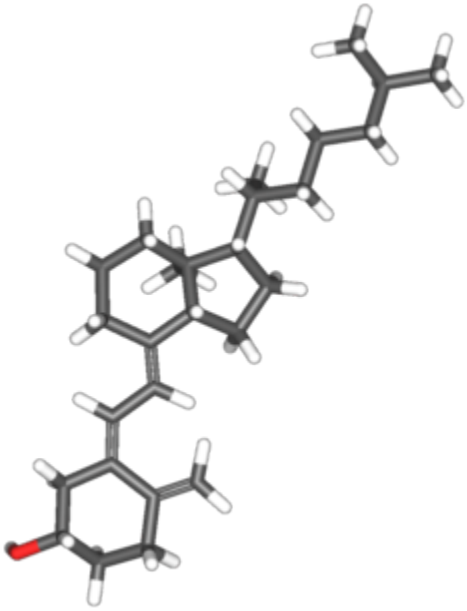
Vitamin D

Vitamin D is a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium, and phosphate, and multiple other biological effects.[1] In humans, the most important compounds in this group are vitamin D_3 (also known as cholecalciferol) and vitamin D_2 (ergocalciferol).[2]

Vitamin D

Drug class



Cholecalciferol (D_3)

Class identifiers

Synonyms

IUPAC name: (1S,3Z)-3-[(2E)-2-[(1R,3aS,7aR)-7a-methyl-1-[(2R)-6-methylheptan-2-yl]-2,3,3a,5,6,7-

	hexahydro-1H-inden-4-ylidene]ethylidene]-4-methylidenecyclohexan-1-ol
Use	Rickets, osteoporosis, vitamin D deficiency
ATC code	A11CC
Biological target	vitamin D receptor
Clinical data	
Drugs.com	MedFacts Natural Products
External links	
MeSH	D014807
In Wikidata	

The major natural source of the vitamin is synthesis of cholecalciferol in the lower layers of skin epidermis through a chemical reaction that is dependent on sun exposure (specifically UVB radiation).[3][4] Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements.[2][5][6] Only a few foods, such as the flesh of fatty fish, naturally contain significant amounts of vitamin D.[7][8] In the U.S. and other countries, cow's milk and plant-derived milk substitutes are fortified with vitamin D, as are many breakfast cereals. Mushrooms exposed to ultraviolet light contribute useful amounts of vitamin D.[7]

Dietary recommendations typically assume that all of a person's vitamin D is taken by mouth, as sun exposure in the population is variable and recommendations about the amount of sun exposure that is safe are uncertain in view of the skin cancer risk.[7]

Vitamin D from the diet, or from skin synthesis, is biologically inactive. It is activated by two protein enzyme hydroxylation steps, the first in the liver and the second in the kidneys. As vitamin D can be synthesized in adequate amounts by most mammals if exposed to sufficient sunlight, it is not essential, so

technically not a vitamin.[6] Instead it can be considered a hormone, with activation of the vitamin D pro-hormone resulting in the active form, calcitriol, which then produces effects via a nuclear receptor in multiple locations.[6]

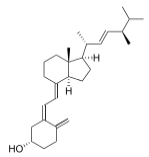
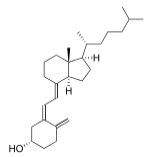
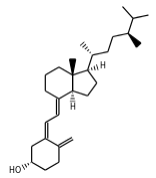
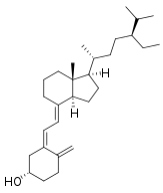
Cholecalciferol is converted in the liver to calcifediol (25-hydroxycholecalciferol); ergocalciferol is converted to 25-hydroxyergocalciferol. These two vitamin D metabolites (called 25-hydroxyvitamin D or 25(OH)D) are measured in serum to determine a person's vitamin D status.[9][10] Calcifediol is further hydroxylated by the kidneys to form calcitriol (also known as

1,25-dihydroxycholecalciferol), the biologically active form of vitamin D.[11] Calcitriol circulates as a hormone in the blood, having a major role regulating the concentration of calcium and phosphate, and promoting the healthy growth and remodeling of bone. Calcitriol also has other effects, including some on cell growth, neuromuscular and immune functions, and reduction of inflammation.[7]

Vitamin D has a significant role in calcium homeostasis and metabolism. Its discovery was due to effort to find the dietary substance lacking in children with

rickets (the childhood form of osteomalacia).[12] Vitamin D supplements are given to treat or to prevent osteomalacia and rickets. The evidence for other health effects of vitamin D supplementation in the general population is inconsistent.[13][14] The effect of vitamin D supplementation on mortality is not clear, with one meta-analysis finding a small decrease in mortality in elderly people,[15] and another concluding no clear justification exists for recommending supplementation for preventing many diseases, and that further research of similar design is not needed in these areas.[16]

Types

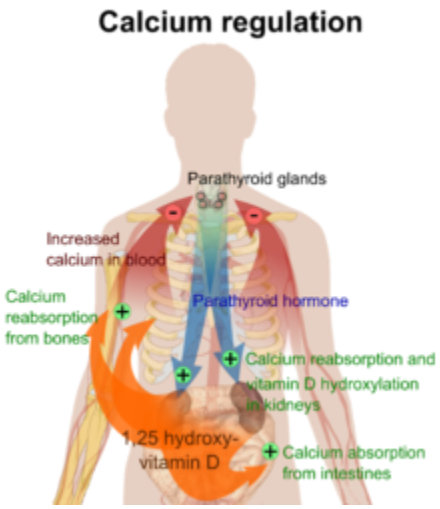
Name	Chemical composition	Structure
Vitamin D_1	Mixture of molecular compounds of ergocalciferol with lumisterol, 1:1	
Vitamin D_2	ergocalciferol (made from ergosterol)	
Vitamin D_3	cholecalciferol (made from 7-dehydrocholesterol in the skin).	
Vitamin D_4	22-dihydroergocalciferol	
Vitamin D_5	sitocalciferol (made from 7-dehydrositosterol)	

Several forms (vitamers) of vitamin D exist. The two major forms are vitamin D_2 or ergocalciferol, and vitamin D_3 or cholecalciferol; vitamin D without a subscript refers to either D_2 or D_3 or both. These are known collectively as calciferol.[17] Vitamin D_2 was chemically characterized in 1931. In 1935, the chemical structure of vitamin D_3 was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol.[18]

Chemically, the various forms of vitamin D are secosteroids, i.e., steroids in which one of the bonds in the steroid rings is

broken.[18] The structural difference between vitamin D_2 and vitamin D_3 is the side chain of D_2 contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

Biology



Calcium regulation in the human body.[19] *The role of active vitamin D (1,25-dihydroxyvitamin D, calcitriol) is shown in orange.*

The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells.[18] The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine.[20] The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by

cells in most organs, including the brain, heart, skin, gonads, prostate, and breast.

VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content.[1]

One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining

calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body.[21] Thus, vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption.[21]

The VDR regulates cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed

in several white blood cells, including monocytes and activated T and B cells.[22] In vitro, vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells, and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione.[23]

Vitamin D receptor expression decreases with age and findings suggest that vitamin D is directly related to muscle strength, mass and function, all being important factors to an athlete's performance.[24]

Deficiency

An estimated one billion people worldwide are either vitamin D insufficient or deficient.[24] A diet with insufficient vitamin D in conjunction with inadequate sun exposure causes vitamin D deficiency. Severe vitamin D deficiency in children causes rickets, a softening and weakening of bones, which is a rare disease in the developed world.[25] Vitamin D deficiency is found worldwide in the elderly and remains common in children and adults.[26][27][28] Deficiency results in impaired bone mineralization and bone damage which leads to bone-softening diseases,[29] including rickets in children and osteomalacia in adults. Low blood

calcifediol (25-hydroxy-vitamin D) can result from avoiding the sun.[30] Being deficient in vitamin D can cause intestinal absorption of dietary calcium to fall to 15%.[1] When not deficient, an individual usually absorbs between 60-80%.[1]

Bone health

Rickets

Rickets, a childhood disease, is characterized by impeded growth and soft, weak, deformed long bones that bend and bow under their weight as children start to walk. Rickets typically appears between 3

and 18 months of age.[31] Cases continue to be reported in North American and other Western Countries and is primarily seen in breastfed infants and those with darker skin complexions.[31] This condition is characterized by bow legs,[29] which can be caused by calcium or phosphorus deficiency, as well as a lack of vitamin D; today, it is largely found in low-income countries in Africa, Asia, or the Middle East[32] and in those with genetic disorders such as pseudovitamin D deficiency rickets.[33]

Maternal vitamin D deficiency may cause overt bone disease from before birth and

impairment of bone quality after birth.[34][35] Nutritional rickets exists in countries with intense year-round sunlight such as Nigeria and can occur without vitamin D deficiency.[36][37]

Although rickets and osteomalacia are now rare in the UK, outbreaks have happened in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing.[38] Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore

pattern characterized by high intakes of meat, fish, and eggs, and low intakes of high-extraction cereals.[39][40][41] The dietary risk factors for rickets include abstaining from animal foods.[38][42]

Vitamin D deficiency remains the main cause of rickets among young infants in most countries because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate sun exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh, where rickets occurs among older toddlers and children, it has been attributed to low dietary calcium intakes, which are

characteristic of cereal-based diets with limited access to dairy products.[41]

Rickets was formerly a major public health problem among the US population; in Denver, where ultraviolet rays are about 20% stronger than at sea level on the same latitude,[43] almost two-thirds of 500 children had mild rickets in the late 1920s.[44] An increase in the proportion of animal protein[42][45] in the 20th century American diet coupled with increased consumption of milk[46][47] fortified with relatively small quantities of vitamin D coincided with a dramatic decline in the number of rickets cases.[1] Also, in the

United States and Canada, vitamin D-fortified milk, infant vitamin supplements, and vitamin supplements have helped to eradicate the majority of cases of rickets for children with fat malabsorption conditions.[29]

Osteoporosis and osteomalacia

Osteomalacia is a disease in adults that results from vitamin D deficiency. Characteristics of this disease are softening of the bones, leading to bending of the spine, bowing of the legs, proximal muscle weakness, bone fragility, and increased risk for fractures.[48]

Osteomalacia reduces calcium absorption and increases calcium loss from bone, which increases the risk for bone fractures. Osteomalacia is usually present when 25-hydroxyvitamin D levels are less than about 10 ng/mL.[2] Although the effects of osteomalacia are thought to contribute to chronic musculoskeletal pain,[49] there is no persuasive evidence of lower vitamin D levels in chronic pain sufferers[50] or that supplementation alleviates chronic nonspecific musculoskeletal pain.[51]

Skin pigmentation

Dark-skinned people living in temperate climates have been shown to have low vitamin D levels but the significance of this is not certain.[52][53][54] Dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis.[55] Vitamin D deficiency is common in Hispanic and African-Americans in the United States, with levels dropping significantly in the winter.[56] This is due to the levels of melanin in their skin, as it acts as a natural protectant from sun exposure.[56]

Use of supplements

Supplementation with vitamin D is a reliable method for preventing or treating rickets. The effects of vitamin D supplementation on non-skeletal health are uncertain.[14][57] A 2013 review did not find any effect from supplementation on the rates of non-skeletal disease, other than a tentative decrease in mortality in the elderly.[58] Vitamin D supplements do not alter the outcomes for myocardial infarction, stroke or cerebrovascular disease, cancer, bone fractures or knee osteoarthritis.[16][59] Low vitamin D levels may result from disease rather than cause disease.[58]

A United States Institute of Medicine (IOM) report states: "Outcomes related to cancer, cardiovascular disease and hypertension, and diabetes and metabolic syndrome, falls and physical performance, immune functioning and autoimmune disorders, infections, neuropsychological functioning, and preeclampsia could not be linked reliably with calcium or vitamin D intake and were often conflicting."[60]:5 Some researchers claim the IOM was too definitive in its recommendations and made a mathematical mistake when calculating the blood level of vitamin D associated with bone health.[61] Members of the IOM panel maintain that they used a

"standard procedure for dietary recommendations" and that the report is solidly based on the data. Research on vitamin D supplements, including large-scale clinical trials, is continuing.[61]

Mortality, all-causes

Vitamin D_3 supplementation has been tentatively found to lead to a reduced risk of death in the elderly,[15][58] but the effect has not been deemed pronounced, or certain enough, to make taking supplements recommendable.[16] Other forms (vitamin D_2, alfacalcidol, and calcitriol) do not appear to have any

beneficial effects with regard to the risk of death.[15] High blood levels appear to be associated with a lower risk of death, but it is unclear if supplementation can result in this benefit.[62] Both an excess and a deficiency in vitamin D appear to cause abnormal functioning and premature aging.[63][64][65] The relationship between serum calcifediol level and all-cause mortality is parabolic.[60] Harm from vitamin D appears to occur at a lower vitamin D level in the black population than in the white population.[60]:435

