Vitamin D

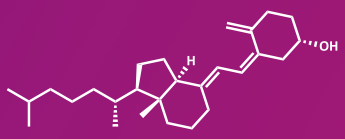
Synonyms:

'Sunshine' vitamin, antirachitic factor, cholecalciferol, ergocalciferol.

Chemistry:

Vitamin D refers to a family of structurally related compounds that display antirachitic activity. Members of the D-family are derived from the cyclopentanoperhydro- phenanthrene ring structure for steroids.

Technically, vitamin D is classified as aseco-steroid. Seco-steroids are those in which one of the rings has been broken; in vitamin D, the 9,10 carbon-carbon bond is broken.



Molecular formula of vitamin D

Food:

	(µg)/100g
Herring	25
Salmon	16
Sardines	11
Mackerel	4
Eggs	2.9
Butter	1.2
Milk (whole)	0.07

Main functions:

- Regulation of calcium and phosphate homeostasis
- Bone mineralization and teeth formation
- Cell function, proliferation and differentiation
- Modulation of the immune system
- Neurotransmitter signaling
- Muscle contraction
- Heartbeat regulation
- Reduces blood clotting

For scientific sources, please contact **info.nutritionscience@dsm.com.**

Vitamin D

Vitamin D comprises a group of fat-soluble compounds that are essential for regulating the amount of calcium and phosphate in the body i.e. the nutrients needed to keep bones, teeth and muscles healthy. It is synthesized by the skin when exposed to UV light, such as sunlight. However, it can also be found in some foods including oily fish, red meat, liver and egg yolks, as well as fortified foods and dietary supplements. If vitamin D deficiency occurs, individuals may experience rickets, a frequent childhood disease in many developing countries, or osteoporosis, also known as 'brittle bone' disease.

Functions

Following absorption or endogenous synthesis, the vitamin must be converted before it can perform its biological functions. Calciferol is transformed in the liver to 25-hydroxycholecalciferol (25(OH)D), also known as calcidiol. This is the major circulating form, which is metabolized in the kidney to the active form as required. The most important of these is 1,25-dihydroxy-cholecalciferol (1,25(OH)2D), or calcitriol, because it is the hormone responsible for most of the biological functions in the human body. The formation of 1,25(OH)2D is strictly controlled according to the body's calcium needs. The main controlling factors are the existing levels of 1,25(OH)2D itself and the blood levels of parathyroid hormone, calcium and phosphorus. As such, 1,25(OH)2D plays an important role for the proper functioning of muscles, nerves and blood clotting and for normal bone formation and mineralization.

To perform its biological functions, 1,25(OH)2D, like other hormones, binds to a specific nuclear receptor (vitamin D receptor, VDR).

Upon interaction with this receptor, 1,25(OH)2D regulates more than 250 genes in a wide variety of tissues. Vitamin D is also essential for the control of normal calcium and phosphate blood concentrations. It is required for the absorption of calcium and phosphate in the small intestine and can maintain blood calcium and phosphate concentrations through bone mobilization and increased reabsorption in the kidney.

It has also been suggested that vitamin D plays an important role in controlling cell proliferation, differentiation, immune responses and insulin secretion.

Dietary sources

Vitamin D is found only in a few foods. The richest natural sources of vitamin D are fish liver oils and salt-water fish such as sardines, herring, salmon and mackerel. Eggs, meat, milk and butter also contain small amounts, and plants are considered poor sources, with fruit and nuts containing no vitamin D at all. The amount of vitamin D in breastmilk is often insufficient to cover infant requirements, and needs to be supplemented.

Absorption and body stores

Absorption of dietary vitamin D takes place in the upper part of the small intestine with the aid of bile salts. It is stored in adipose tissue and must be metabolized to become active and carry out its biological functions.

Measurement

Vitamin D status is best determined by the plasma 25(OH) D concentration as this reflects dietary sources, as well as vitamin D production by UV light in the skin. Usual plasma 25(OH)D values are between 25 and 130 nmol/L depending on geographic location. 1 µg vitamin D is equivalent to 40 IU (international unit). Concentrations less than 25 nmol/L are considered to be deficient.

Stability

Vitamin D is relatively stable in foods. Storage, processing and cooking have little effect on its activity, although in fortified milk up to 40% of the vitamin D added may be lost as a result of exposure to light.

Physiological interactions

- Vitamin D, together with vitamin K, vitamin C, vitamin B6 and calcium are required for bone formation
- Women taking oral contraceptives have been found to have slightly elevated blood levels of 1,25(OH)D
- There is evidence to suggest that statins are also associated with elevated vitamin D concentrations
- Cholestyramine (a resin used to stop reabsorption of bile salts) and laxatives, based on mineral oil, inhibit the absorption of vitamin D from the intestine
- Orticosteroid hormones, anticonvulsant drugs and alcohol may affect the absorption of calcium by reducing the body's response to vitamin D
- Animal studies also suggest that anticonvulsant drugs stimulate enzymes in the liver, resulting in an increased breakdown and excretion of the vitamin D
- Certain anti-epileptic drugs may decrease plasma 25(OH)D levels and thus induce vitamin D insufficiency

Deficiency

Vitamin D deficiency leads to increased parathyroid hormone (PTH) levels, followed by a disturbance of the normal calcium and phosphate homeostasis. In children, unspecific symptoms such as restlessness, irritability, excessive sweating and impaired appetite may appear. Prolonged vitamin D deficiency can induce rickets, a condition that is characterized by developmental delay and skeletal abnormalities as a result of decreased calcium and phosphate availability. Rickets also results in inadequate mineralization of tooth enamel leading to tooth decay.

