

Vitamin D:

A Clinical Perspective

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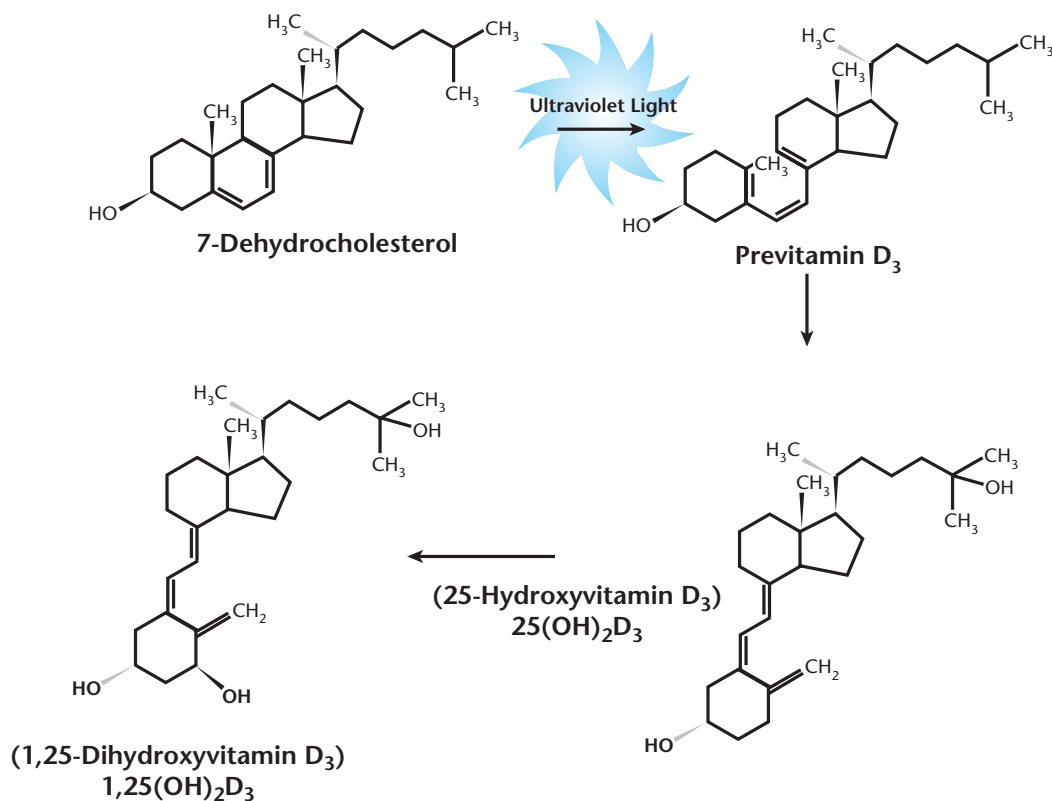
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Introduction

Vitamin D, also known as cholecalciferol, may be one of the least understood and most under utilized therapeutic interventions available. Despite overwhelming research concerning the use of vitamin D, it continues to be largely neglected as a powerful clinical tool. Evidence continues to mount regarding a high prevalence of vitamin D deficiency. Original methodology for establishing a recommended daily allowance for vitamin D was flawed and new ranges need to be adopted to prevent insufficiencies. One study showed that no subject received the recommended vitamin D dose from dietary sources alone, adequate sun exposure provided approximately 90% of vitamin D.[1] The well-known potential for toxicity from excess vitamin D underscores the importance of monitoring vitamin D status following a period of supplementation. Testing at risk populations is well warranted. For example, vitamin D has been shown to reduce hip fracture by 20%. Just this one applicable use of vitamin D would lead to an estimated annual savings of 1.5 to 2 billion dollars from reduction in fracture incidence. [2]