Bone health

In general, no good evidence supports the commonly held belief that vitamin D supplements can help prevent osteoporosis.[16] Its general use for prevention of this disease in those without vitamin D deficiency is thus likely not needed.[66] For older people with osteoporosis, taking vitamin D with calcium may help prevent hip fractures, but it also slightly increases the risk of stomach and kidney problems.[67] Supplementation with higher doses of vitamin D, in those older than 65 years, may decrease fracture risk.[68] The effect is small or none for people living independently.[69][70] Low serum vitamin D

levels have been associated with falls, and low bone mineral density.[71] Taking extra vitamin D, however, does not appear to change the risk.[72] Athletes who are vitamin D deficient are at an increased risk of stress fractures and/or major breaks, particularly those engaging in contact sports. The greatest benefit with supplementation is seen in athletes who are deficient (25(OH)D serum levels <30 ng/mL), or severely deficient (25(OH)D serum levels <25 ng/mL). Incremental decreases in risks are observed with rising serum 25(OH)D concentrations plateauing at 50 ng/mL with no additional benefits seen in levels beyond this point.[73]

Because it found mounting evidence for a benefit to bone health, though it had not found good evidence of other benefits, the US Food and Drug Administration (FDA) has required manufacturers to declare the amount of vitamin D on nutrition facts labels, as "nutrients of public health significance", since May 2016. By a proposed deadline extension, small manufacturers with less than $10 million in annual food sales will have to comply by January 1, 2021, while larger ones have to comply by January 1, 2020.[74]

Manufacturers of single-ingredient sugars such as honey and maple syrup and certain cranberry products have until July 1, 2021, to make the changes.[74]

Cancer

Vitamin D supplements have been widely marketed for their claimed anticancer properties.[75] Associations have been shown in observational studies between low vitamin D levels and the risk of development of certain cancers.[76] It is unclear, however, if taking additional vitamin D in the diet or as supplements affects the risk of cancer. Reviews have

described the evidence as being "inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements"[60] and "not sufficiently robust to draw conclusions".[69] One 2014 review found that supplements had no significant effect on cancer risk.[16]

Another 2014 review concluded that vitamin D_3 may decrease the risk of death from cancer (one fewer death in 150 people treated over 5 years), but concerns with the quality of the data were noted.[15] Insufficient evidence exists to recommend vitamin D supplements for people with cancer, although some evidence suggests

that low vitamin D may be associated with a worse outcome for some cancers,[77] and that higher 25-hydroxy vitamin D levels at the time of diagnosis are associated with better outcomes.[78]

Cardiovascular disease

Taking vitamin D supplements does not meaningfully reduce the risk of stroke, cerebrovascular disease, cardial infarction, or ischemic heart disease.[16][79] Supplementation may have no effect on blood pressure.[80]

Immune system

Infectious diseases and COVID-19

In general, vitamin D functions to activate the innate and dampen the adaptive immune systems.[81] Deficiency has been linked to increased risk or severity of viral infections, including HIV.[82][83] Low levels of vitamin D appear to be a risk factor for tuberculosis,[84] and historically it was used as a treatment.[85]

Supplementation slightly decreases the risk and severity of acute respiratory tract infections, and also the exacerbation of asthma.[86][87] There is no evidence for

vitamin D affecting respiratory infections in children under five years of age.[88]

The COVID-19 pandemic raised concerns that vitamin D deficiency may be a risk factor for respiratory infection,[87][89][90][91] but there is only preliminary evidence of a direct association between vitamin D deficiency and COVID-19 infection.[92] One UK study found no association between previously measured vitamin D levels and the incidence of COVID-19 infection when adjustments were made for potential confounding factors, such as ethnicity.[93] Vitamin D deficiency is prevalent in many countries with the highest numbers of

COVID-19 cases and deaths, such as the United States, Spain, the UK, Italy, and Iran.[89][91] An evidence summary published by the UK NICE concluded there was nothing to support the use of vitamin D supplements for the prevention or treatment of COVID-19.[94]

According to ClinicalTrials.gov, several Phase II-IV clinical trials are underway to assess the use of vitamin D for prevention or treatment of COVID-19 infection, with most in preliminary stages and none completed, as of May 2020.[95] Most trials have the design of studying COVID-19-

infected people who are vitamin D deficient.[95]

Autoimmune diseases

Although tentative data link low levels of vitamin D to asthma, evidence to support a beneficial effect on asthmatics from supplementation is inconclusive.[96] One review found that vitamin D supplementation could reduce the need for steroids used to inhibit episode frequency in people with mild to moderate asthma, and that supplementation had no effect on day-to-day asthma symptoms.[97] In general practice, supplementation with

vitamin D is not recommended for treatment or prevention of asthma.[98]

Inflammatory bowel disease

Low levels of vitamin D are associated with two major forms of human inflammatory bowel disease (IBD): Crohn's disease and ulcerative colitis.[99] A meta-analysis of vitamin D therapy in IBD patients with vitamin D deficiency has shown that supplementation is effective at correcting vitamin D levels and is associated with improvements in scores for clinical disease activity and biochemical markers.[100]

Other conditions

Diabetes -- A systematic review of 2014 concluded that the available studies show no evidence of vitamin D3 supplementation having an effect on glucose homeostasis or diabetes prevention.[101] A review article of 2016 reported that while there is increasing evidence that vitamin D deficiency may be a risk factor for diabetes, over-all evidence regarding vitamin D levels and diabetes mellitus is contradictory, requiring further studies.[102]

Depression -- Clinical trials of vitamin D supplementation for depressive symptoms have generally been of low quality and show no overall effect, although subgroup analysis showed supplementation for participants with clinically significant depressive symptoms or depressive disorder had a moderate effect.[103]

Cognition and dementia -- A systematic review of clinical studies found an association between low vitamin D levels with cognitive impairment and a higher risk of developing Alzheimer's disease. However, lower vitamin D concentrations are also associated with poor nutrition and

spending less time outdoors. Therefore, alternative explanations for the increase in cognitive impairment exist and hence a direct causal relationship between vitamin D levels and cognition could not be established.[104]

Pregnancy -- Low levels of vitamin D in pregnancy are associated with gestational diabetes, pre-eclampsia, and small (for gestational age) infants.[105] Although taking vitamin D supplements during pregnancy raises blood levels of vitamin D in the mother at term,[106] the full extent of benefits for the mother or baby is unclear.[105][106][107] Pregnant women who

take an adequate amount of vitamin D during gestation may experience a lower risk of pre-eclampsia[108] and positive immune effects.[109] Vitamin D supplementation is also likely to reduce the risk of gestational diabetes, undersized babies[108] and of their poor rate of growth.[110] Pregnant women often do not take the recommended amount of vitamin D.[109]

Weight loss -- Though hypothesized that vitamin D supplementation may be an effective treatment for obesity apart from calorie restriction, one systematic review found no association of supplementation

with body weight or fat mass.[111] A 2016 meta-analysis found that circulating vitamin D status was improved by weight loss, indicating that fat mass may be inversely associated with blood levels of vitamin D.[112]

Allowable health claims

Governmental regulatory agencies stipulate for the food and dietary supplement industries certain health claims as allowable as statements on packaging.

