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Scientific Name(s): Ergocalciferol (Vitamin D₂) or cholecalciferol (Vitamin D₃)

Common Name(s): Vitamin D, sunshine vitamin


Uses

Vitamin D, long recognized as playing a role in bone and calcium homeostasis, is being investigated for use in cardiovascular disease, cancer, diabetes, infections, multiple sclerosis, psoriasis, respiratory [health](#) , and other conditions. More clinical trials are needed.

SLIDESHOW

Don't Believe The Hype: How Multivitamins Conquered The Land Of The Free

Dosing

The American Academy of Pediatrics recommends 400 units/day of vitamin D in [infants](#) , and adolescents. Clinical data are not yet sufficiently robust to make definitive recommendations for therapeutic dosages of vitamin D; however, in the elderly, 700 to 1,000 units/day have been shown to reduce the risk of falls.

Contraindications

Contraindications have not been identified.

Pregnancy/Lactation

Routine use of supplemental vitamin D [during pregnancy](#) [↗] is not supported by safety evidence. However, adequate maternal intake of vitamin D-containing foods during lactation ensures that breast-fed infants receive sufficient vitamin D.

Interactions

The use of statins has been shown to increase serum vitamin D levels. Corticosteroids decrease the metabolism of vitamin D and orlistat reduces its absorption; phenobarbital and phenytoin increase the hepatic metabolism of vitamin D.

Adverse Reactions

High doses of vitamin D have rarely produced adverse events in clinical trials.



Toxicology

Toxicity due to vitamin D is considered to manifest at serum levels greater than 150 ng/mL of 25-hydroxyvitamin D. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness associated with hypercalcemia.

Vitamin D₃ (cholecalciferol) is synthesized in the skin by transformation of 7-dehydrocholesterol exposed to ultraviolet B rays of the midday sun. Vitamin D binding protein transports D₃ to the liver, where it is hydroxylated to the inactive 25-hydroxyvitamin D form (calcidiol). In the kidneys, it is further hydroxylated by the enzyme 1-alpha-hydroxylase to active 1, 25-dihydroxyvitamin D (calcitriol). ¹

Vitamin D as ergocalciferol (vitamin D₂) is found in some plants and in salmon, sardines, mackerel, tuna, cod liver oil, shiitake mushrooms, egg yolk, and fortified foods. ^{1, 2, 3} Deficiency may result from decreased absorption (such as in cystic fibrosis, celiac and Crohn diseases, and drug interactions), increased catabolism (caused by anticonvulsant and antiretroviral therapy and some immunosuppressant drugs), and hepatic and renal failure, as well as from inadequate intake. ¹

Chemistry

Vitamin D is a hormone precursor and acts to control calcium absorption in the small intestine. It affects parathyroid hormone, which in turn affects the metabolism of skeletal mineralization and calcium homeostasis in the blood. Additionally, effects on cytokines and immune-modulating effects are reported. ¹

The accepted biomarker is 25-hydroxyvitamin D (or calcidiol). Only in advanced renal disease are measurements of 1, 25-dihydroxyvitamin D (calcitriol) relevant. ⁴ Concern over standardization of assays exists. ¹

Uses and Pharmacology

Cancer

Animal data

Preclinical studies have shown an effect of vitamin D on a variety of cancer cell lines. Cell cycle interruption, apoptosis, and other mechanisms have been demonstrated. ^{1, 5, 6}

Clinical data

Meta-analyses of observational studies suggest a lower incidence of cancer with higher vitamin D serum levels. ^{1, 7, 8}

Particular attention has focused on breast, colon, and prostate cancer. In the Women's Health Initiative study, no association was found between vitamin D and breast cancer, ⁹ while the [Health Professionals](#) [↗] Follow-Up Study suggested a decreased risk of cancer with increasing 25-hydroxyvitamin D levels. ^{1, 5}

Cardiovascular

Vitamin D is thought to exert cardiovascular effects by a number of mechanisms, including effects on the renin-angiotensin-aldosterone system, homeostasis of calcium, and secondary effects on hyperparathyroidism and insulin resistance. [10](#)

Animal data

Available data from large clinical trials make animal data largely redundant.