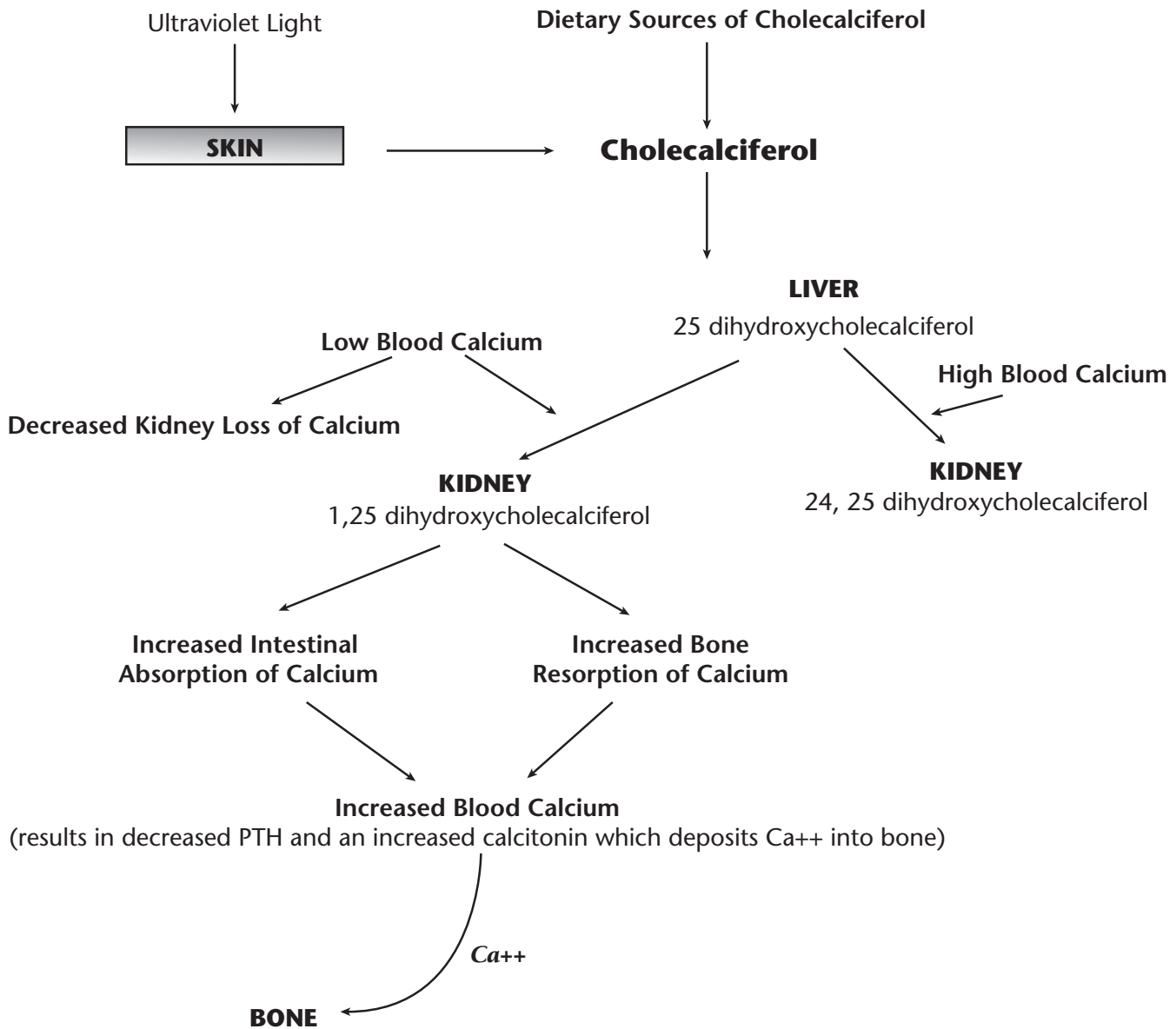
Vitamin D₂ (ergocalciferol) is obtained from plant sources, vitamin D₃ (cholecalciferol) from animal products or the action of sunlight on a cholesterol-like precursor, 7-dehydrocholesterol, that is in the skin.



7-dehydrocholesterol is converted into vitamin D₃ and then into 1,25 (OH)₂D₃, the active hormone.

Vitamin D₂ and D₃ follow the same pathway for activation. After being created in the skin or consumed in the diet, the liver hydroxylates at the 25th carbon to 25-hydroxyvitamin D [25(OH)D]. The kidney as well as other tissue, converts vitamin D₂ and D₃ to its most active metabolite 1 α ,25-dihydroxyvitamin D [1,25(OH)₂D], also known as calcitriol.