European Food Safety Authority

- normal function of the immune system[113]
- normal inflammatory response[113]
- normal muscle function[113]
- reduced risk of falling in people over age 60[114]

US Food and Drug Administration (FDA)

- "Adequate calcium and vitamin D, as part of a well balanced diet, along with physical activity, may reduce the risk of osteoporosis."[115]

Health Canada

- Adequate calcium and regular exercise may help to achieve strong bones in children and adolescents and may reduce the risk of osteoporosis in older adults. An adequate intake of vitamin D is also necessary[116]

Other possible agencies with claim guidance: Japan FOSHU[117] and Australia-New Zealand.[118]

Dietary intake

Recommended levels

United States		
Age group	**RDA (IU/day)**	**(µg/day)**[60]
Infants 0–6 months	400*	10
Infants 6–12 months	400*	10
1–70 years	600	15
71+ years	800	20
Pregnant/Lactating	600	15
Age group	**Tolerable upper intake level (IU/day)**	**(µg/day)**
Infants 0–6 months	1,000	25
Infants 6–12 months	1,500	37.5
1–3 years	2,500	62.5
4–8 years	3,000	75
9+ years	4,000	100
Pregnant/lactating	4,000	100 [60]

Canada		
Age group	**RDA (IU)**	**Tolerable upper intake (IU)**[119]
Infants 0–6 months	400*	1,000
Infants 7–12 months	400*	1,500
Children 1–3 years	600	2,500
Children 4–8 years	600	3,000
Children and Adults 9–70 years	600	4,000
Adults > 70 years	800	4,000
Pregnancy & Lactation	600	4,000
Australia and New Zealand		
Age group	**Adequate Intake (μg)**	**Upper Level of Intake (μg)**[120]

Infants 0–12 months	5*	25
Children 1–18 years	5*	80
Adults 19–50 years	5*	80
Adults 51–70 years	10*	80
Adults > 70 years	15*	80
European Food Safety Authority		
Age group	**Adequate Intake (µg)**[121]	**Tolerable upper limit (µg)**[122]
Infants 0–12 months	10	25
Children 1–10 years	15	50
Children 11–17 years	15	100
Adults	15	100
Pregnancy & Lactation	15	100
* Adequate intake, no RDA/RDI yet established		

Conversion: 1 μg = 40 IU.

Various institutions have proposed different recommendations for the amount of daily intake of vitamin D. These vary according to precise definition, age, pregnancy or lactation, and the extent assumptions are made regarding skin synthesis of vitamin D.[60][119][120][121]

United States

The dietary reference intake for vitamin D issued in 2010 by the Institute of Medicine (IoM) (renamed National Academy of Medicine in 2015), superseded previous recommendations which were expressed

in terms of Adequate Intake. The recommendations were formed assuming the individual has no skin synthesis of vitamin D because of inadequate sun exposure. The reference intake for vitamin D refers to total intake from food, beverages and supplements, and assumes that calcium requirements are being met.[60]:5 The tolerable upper intake level (UL) is defined as "the highest average daily intake of a nutrient that is likely to pose no risk of adverse health effects for nearly all persons in the general population."[60]:403 Although ULs are believed to be safe, information on the long-term effects is incomplete and these

levels of intake are not recommended for long-term consumption.[60]:403:433

For U.S food and dietary supplement labeling purposes, the amount in a serving is expressed as a percent of Daily Value (%DV). For vitamin D labeling purposes, 100% of the Daily Value was 400 IU (10 µg), but on May 27, 2016, it was revised to 800 IU (20 µg) to bring it into agreement with the RDA.[123][124] Compliance with the updated labeling regulations was required by 1 January 2020, for manufacturers with $10 million or more in annual food sales, and by 1 January 2021 for manufacturers with less

than $10 million in annual food sales.[125][74][126] During the first six months following the 1 January 2020 compliance date, the FDA plans to work cooperatively with manufacturers to meet the new Nutrition Facts label requirements and will not focus on enforcement actions regarding these requirements during that time.[125] A table of the old and new adult Daily Values is provided at Reference Daily Intake.

Canada

Health Canada published recommended dietary allowances (RDA) and tolerable

upper intake levels for vitamin D in 2012[119] based on the Institute of Medicine report.[60]

Australia and New Zealand

Australia and New Zealand published nutrient reference values including guidelines for dietary vitamin D intake in 2005.[120] About a third of Australians have vitamin D deficiency.[127]

European Union

The European Food Safety Authority (EFSA) in 2016[121] reviewed the current evidence, finding the relationship between

serum 25(OH)D concentration and musculoskeletal health outcomes is widely variable. They considered that average requirements and population reference intakes values for vitamin D cannot be derived, and that a serum 25(OH)D concentration of 50 nmol/L was a suitable target value. For all people over the age of 1, including women who are pregnant or lactating, they set an adequate intake of 15 μg/day (600 IU).[121]

The EFSA reviewed safe levels of intake in 2012,[122] setting the tolerable upper limit for adults at 100 μg/day (4000 IU), a similar conclusion as the IOM.

The UK National Health Service recommends babies and young children aged six months to five years, pregnant or breastfeeding women, and sun-deprived elderly people should take daily vitamin supplements to ensure sufficient vitamin D intake.[128] In July 2016, Public Health England recommended that everyone consider taking a daily supplement containing 10 µg of vitamin D during autumn and winter because of inadequate sunlight for vitamin D synthesis.[129]

The Swedish National Food Agency recommends a daily intake of 10 µg (400 IU) of vitamin D3 for children and

adults up to 75 years, and 20 µg (800 IU) for adults 75 and older.[130]

Non-government organisations in Europe have made their own recommendations. The German Society for Nutrition recommends 20 µg.[131] The European Menopause and Andropause Society recommends postmenopausal women consume 15 µg (600 IU) until age 70, and 20 µg (800 IU) from age 71. This dose should be increased to 100 µg (4,000 IU) in some patients with very low vitamin D status or in case of co-morbid conditions.[132]

Sources

Although vitamin D is not present naturally in most foods,[2][6] it is commonly added as a fortification in manufactured foods. In some countries, staple foods are artificially fortified with vitamin D.[133]

Natural sources

In general, vitamin D_2 is found in fungi and vitamin D_3 is found in animals.[134][135] Vitamin D_2 is produced by ultraviolet irradiation of ergosterol found in many fungi. The vitamin D_2 content in mushrooms and *Cladina arbuscula*, a lichen, increase with exposure to

ultraviolet light.[136][137] This process is emulated by industrial ultraviolet lamps, concentrating vitamin D_2 levels to higher levels.[135]

The United States Department of Agriculture reports D_2 and D_3 content combined in one value.

