain bone density in patients at risk for osteoporosis when treated with luteinizing hormone-releasing hormone analogue (LHRH-a).

Some drugs can affect vitamin D levels, including: Carbamazepine (Tegretol), Cholestyramine, Colestipol (Colestid), Corticosteroids, mineral oil, Orlistat (Xenical, Alli), Phenobarbital, Phenytoin (Dilantin), Fosphenytoin (Cerebyx), Rifampin, stimulant laxatives and sunscreens. Vitamin D is given to prevent nutrient depletion in patients on these medications.

Intramuscularly, vitamin D is administered as ergocalciferol for hepatic osteodystrophy, as an injectable source of vitamin D, and to treat severe proximal myopathy associated with vitamin D deficiency.

**USUAL DOSE AND ADMINISTRATION**

Vitamin D is usually taken by mouth. Most vitamin D supplements available without a prescription contain cholecalciferol (vitamin D3). It is available in chewable tablets and gummies, tablets, capsules, powders, drops, and liquids. Vitamin D is best taken with a meal that contains fat. It turns out that vitamin D is best absorbed with a low-to-moderate amount of fat, compared to no fat or lots of fat. Specifically, researchers have shown that 11 grams of fat leads to higher absorption than either 35 grams or 0 grams, at 16% higher and 20% higher respectively. (5)
Vitamin D dose is listed in both micrograms (µg) and international units (IU). 1 IU of vitamin D is the same as 0.025 µg of vitamin D2 or D3.

Vitamin D has been safely used in a wide range of doses, and dosing recommendations still vary widely in guidelines set by different medical organizations and institutions. Most research on dosing has revolved around bone health. Research has been inadequate in determining the daily dose of vitamin D needed for optimal function of the immune system, musculoskeletal system and nervous system. Such studies need to be conducted, as well as studies which determine optimal dose for treatment of infection and nervous system disorders. (6)

In 2001, the American Journal of Clinical Nutrition published a study reporting that prolonged intake of 100 mcg (4000 IU) of vitamin D3 daily resulted in plateau [25(OH)D] concentrations averaging 96 nmol/L (38.4 ng/ml). (6)

In 2003, the American Journal of Clinical Nutrition published a study on maintaining the serum 25-hydroxycholecalciferol concentration present in the autumn in 67 men living in Omaha, NB. Regardless of the starting level, it required 3000-5000 IU (100-125 mcg) per day, to maintain the initial level throughout the winter. (7)

Many physicians look to the national Institute of Medicine to advise on matters of health and medicine in the US. In 2010, the Food and Nutrition Board (FNB) of the IOM set a Recommended Dietary Allowance (RDA) based on the amount of vitamin D needed for bone health. While their daily intake recommendations are very conservative and perhaps outdated at this point, one notable change was an increase in their safe upper limits (ULs) for vitamin D which increased to 1,000 IU for ages 0-6 months, 1,500 IU for ages 7-12 months, 2,500 IU for ages 1-3 years, 3,000 IU for ages 4-8 years and 4,000 IU for those over age nine.(8)

In 2011, the Endocrine Society published their guidelines for vitamin D intakes, which were generally higher than the IOM recommendations based on a requirement for a higher minimum blood level of vitamin D. (9) Table 1 (below) compares the guidelines.

<table>
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<tr>
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AI, Adequate intake; EAR, estimated average requirement; UL, tolerable upper intake level.

Lactation requirement: 4,000–6,000 IU/d (mother’s intake for infant’s requirement if infant is not receiving 400 IU/d).
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When used orally long-term, the general recommendation is not to exceed the tolerable upper intake level of 4,000 IU per day for adults; however, much higher doses such as 50,000 IU/week orally for six to 12 weeks are often needed for the short-term treatment of vitamin D deficiency. Also, higher daily doses may be necessary to achieve optimal blood levels of 25-hydroxyvitamin D for maintaining bone density at 30-100 ng/mL for many individuals due to age, race, body weight and other individual variances.

In general, for adults, research suggests that vitamin D toxicity is very unlikely in healthy people at intake levels lower than 10,000 IU/day. (10)

It’s helpful to know that magnesium deficiency negatively affects vitamin D status, and that adequate magnesium intakes may reduce the risk of vitamin D insufficiency. Recent findings suggest that magnesium regulates the activity of critical enzymes in vitamin D metabolism. (11)

ACTIVE CONSTITUENTS

The term “vitamin D” refers to several different forms of this vitamin. The two main forms important to humans are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) which differ chemically in their side-chain structures. Vitamin D3 is synthesized by humans in the skin when it is exposed to ultraviolet B (UVB) rays from sunlight. It is the preferred form for dietary supplements. Vitamin D2 is an analog photosynthesized by plants, mushrooms and yeasts. Both cholecalciferol and ergocalciferol are biologically inactive precursors of vitamin D and must be converted to biologically active forms in the liver and kidneys. (3)