Figure 2. Metabolic Summary of Vitamin D



Clinical Significance

Although its primary role is to regulate calcium and phosphorus absorption/resorption to maintain bone health, the clinical significance of vitamin D is very broad. Deficiency of vitamin D during pregnancy and lactation greatly increases the risk of maternal bone loss. Insufficient vitamin D levels during infancy can result in biochemical disturbances of reduced growth, increased bone deformities and rickets. Low birth weight is also a consequence of inadequate vitamin D status. Beyond bone status, maternal and, therefore, infant 25(OH)D levels are correlated with the risk of type 1 diabetes mellitus. Population studies show, the higher the level of vitamin D the lower the risk of diabetes mellitus type I and II.[3] In

a study of elderly people given vitamin D supplements, functional performance, reaction time and balance all improved significantly. [4]

Most tissues express vitamin D receptor, including immune cells such as macrophages and lymphocytes, and neurologic tissue such as microglia, neurons, astrocytes, glial cells, neurons and oligodendrocytes. The numerous effects of 1,25(OH)₂D₃ on the immune system include suppression of T cell activation, shaping of cytokine secretion patterns, induction of regulatory T cells, modulation of proliferation, and apoptosis. 1,25(OH)₂D₃ further influences maturation, differentiation, and migration of antigen presenting cells serving as a powerful regulator of the Th1/Th2 response.[5] Underlying, unresolved inflammation perpetuates autoimmune processes. It is hypothesized that vitamin D upregulates apoptotic mechanisms in pro-inflammatory cells, allowing the inflammatory cells to arrest appropriately, preventing on-going inflammation that damages tissue. T-helper cells, dendritic cells and macrophages have improved function with adequate vitamin D levels. [6] This makes vitamin D of obvious importance for neurologic autoimmune processes like MS.

Other conditions that benefit from or are prevented by adequate Vitamin D levels include the following:

Conditions associated with suboptimal Vitamin D status

Testing

Cancers	Autoimmune	Endocrine
Colon cancer[7]	Multiple Sclerosis[12, 13]	Diabetes Mellitus [18]
Breast cancer[7]	Vitiligo[16]	Syndrome X[17]
Ovarian cancer[7]	SLE [14]	Low epinephrine/norepi [19]
Osteoporosis[8]	Crohn’s[17]	Low dopamine[19]
Tuberculosis[9]	Rheumatoid arthritis[15]	Thyroiditis[17]
Cervical cancer[10]	Sjogren’s Syndrome[17]	Obesity[17]
Bladder cancer[7]		
Esophageal cancer[7]		
Uterine cancer[11]		
Musculoskeletal	Neurologic	Cardiovascular
Myalgia[20]	Parkinson’s[17]	Hypertension[12, 25]
Fractures[22]	Schizophrenia [24]	Arteriosclerosis[17]
Osteopenia[21]	Seasonal Affective Disorder[23]	MI [17]
Osteoarthritis[12]	Autism[17]	
Fibromyalgia[14]		
Rickets[9]		
Gastrointestinal	Dermatology	
Pancreatitis [26]	Psoriasis [27]	
IBS [18]	Senile warts [28]	

25(OH)D is regarded as the single best assessment of vitamin D nutritional status. [29] Within hours, vitamin D from sunlight and diet is removed from circulation and recirculates again a few hours later as 25(OH)D. Testing of unconverted vitamin D, from diet and sun, only gives transient information about recent nutritional intake or sun exposure. 25(OH)D has the longest half life, of about three weeks, making it the more useful indicator of true Vitamin D status. [13] Vitamin 25(OH)D is converted to an active form, 1,25(OH)₂D, in the kidney as well as in other tissue. For this reason the main circulating form of Vitamin D is the 25(OH)D.

Even though 1,25(OH)₂D₃ is the biologically more active metabolite, plasma concentrations of the dihydroxy form are mainly dependent on renal function, appropriate parathyroid hormone levels, and the supply of calcium and phosphate. [30] Testing for 1,25(OH)₂D is only warranted in cases when disorders in calcium and bone metabolism is of concern related to either an acquired or inborn error in the conversion of 25(OH)D to 1,25(OH)₂D. [31] 1,25(OH)₂D levels decline only once vitamin D depletion is virtually complete. Because of this tight regulation by the kidney, measurement of 1,25(OH)₂D is of limited clinical utility.

Early studies aimed at determination of adequate vitamin D levels are of little value because they did not control for variables such as race, lifestyle habits, sunscreen usage, age, latitude and inappropriately low dietary intake recommendations for vitamin D. Research that used signs and symptoms as functional biomarkers for determining vitamin D levels found that to prevent pathology involving bone mineral density, muscle health, parathyroid hormone, and calcium absorption, 25(OH)D levels above 80 nmol/L are required.[20, 32] Values below 80 nmol/L are therefore considered insufficient.