Fungal sources

Source		µg/g	IU/g
C. arbuscula (lichen), thalli, dry[136]	**vitamin D_3**	0.67–2.04	27–82
	vitamin D_2	0.22–0.55	8.8–22
Agaricus bisporus (common mushroom): D_2 + D_3			
Portobello	Raw	0.003	0.1
	Exposed to ultraviolet light	0.112	4.46
Crimini	Raw	0.001	0.03
	Exposed to ultraviolet light	0.319	12.76

Animal sources[138]

Source	IU/g	Irregular
Cooked egg yolk	0.7	44 IU for a 61g egg
Beef liver, cooked, braised	0.5	
Fish liver oils, such as cod liver oil	100	450 IU per teaspoon (4.5 g)
Fatty fish species		
Salmon, pink, cooked, dry heat	5.2	
Mackerel, Pacific and jack, mixed species, cooked, dry heat	4.6	
Tuna, canned in oil	2.7	
Sardines, canned in oil, drained	1.9	

Food fortification

...

Manufactured foods fortified with vitamin D include some fruit juices and fruit juice drinks, meal replacement energy bars, soy protein-based beverages, certain cheese and cheese products, flour products, infant formulas, many breakfast cereals, and milk.[139][140]

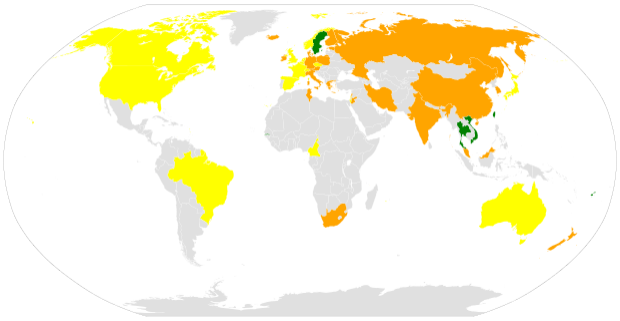
In 2016 in the United States, the Food and Drug Administration (FDA) amended food additive regulations for milk fortification,[141] stating that vitamin D_3 levels not exceed 42 IU vitamin D per 100 g (400 IU per US quart) of dairy milk, 84 IU of vitamin D_2 per 100 g (800 IU per quart) of plant milks, and 89 IU per 100 g (800 IU per quart) in plant-based yogurts or in soy beverage products.[142][143][144] Plant milks are defined as beverages made from soy, almond, rice, among other plant sources intended as alternatives to dairy milk.[145][146]

While some studies have found that vitamin D_3 raises 25(OH)D blood levels faster and remains active in the body longer,[147][148] others contend that vitamin D_2 sources are equally bioavailable and effective as D_3 for raising and sustaining 25(OH)D.[135][149][150]

Food preparation

Vitamin D content in typical foods is reduced variably by cooking. Boiled, fried and baked foods retained 69–89% of original vitamin D.[151]

Recommended serum levels



Global vitamin D serum levels among adults (nmol/L).[152][153]

- *> 75*
- *50-74*
- *25-49*

Recommendations on recommended 25(OH)D serum levels vary across authorities, and vary based on factors like age.[7] US labs generally report 25(OH)D levels in ng/mL.[154] Other countries often

use nmol/L.[154] One ng/mL is approximately equal to 2.5 nmol/L.[155]

A 2014 review concluded that the most advantageous serum levels for 25(OH)D for all outcomes appeared to be close to 30 ng/mL (75 nmol/L).[156] The optimal vitamin D levels are still controversial and another review concluded that ranges from 30 to 40 ng/mL (75 to 100 nmol/L) were to be recommended for athletes.[157] Part of the controversy is because numerous studies have found differences in serum levels of 25(OH)D between ethnic groups; studies point to genetic as well as environmental reasons behind these

variations.[158] Supplementation to achieve these standard levels could cause harmful vascular calcification.[54]

A 2012 meta-analysis showed that the risk of cardiovascular diseases increases when blood levels of vitamin D are lowest in a range of 8 to 24 ng/mL (20 to 60 nmol/L), although results among the studies analyzed were inconsistent.[159]

In 2011 an IOM committee concluded a serum 25(OH)D level of 20 ng/mL (50 nmol/L) is needed for bone and overall health. The dietary reference intakes for vitamin D are chosen with a margin of

safety and 'overshoot' the targeted serum value to ensure the specified levels of intake achieve the desired serum 25(OH)D levels in almost all persons. No contributions to serum 25(OH)D level are assumed from sun exposure and the recommendations are fully applicable to people with dark skin or negligible exposure to sunlight. The Institute found serum 25(OH)D concentrations above 30 ng/mL (75 nmol/L) are "not consistently associated with increased benefit". Serum 25(OH)D levels above 50 ng/mL (125 nmol/L) may be cause for concern. However, some people with serum 25(OH)D between 30 and 50 ng/mL

(75 nmol/L-125 nmol/L) will also have inadequate vitamin D.[60]

Excess

Vitamin D toxicity is rare.[28] It is caused by supplementing with high doses of vitamin D rather than sunlight. The threshold for vitamin D toxicity has not been established; however, according to some research, the tolerable upper intake level (UL) is 4,000 IU/day for ages 9–71[160] (100 µg/day), while other research concludes that, in healthy adults, sustained intake of more than 1250 µg/day (50,000 IU) can produce overt

toxicity after several months and can increase serum 25-hydroxyvitamin D levels to 150 ng/mL and greater.[28][161] Those with certain medical conditions, such as primary hyperparathyroidism,[162] are far more sensitive to vitamin D and develop hypercalcemia in response to any increase in vitamin D nutrition, while maternal hypercalcemia during pregnancy may increase fetal sensitivity to effects of vitamin D and lead to a syndrome of mental retardation and facial deformities.[162][163]

Idiopathic infantile hypercalcemia is caused by a mutation of the CYP24A1

gene, leading to a reduction in the degradation of vitamin D. Infants suffering from such a mutation have an increased sensitivity to vitamin D and in case of additional intake a risk of hypercalcaemia.[164][165] The disorder can continue into adulthood.[166]

A review published in 2015 noted that adverse effects have been reported only at 25(OH)D serum concentrations above 200 nmol/L.[157]

Published cases of toxicity involving hypercalcemia in which the vitamin D dose and the 25-hydroxy-vitamin D levels are

known all involve an intake of ≥40,000 IU (1,000 µg) per day.[162]