Clinical data

No clinically important effect on coronary or cerebrovascular risk or outcomes was found with vitamin D and calcium supplementation over 7 years in the Women's Health Initiative randomized trial. [11](#) , [12](#) Other systematic reviews of clinical trials have largely found no effect or only a small effect of vitamin D supplementation on cardiovascular outcomes and hypertension. [13](#) , [14](#) Based on limited trial data in populations with vitamin D insufficiency, moderate to high doses of vitamin D increase the serum vitamin D metabolite status and may reduce cardiovascular risk; however, further studies are required before a definitive place in therapy can be established. [15](#) , [16](#)

Diabetes

Animal data

Animal studies suggest vitamin D exerts effects on the homeostasis of glucose metabolism, as supplementation in animals has led to decreases in plasma glucose. [1](#) , [17](#) A direct effect on insulin secretion has been suggested, as well as effects on insulin receptor expression, insulin sensitivity, and direct action on insulin itself. [1](#) , [18](#) , [19](#)

Clinical data

Epidemiological data support a role of vitamin D in reducing the incidence of diabetes. Vitamin D supplementation in infants has been associated with a decreased risk of type 1 diabetes, and a meta-analysis has demonstrated an association between low vitamin D status and the prevalence of type 2 diabetes or metabolic syndrome. [1](#) , [14](#) However, limited, small studies have shown equivocal results on the impact of vitamin D on serum glucose; further studies are required. [17](#)

Infectious disease

Vitamin D receptors are ubiquitous in the body and are found in immune system-related cells, such as B and T lymphocytes, neutrophils, and macrophages. An emerging role is being described for vitamin D in immune response. [7](#) , [20](#) , [21](#)

The Randomized Evaluation of Calcium or Vitamin D (RECORD) trial investigated the effect of vitamin D supplementation (800 units/day) on self-reported infections and antibiotic use but did not find a statistically significant association. [22](#) A single dose of vitamin D demonstrated an enhanced immune response in a randomized clinical trial in tuberculosis patients, [23](#) while a systematic review of clinical trials evaluating the effect of vitamin D supplementation (largely in tuberculosis, influenza, and other viral infections) concluded that further studies are warranted. [24](#)

Multiple sclerosis

Theoretical and epidemiological models support a place in therapy for vitamin D in multiple sclerosis. An inverse relationship has been demonstrated between vitamin D levels and multiple sclerosis, especially in patients younger than 20 years of age, while the development of multiple sclerosis in women has been associated with low 25-hydroxyvitamin D levels. Lower serum vitamin D and severity of multiple sclerosis, as well as incidence of relapses, has also been demonstrated. [1](#) , [25](#) , [26](#) , [27](#)

Little prospective data exist; however, a small clinical study (N = 12) showed a decrease in the number of lesions with magnetic resonance imaging with administration of 1 mg (40,000 units) daily over 28 weeks. [1](#) No serious adverse events were reported at this dosage, and no hypercalcemia or hypercalciuria was reported.

Renal

Animal data

Available data from large clinical trials make animal data largely redundant.

Clinical data

As kidney function is impaired, the inability to maintain adequate phosphorus and calcium levels results in compensatory mechanisms involving parathyroid hormone. Resultant increases in bone metabolism to release calcium to the system cause bone deformation, pain, and an increased risk of fractures. Supplementation of vitamin D suppresses parathyroid hormone, but it may also slow the progression of chronic kidney disease via novel pathways. Vitamin D analogs, such as paricalcitol, may exert anti-inflammatory effects, as well as affect the renin-angiotensin systems and decrease morbidity and mortality. However, studies are limited. [28](#) , [29](#) , [30](#)