Vitamin D obtained from sun exposure, foods, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver, converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as “calcidiol.” 25-Hydroxyvitamin D constitutes the major circulating form of vitamin D, and the sum of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 concentrations in serum is used as an indicator of vitamin D nutritional status. (12)

The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as “calcitriol”. The production of 1α,25-dihydroxyvitamin D in the kidneys is regulated by several factors, including serum phosphorus, calcium, parathyroid hormone (PTH), fibroblast growth factor-23 (FGF-23), and 1α,25-dihydroxyvitamin D itself. (12)

Although the kidneys play a critical role in producing 1,25-dihydroxyvitamin D, it is now recognized that a wide variety of other tissues have vitamin D receptors, and the enzymatic ability to convert 25(OH)D to 1,25(OH)2D. (4,13)

Despite historically being considered equally effective, conflicting evidence has led to uncertainty as to whether vitamin D2 and vitamin D3 are equally efficacious in improving vitamin D status equally for all people. (14,15,16) There is general consensus that vitamin D3 is the preferred form because it is the form humans endogenously synthesize.

MECHANISMS OF ACTION

In many ways, it’s much easier to think of vitamin D less as a vitamin and more as an essential hormone that the body requires for normal physiological function. Through binding to the vitamin D receptor (VDR), 1,25-dihydroxyvitamin D can regulate the expression of hundreds of genes involved in regulating our biological functions. Vitamin D enters the body either from its production in the skin or absorption from the intestine. Circulating vitamin D molecules are transported bound to the vitamin D-binding protein and enter into the cell through the megalin/tubulin complex. Upon entering the nucleus of a cell, 1α,25-dihydroxyvitamin D binds to the VDR and recruits another nuclear receptor known as retinoid X receptor (RXR). In the presence of 1α,25-dihydroxyvitamin D, the VDR/RXR complex binds small sequences of DNA known as vitamin D response elements (VDREs) and initiates a cascade of molecular interactions that modulate the transcription of specific genes. VDR activation by 1α,25-dihydroxyvitamin D is thought to directly and/or indirectly regulate 100 to 1,250 genes. (17)
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The major functions of vitamin D3 are to:

1. **Maintain normal blood levels of calcium.**
   Maintenance of serum calcium concentrations within a narrow range is vital for normal functioning of the nervous system and muscle function, as well as for bone growth and maintenance of bone density. Within target cells, 1α,25-dihydroxyvitamin binds to and activates the VDR, which leads to changes in gene expression that normalize serum calcium by (1) increasing the intestinal absorption of dietary calcium, (2) increasing the reabsorption of calcium filtered by the kidneys, and (3) mobilizing calcium from bone when there is insufficient dietary calcium to maintain normal serum calcium concentrations.

2. **Aid in the absorption of calcium and phosphorus,** essential for bone development.

3. **Support optimal immune function,** and healthy inflammatory balance. Vitamin D enhances innate immunity and inhibits the development of autoimmunity.

4. **Influence cell cycling and proliferation,** differentiation, maturation and apoptosis. Vitamin D controls proliferation and stimulates cell differentiation and growth.

5. **Support glucose metabolism.** The VDR is expressed by insulin-secreting cells of the pancreas, showing that vitamin D plays a role in insulin secretion, but further research is needed to define its mechanisms.

6. **Regulate blood pressure.** The renin-angiotensin system plays an important role in the regulation of blood pressure. Angiotensin-converting enzyme (ACE) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing sodium and water retention. The rate of angiotensin II synthesis is dependent on renin. Research in mice lacking the gene encoding the VDR indicates that 1α,25-dihydroxyvitamin D decreases the expression of the gene encoding renin through its interaction with the VDR.

**MEASURING VITAMIN D STATUS**

The Endocrine Society stated that, for clinical practice, a serum 25(OH)D concentration of more than 75 nmol/L (30 ng/mL) is necessary to maximize the effect of vitamin D on calcium, bone, and muscle metabolism and they recommend levels between 40-60 ng/ml.

**SIDE EFFECTS / CONTRAINDICATIONS**

Vitamin D supplementation may cause hypercalcemia and hypercalciuria, particularly at high doses, according to human research. Hypoparathyroid patients taking thiazide diuretics who also take vitamin D are at risk of developing hypercalcemia. Vitamin D should be used with moderation in patients taking digoxin because hypercalcemia (which may result with excessive vitamin D use) may cause abnormal heart rhythms.

Vitamin D may interact with certain drugs, and caution is advised when used in combination with these agents. These include aluminum, Atorvastatin (Lipitor), Calcipotriene (Dovonex), Cimetidine (Tagamet), Cytochrome P450 3A4 Substrates, Digoxin (Lanoxin), Diltiazem, Heparin, Low-molecular weight heparins, Thiazide Diuretics and Verapamil. Laxatives can inhibit dietary vitamin D absorption.

Vitamin D toxicity can result from regular excess intake of this vitamin and may lead to hypercalcemia and bone loss. Individuals at particular risk include those with hyperparathyroidism, kidney disease, sarcoidosis, tuberculosis or histoplasmosis.

**REFERENCES**

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