Pregnant or breastfeeding women should consult a doctor before taking a vitamin D supplement. The FDA advised manufacturers of liquid vitamin D supplements that droppers accompanying these products should be clearly and accurately marked for 400 international units (1 IU is the biological equivalent of 25 ng cholecalciferol/ergocalciferol). In addition, for products intended for infants, the FDA recommends the dropper hold no more than 400 IU.[167] For infants (birth to 12 months), the tolerable upper limit

(maximum amount that can be tolerated without harm) is set at 25 µg/day (1,000 IU). One thousand micrograms per day in infants has produced toxicity within one month.[161] After being commissioned by the Canadian and American governments, the Institute of Medicine (IOM) as of 30 November 2010, has increased the tolerable upper limit (UL) to 2,500 IU per day for ages 1–3 years, 3,000 IU per day for ages 4–8 years and 4,000 IU per day for ages 9–71+ years (including pregnant or lactating women).[160]

Calcitriol itself is auto-regulated in a negative feedback cycle, and is also affected by parathyroid hormone, fibroblast growth factor 23, cytokines, calcium, and phosphate.[168]

Effect of excess

Vitamin D overdose causes hypercalcemia, which is a strong indication of vitamin D toxicity – this can be noted with an increase in urination and thirst. If hypercalcemia is not treated, it results in excess deposits of calcium in soft tissues and organs such as the

kidneys, liver, and heart, resulting in pain and organ damage.[28][29][48]

The main symptoms of vitamin D overdose which are those of hypercalcemia including anorexia, nausea, and vomiting. These may be followed by polyuria, polydipsia, weakness, insomnia, nervousness, pruritus and ultimately kidney failure. Furthermore, proteinuria, urinary casts, azotemia, and metastatic calcification (especially in the kidneys) may develop.[161] Other symptoms of vitamin D toxicity include mental retardation in young children, abnormal bone growth and formation, diarrhea,

irritability, weight loss, and severe depression.[28][48]

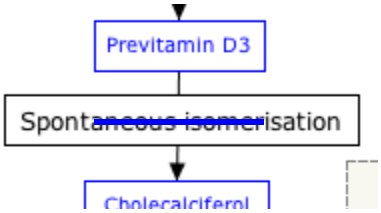
Vitamin D toxicity is treated by discontinuing vitamin D supplementation and restricting calcium intake. Kidney damage may be irreversible. Exposure to sunlight for extended periods of time does not normally cause vitamin D toxicity. The concentrations of vitamin D precursors produced in the skin reach an equilibrium, and any further vitamin D produced is degraded.[162]

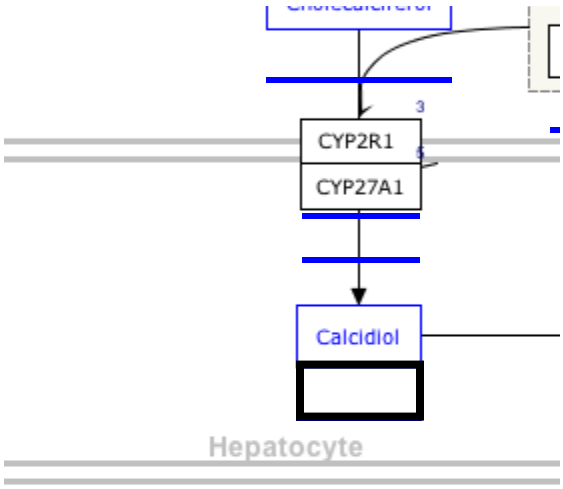
Biosynthesis

Synthesis of vitamin D in nature is dependent on the presence of UV radiation and subsequent activation in the liver and in the kidneys. Many animals synthesize vitamin D_3 from 7-dehydrocholesterol, and many fungi synthesize vitamin D_2 from ergosterol.[134][135]

Interactive pathway

Click on icon in lower right corner to open.
Click on genes, proteins and metabolites below to link to respective articles. [§ 1]



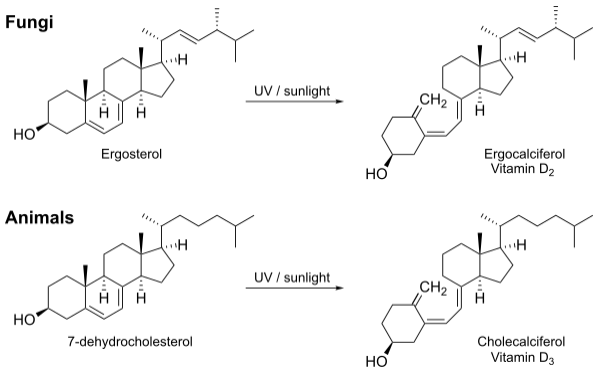


Vitamin D Synthesis Pathway (view / edit)

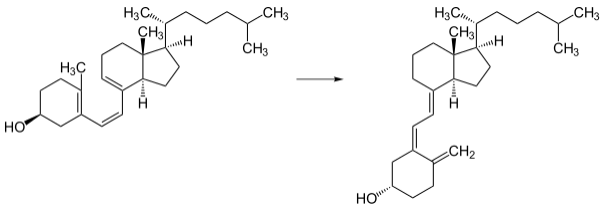
1. *The interactive pathway map can be edited at WikiPathways: "VitaminDSynthesis_WP1531" .*

Photochemistry

...



The photochemistry of vitamin D biosynthesis in animal and fungi



Thermal isomerization of previtamin D_3 to vitamin D_3

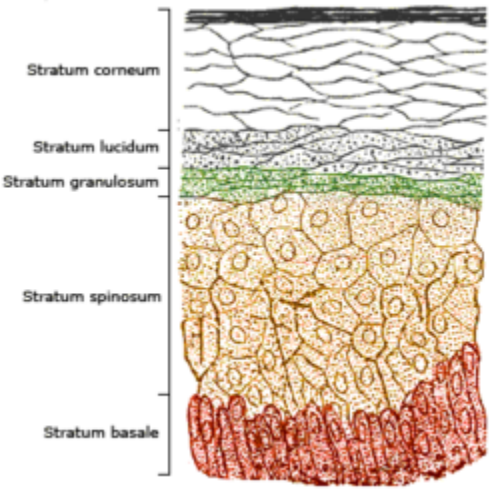
The transformation that converts 7-dehydrocholesterol to vitamin D_3 occurs in two steps.[169][170] First, 7-dehydrocholesterol is photolyzed by ultraviolet light in a 6-electron conrotatory ring-opening electrocyclic reaction; the product is previtamin D_3. Second, previtamin D_3 spontaneously isomerizes to vitamin D_3 (cholecalciferol) in an

antarafacial sigmatropic [1,7] hydride shift. At room temperature, the transformation of previtamin D_3 to vitamin D_3 in an organic solvent takes about 12 days to complete. The conversion of previtamin D_3 to vitamin D_3 in the skin is about 10 times faster than in an organic solvent.[171]

The conversion from ergosterol to vitamin D_2 follows a similar procedure, forming previtamin D_2 by photolysis, which isomerizes to vitamin D_2.[172] The transformation of previtamin D_2 to vitamin D_2 in methanol has a rate comparable to that of previtamin D_3. The process is

faster in white button mushrooms.[135](fig. 3)

Synthesis in the skin



In the epidermal strata of the skin, vitamin D production is greatest in the stratum basale (colored red in the illustration) and stratum spinosum (colored light brown).