Dosing

For patients with low serum 25(OH)D, short term treatment with high doses of vitamin D is safe. [33] In 1941 when the original recommended daily allowance was established, vitamin D levels were based on the observation that the amount of vitamin D activity in a teaspoon of cod liver oil was sufficient to prevent rickets in infants. This resulted in a vitamin D recommendation that was more conjecture than science. Current research indicates that the RDA should at least be set at 500 IU, [27] and higher doses are needed in one who has low serum 25(OH)D levels. When nursing mothers were given either 2000 IU/d or 4000 IU/d of vitamin D, levels of 25(OH)D in their breast milk increased by 34.2 IU/L or 94.2 IU/L respectively. Circulating 25(OH)D status also improved in their nursing infants. No toxicity was seen in either mothers or nursing infants, demonstrating that higher levels are well tolerated in this population. [34] In another study serum levels only increased by approximately 6.5 nmol/liter when women and men supplemented with 800 IU a day of vitamin D. [35] It is reported that high dose vitamin D may take 3 months to a year to cause normalization. Large doses of vitamin D should be decreased when serum levels exceed 110 nmol/L. Vitamin D serum levels may remain relatively constant until amounts as high as 10,000 IU a day are given.[12] It was recently reported that tanners with levels of 25(OH)D greater than 40 nmol/L had higher bone density than the controls. Concentrations of 25(OH)D that correlate with desirable effects extend to at least 70 nmol/L, with no obvious upper threshold. [25]

Exposure to mid-day sunlight rays when the sun is highest in the sky provides the best vitamin D production because of the high UVB:UVA ratio. Since most people acquire only 6-47% of their vitamin D through dietary sources, [36] the absence of UVB exposure greatly increases the chance of deficiency. It is estimated that 90% or more of required vitamin D comes from sunlight exposure. [17] Melanoma, the most deadly form of skin cancer, is not caused by UVB rays but by UVA rays.

An alternative to daily dosing is a single oral dose of 100,000 IU of vitamin D every 3 to 6 months. This method of dosing can be helpful in those who may have difficulty with daily compliance and in the chronically ill patient who can have routine office visits only every few months to allow for administration. This dosing regimen has not been associated with toxicity and has safely been given in the housebound elderly. [37]

Patients that consume large quantities of milk may have an increased need for Vitamin D as milk may block vitamin D receptors due to the bovine albumin protein, which is a molecular mimic of the vitamin D receptor. Immune reaction against the milk protein, may result in an autoimmune reaction against the vitamin D receptor, making it difficult for the vitamin D hormone to bind. [38] Mushrooms contain high amounts of Vitamin D, especially wild ones of the genus *Cantharellus*. [39] Oily fish and fortified foods are major Vitamin D contributors to the diet. The following table gives Vitamin D levels in foods:

FOOD	IU per 100mg		FOOD	IU per 100mg
Sardine	1150 - 1570		Mackerel	820 - 1100
Cod Liver Oil	1200		Herring	320 - 840
Tuna	250		Salmon	150 -550
Mushrooms	60 - 90		Pork	45
Egg Yolk	25		Beef	9 - 42

Nutrient Interactions

Calcium should be given alongside Vitamin D. Vitamin D will raise serum calcium levels. If adequate calcium is not available from diet then calcium will be taken from the bones. Activated vitamin D controls the bodies ability to use tyrosine in the adrenal gland by regulating tyrosine hydroxylase, the rate limiting enzyme in production of dopamine, epinephrine, norepinephrine.[19] Hydroxylation of Vitamin D is increased by the activity of cytochrome P450 enzymes. Isoflavones in soy are the active constituent that augment hydroxylation. This may be one reason soy is associated with decrease risk of some cancers and improved bone density.[40] Essential fatty acid deficiency impairs vitamin D receptors, decreasing responsiveness to vitamin D.[41]

Toxicity

Osteopenia is the primary toxic effect of excess vitamin D. If calcium intake is inadequate, then calcium will be taken from the bones. Levels of oral vitamin D as high as 4000 IU/day have been demonstrated to be safe for up to six months. [25] There is some concern that higher doses over extended periods of time may produce other adverse effects such as increased risk of prostate cancer. However, 600,000 IU of ergocalciferol (D₂) was given to elderly men and women with no evidence of toxicity [4] and 15,000 IU of vitamin D was given for two months once a week to menopausal women with no negative impact. [42] The only published data concerning vitamin D toxicity occurred when 40,000 IU of vitamin D were given for many months.[12] Some evidence indicates that co-supplementation with vitamin A may minimize potential toxicity from D. [43] Cholecalciferol is 10 times less potent than 1,25(OH)₂D₃, and 5x less potent than 25(OH)D₃.

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