Other uses

Alopecia

The role of vitamin D and its receptors is not well understood, but the potential for topical calcitriol to upregulate the receptors has been evaluated in animal models of chemotherapy-induced alopecia. Hair loss is not prevented; however, hair regrowth over the entire animal has been demonstrated. [31](#) Limited clinical studies have produced varying results, possibly dependent on the chemotherapeutic agent. [31](#)

Dementia/Depression

Observational studies and animal models suggest a role for vitamin D in treating dementia. Vitamin D exerts antioxidant effects, and receptors are found in the human cortex and hippocampus. Correlations between the Mini-Mental State Examination scores and vitamin D serum levels, as well as global cognitive function, have been shown. [1](#) , [32](#) , [33](#) One clinical trial demonstrated an improvement in mild depression with vitamin D supplementation. [34](#)

Falls in the elderly

Systematic reviews have been conducted on the effects of supplemental vitamin D and the risk of falls in the elderly.^{1, 35} Low doses (200 to 600 units/day) showed no effect, while higher doses (700 to 1,000 units/day) reduced the risk of falling in the elderly by 19% to 22%. ¹

Psoriasis

Topical synthetic vitamin D (eg, tacalcitol) may be an alternative to topical steroids and may inhibit keratinocyte proliferation, as well as influence immune modulation. ^{36, 37, 38}

Respiratory health

Vitamin D appears to be capable of inhibiting the pulmonary inflammatory response and enhancing pulmonary defense against pathogens. Population-based studies support an association between circulating vitamin D levels and lung function. ³⁹ The use of vitamin D in cystic fibrosis is based on knowledge of vitamin insufficiency due to pancreatic insufficiency; however, evidence of benefit is lacking for vitamin D supplementation despite routine use. ⁴⁰

Dosage

Clinical response to vitamin D does not always correspond with serum levels of the markers.¹ Generally a serum level of less than 20 ng/mL of 25-hydroxyvitamin D constitutes a deficiency in adults and children. ^{1, 2, 41}

The American Academy of Pediatrics recommends 400 units/day vitamin of D in infants and adolescents.^{41, 42}

To maintain a serum 25-hydroxyvitamin D level of 25 ng/mL, independently living elderly adults required vitamin D 7.9 to 42.8 mcg daily in a clinical study ⁴³ (20 mcg is equivalent to 800 units).²² Data from clinical studies are not yet sufficiently robust to make definitive recommendations for therapeutic dosages of vitamin D; however, in the elderly, 700 to 1,000 units/day have been shown to reduce the risk of falls. ³⁵

Pregnancy/Lactation

The safety and efficacy of vitamin D in pregnancy has not been confirmed. Clinical trials have evaluated the excretion of vitamin D in breast milk by mothers given supplementation. Adequate levels of vitamin D are achieved in breast-fed infants from mothers with a vitamin D intake of 400 units/day. All milk formulas sold in the United States contain at least 400 units/L of vitamin D. ¹

Interactions

The use of statins has been shown to increase serum vitamin D levels.⁴⁴ Corticosteroids decrease the metabolism and orlistat reduces absorption of vitamin D, while phenobarbital and phenytoin increase the hepatic metabolism of vitamin D. ²

Adverse Reactions

High doses of vitamin D have rarely produced adverse events in clinical trials.¹

Apart from the obvious hazards, prolonged sun exposure alone cannot cause vitamin D overdose because sunlight destroys excess vitamin D₃. ¹

Toxicology

Toxicity due to vitamin D is considered to manifest at levels greater than 150 ng/mL of serum 25-hydroxyvitamin D. Symptoms of hypervitaminosis D include fatigue, nausea, vomiting, and weakness associated with hypercalcemia. ^{1, 2} Reports of toxicity exist for children administered high-dose vitamin D after World War II in Europe. Hypercalcemia, nephrocalcinosis, adverse cardiovascular effects, early aging, and premature death were reported. ⁴⁵

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