Vitamin D_3 is produced photochemically from 7-dehydrocholesterol in the skin of most vertebrate animals, including humans.[173] The precursor of vitamin D_3, 7-dehydrocholesterol is produced in relatively large quantities. 7-Dehydrocholesterol reacts with UVB light at wavelengths of 290–315 nm.[174] These wavelengths are present in sunlight, as well as in the light emitted by the UV lamps in tanning beds (which produce ultraviolet primarily in the UVA spectrum, but typically produce 4% to 10% of the total UV emissions as UVB). Exposure to light through windows is insufficient

because glass almost completely blocks UVB light.[175][176]

Adequate amounts of vitamin D can be produced with moderate sun exposure to the face, arms and legs, averaging 5–30 minutes twice per week, or approximately 25% of the time for minimal sunburn. The darker the skin, and the weaker the sunlight, the more minutes of exposure are needed. Vitamin-D overdose is impossible from UV exposure: the skin reaches an equilibrium where the vitamin degrades as fast as it is created.[28][177][178]

Sunscreen absorbs or reflects ultraviolet light and prevents much of it from reaching the skin.[179] Sunscreen with a sun protection factor (SPF) of 8 based on the UVB spectrum decreases vitamin D synthetic capacity by 95%, and SPF 15 decreases it by 98%.[60]

The skin consists of two primary layers: the inner layer called the dermis, composed largely of connective tissue, and the outer, thinner epidermis.[180] Thick epidermis in the soles and palms consists of five strata; from outer to inner, they are: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum,

and stratum basale. Vitamin D is produced in the keratinocytes[181] of two innermost strata, the stratum basale and stratum spinosum.[179]

Evolution

Vitamin D can be synthesized only by a photochemical process. Phytoplankton in the ocean (such as coccolithophore and *Emiliania huxleyi*) have been photosynthesizing vitamin D for more than 500 million years. Primitive vertebrates in the ocean could absorb calcium from the ocean into their skeletons and eat plankton rich in vitamin D.

Land vertebrates required another source of vitamin D other than plants for their calcified skeletons. They had to either ingest it or be exposed to sunlight to photosynthesize it in their skin.[134][171] Land vertebrates have been photosynthesizing vitamin D for more than 350 million years.[182]

In birds and fur-bearing mammals, fur or feathers block UV rays from reaching the skin. Instead, vitamin D is created from oily secretions of the skin deposited onto the feathers or fur, and is obtained orally during grooming.[183] However, some animals, such as the naked mole-rat, are

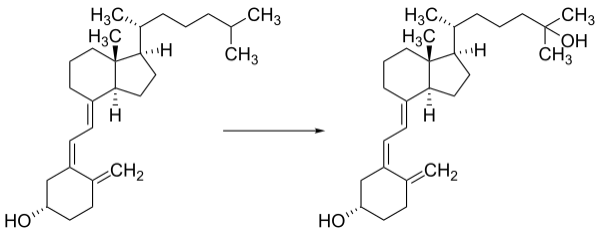
naturally cholecalciferol-deficient, as serum 25-OH vitamin D levels are undetectable.[184]

Industrial synthesis

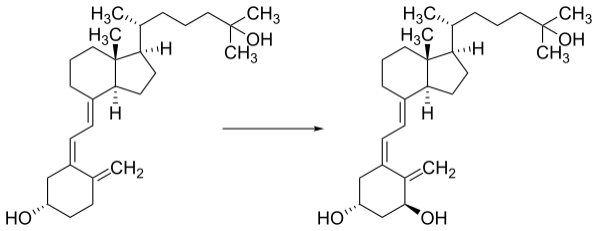
Vitamin D_3 (cholecalciferol) is produced industrially by exposing 7-dehydrocholesterol to UVB light, followed by purification.[185] The 7-dehydrocholesterol is a natural substance in fish organs, especially the liver,[186] or in wool grease (lanolin) from sheep. Vitamin D_2 (ergocalciferol) is produced in a similar way using ergosterol from yeast or mushrooms as a starting material.[185][135]

Mechanism of action

Metabolic activation



Liver hydroxylation of cholecalciferol to calcifediol



Kidney hydroxylation of calcifediol to calcitriol

Vitamin D is carried in the bloodstream to the liver, where it is converted into the

prohormone calcifediol. Circulating calcifediol may then be converted into calcitriol, the biologically active form of vitamin D, in the kidneys.[187]

Whether it is made in the skin or ingested, vitamin D is hydroxylated in the liver at position 25 (upper right of the molecule) to form 25-hydroxycholecalciferol (calcifediol or 25(OH)D).[188] This reaction is catalyzed by the microsomal enzyme vitamin D 25-hydroxylase, the product of the *CYP2R1* human gene, and expressed by hepatocytes.[189] Once made, the product is released into the plasma, where it is

bound to an α-globulin carrier protein named the vitamin D-binding protein.[190]

Calcifediol is transported to the proximal tubules of the kidneys, where it is hydroxylated at the 1-α position (lower right of the molecule) to form calcitriol (1,25-dihydroxycholecalciferol, $1,25(OH)_2D$). The conversion of calcifediol to calcitriol is catalyzed by the enzyme 25-hydroxyvitamin D_3 1-alpha-hydroxylase, which is the product of the *CYP27B1* human gene. The activity of CYP27B1 is increased by parathyroid hormone, and also by low calcium or phosphate.[6][187]

Following the final converting step in the kidney, calcitriol is released into the circulation. By binding to vitamin D-binding protein, calcitriol is transported throughout the body, including to the classical target organs of intestine, kidney and bone.[18] Calcitriol is the most potent natural ligand of the vitamin D receptor, which mediates most of the physiological actions of vitamin D.[6][187]

In addition to the kidneys, calcitriol is also synthesized by certain other cells including monocyte-macrophages in the immune system. When synthesized by monocyte-macrophages, calcitriol acts

locally as a cytokine, modulating body defenses against microbial invaders by stimulating the innate immune system.[187]

Inactivation

The activity of calcifediol and calcitriol can be reduced by hydroxylation at position 24 by vitamin D3 24-hydroxylase, forming secalciferol and calcitetrol, respectively.[188]

Difference between substrates

Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) share a similar

mechanism of action as outlined above.[188] Metabolites produced by vitamin D_2 are sometimes named with an *er-* or *ergo* prefix to differentiate them from the D_3-based counterparts.[191]

- Metabolites produced from vitamin D_2 tend to bind less well to the vitamin D-binding protein.
- Vitamin D_3 can alternatively be hydroxylated to calcifediol by sterol 27-hydroxylase (CYP27A1), but vitamin D_2 cannot.
- Ergocalciferol can be directly hydroxylated at position 24. This hydroxylation also leads to a greater

degree of inactivation: while calcitriol's activity decreases to 60% of original after 24-hydroxylation,[192] ercalcitriol suffers a 10-fold decrease in activity on conversion to ercalcitetrol.[193]

History

American researchers Elmer McCollum and Marguerite Davis in 1914[12] discovered a substance in cod liver oil which later was called "vitamin A". British doctor Edward Mellanby noticed dogs that were fed cod liver oil did not develop rickets and concluded vitamin A, or a closely associated factor, could prevent the disease. In 1922, Elmer McCollum

tested modified cod liver oil in which the vitamin A had been destroyed.[12] The modified oil cured the sick dogs, so McCollum concluded the factor in cod liver oil which cured rickets was distinct from vitamin A. He called it vitamin D because it was the fourth vitamin to be named.[194][195][196] It was not initially realized that, unlike other vitamins, vitamin D can be synthesised by humans through exposure to UV light.

In 1925,[12] it was established that when 7-dehydrocholesterol is irradiated with light, a form of a fat-soluble vitamin is produced (now known as D_3). Alfred Fabian Hess

stated: "Light equals vitamin D."[197] Adolf Windaus, at the University of Göttingen in Germany, received the Nobel Prize in Chemistry in 1928 for his work on the constitution of sterols and their connection with vitamins.[198] In 1929, a group at NIMR in Hampstead, London, were working on the structure of vitamin D, which was still unknown, as well as the structure of steroids. A meeting took place with J.B.S. Haldane, J.D. Bernal, and Dorothy Crowfoot to discuss possible structures, which contributed to bringing a team together. X-ray crystallography demonstrated the sterol molecules were flat, not as proposed by the German team

led by Windaus. In 1932, Otto Rosenheim and Harold King published a paper putting forward structures for sterols and bile acids which found immediate acceptance.[199] The informal academic collaboration between the team members Robert Benedict Bourdillon, Otto Rosenheim, Harold King, and Kenneth Callow was very productive and led to the isolation and characterization of vitamin D.[200] At this time, the policy of the Medical Research Council was not to patent discoveries, believing the results of medical research should be open to everybody. In the 1930s, Windaus clarified

further the chemical structure of vitamin D.[201]

In 1923, American biochemist Harry Steenbock at the University of Wisconsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic materials.[202] After irradiating rodent food, Steenbock discovered the rodents were cured of rickets. A vitamin D deficiency is a known cause of rickets. Using $300 of his own money, Steenbock patented his invention. His irradiation technique was used for foodstuffs, most memorably for milk. By

the expiration of his patent in 1945, rickets had been all but eliminated in the US.[203]

In 1969, after studying nuclear fragments of intestinal cells, a specific binding protein for vitamin D called the vitamin D receptor was identified by Mark Haussler and Tony Norman.[204] In 1971–72, the further metabolism of vitamin D to active forms was discovered. In the liver, vitamin D was found to be converted to calcifediol. Calcifediol is then converted by the kidneys to calcitriol, the biologically active form of vitamin D.[11] Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in

the bloodstream and promoting the healthy growth and remodeling of bone. The vitamin D metabolites, calcifediol and calcitriol, were identified by competing teams led by Michael F. Holick in the laboratory of Hector DeLuca and by Tony Norman and colleagues.[205][206][207]

Research

There is conflicting evidence about the benefits of interventions with vitamin D,[208] one view purporting an intake of 4,000–12,000 IU/day from sun exposure with concomitant serum 25-hydroxyvitamin D levels of 40 to

80 ng/mL,[209] while another view is that serum concentrations above 50 ng/mL are not plausible.[56][209]

The United States National Institutes of Health Office of Dietary Supplements established a Vitamin D Initiative in 2014 to track current research and provide education to consumers.[210] In their 2016 review, they recognize that a growing body of research suggests that vitamin D might play some role in the prevention and treatment of types 1 and 2 diabetes, glucose intolerance, hypertension, multiple sclerosis, and other medical conditions. They state further: "however, most

evidence for these roles comes from in vitro, animal, and epidemiological studies, not the randomized clinical trials considered to be more definitive. Until such trials are conducted, the implications of the available evidence for public health and patient care will be debated".[7]

Some preliminary studies link low vitamin D levels with disease later in life.[211] Evidence as of 2013 is insufficient to determine whether vitamin D affects the risk of cancer.[212] One meta-analysis found a decrease in mortality in elderly people.[15] Another meta-analysis covering over 350,000 people concluded that

vitamin D supplementation in unselected community-dwelling individuals does not reduce skeletal (total fracture) or non-skeletal outcomes (myocardial infarction, ischemic heart disease, stroke, cerebrovascular disease, cancer) by more than 15%, and that further research trials with similar design are unlikely to change these conclusions.[16] A 2019 meta-analysis found that there may be an increased risk of stroke when taking both calcium and vitamin D.[213]

Vitamin D deficiency is widespread in the European population.[214] European research is assessing vitamin D intake

levels in association with disease rates and policies of dietary recommendations, food fortification, vitamin D supplementation, and small amounts of sun exposure.[140]

Apart from VDR activation, various alternative mechanisms of action are under study, such as inhibition of signal transduction by hedgehog, a hormone involved in morphogenesis.[215]

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vitamin D generated from the oils secreted by skin into fur. Although much of the vitamin D produced within human skin is absorbed directly, birds and furbearing animals acquire most of their vitamin D orally, as they groom themselves (Bicknell and Prescott, 1946; Carpenter and Zhao, 1999). Vitamin D is generated from the oily secretions of skin into fur. The oral consumption of UV-exposed dermal excretion is the way many animals acquire the "nutrient," vitamin D. Although Fraser (1983) has argued that dermal absorption of vitamin D may be more natural, what we know

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Further reading

- NIH Vitamin D Fact Sheet for Health Professionals from the U.S. National Institutes of Health

External links

- "Vitamin D" . *Drug Information Portal*. U.S. National Library of Medicine.
- "Ergocalciferol" . *Drug Information Portal*. U.S. National Library of Medicine.
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