Among the first signs of osteomalacia, a similar condition to rickets in adults, is bone and muscle pain that can progress to muscle weakness and muscular spasms, as well as an increased risk of infection. Severe vitamin D deficiency will result in bone brittleness. Insufficient vitamin D status has also been strongly associated with osteoporosis, a condition where a loss of bone density results in weaker bones and an increased risk of falling, fractures and muscle weakness. Besides the skeletal effects, vitamin D deficiency has also been linked to a heightened risk of chronic diseases, including autoimmune diseases, heart diseases, infectious diseases and type 2 diabetes.

Groups at risk

- All ages living in a geographic location higher than 40 degrees latitude during wintertime
- Individuals with naturally darker skin
- Vegetarians and vegans
- Individuals with little or no sun exposure including:
  - Elderly individuals living in care homes
  - Individuals that avoid sun exposure for cosmetic or health reasons
  - Shift workers and coal miners
  - Individuals with protective dress code (e.g. religious or cultural)
  - Individuals with diseases or illnesses (e.g. skin cancer patients and long term hospitalized patients)
- Certain medical conditions, such as obesity or being underweight, end stage liver disease, renal disease and nutrient malabsorption syndromes (such as cystic fibrosis, coeliac disease and inflammatory bowel disease), or medications, affect vitamin D metabolism
- Infants (if breastmilk contains little vitamin D)

Reducing disease risk: therapeutic use

In the treatment of rickets, a daily dose of 40 µg (1,600 IU) vitamin D usually results in normal plasma concentrations of calcium and phosphorus within 10 days. The dose can be reduced gradually to 10 µg (400 IU) per day after one month of therapy. Vitamin D analogues (synthetic vitamin D) are commonly used in the treatment of inflammatory skin conditions such as psoriasis. Vitamin D is also discussed as a prevention factor for a number of diseases. Results from epidemiological studies and evidence from animal models suggest that the risk of several autoimmune diseases (including multiple sclerosis, insulin-dependent diabetes mellitus and rheumatoid arthritis) may be reduced through adequate vitamin D status.

It is already well-documented that vitamin D plays a major role in the prevention of osteoporosis as vitamin D insufficiency is an important contributing factor in this disease. A prospective study among 72,000 postmenopausal women over a period of 18 years, indicated that women consuming at least 15 µg/d (600IU vitamin D/day) from food and supplements had a 37% lower risk of hip fracture. Evidence from clinical trials suggest that vitamin D supplementation slows down bone mineral density loss and decreases the risk of osteoporotic fracture in men and women. Various surveys and studies indicate that poor vitamin D intake or status may be associated with an increased risk of colon, breast and prostate cancer. Recent studies have also shown that vitamin D3 is up to 87% more potent than vitamin D2, which may explain why vitamin D3 exerts stronger effects on the prevention of fractures and falls.

Hereditary vitamin D-dependent rickets (type I and II):

These rare forms of rickets occur in spite of an adequate supply of vitamin D. They are inherited illnesses in which the formation or utilization of 1,25(OH)2D is impaired.

Recommended Daily Intake (RDI)

In 1997, the Food and Nutrition Board based AI on the assumption that vitamin D is not produced by UV light in the skin. An AI of 5 µg (200 IU)/day was recommended for infants, children and adults (ages 19 – 50 years). Based on the considerable number of scientific studies that have been published since, vitamin D is now recommended at 5 µg to 15 µg (200 - 600 IU)/day for children through to adulthood. For the elderly, higher intakes of 15 µg to 20 µg (600 - 800IU)/day are also recommended to maintain normal calcium metabolism and maximize bone health, which is essential for the control of normal calcium and phosphate blood concentrations. It is required for the absorption of calcium and phosphate in the small intestine and can maintain blood calcium and phosphate concentrations through bone mobilization and increased reabsorption in the kidney.

It has also been suggested that vitamin D plays an important role in controlling cell proliferation, differentiation, immune responses and insulin secretion.

Safety

Vitamin D toxicity has only been associated with excessive supplement intake of daily doses greater than 50,000 IU of vitamin D. Hypervitaminosis D is a potentially serious problem though as it can cause permanent kidney damage, growth retardation, calcification of soft tissues and even death. Mild symptoms of intoxication include nausea, weakness, constipation and irritability.

Hypervitaminosis D is not associated with overexposure to the sun because a regulating mechanism prevents overproduction of vitamin D.

The upper intake level for vitamin D is set to 1,500 IU/day for infants, 2,500 - 3,000 IU/day for children and 4,000 IU/day for adults.

Supplements and food fortification

Mono-preparations of vitamin D and related compounds are available as tablets, capsules, oily solutions and injections. Vitamin D is also incorporated in combination with vitamin A, calcium and in multivitamins. In many countries, milk and milk products, margarine and vegetable oils fortified with vitamin D serve as a major dietary source of the vitamin.

Production

Cholecalciferol is produced commercially by the action of ultraviolet light on 7-dehydrocholesterol, which is obtained from cholesterol by various methods. Ergocalciferol is produced in a similar manner from ergosterol, which is extracted from yeast. The starting material for the production of calcitriol is the cholesterol derivative pregnenolone.

Recommended daily intakes (RDI) *

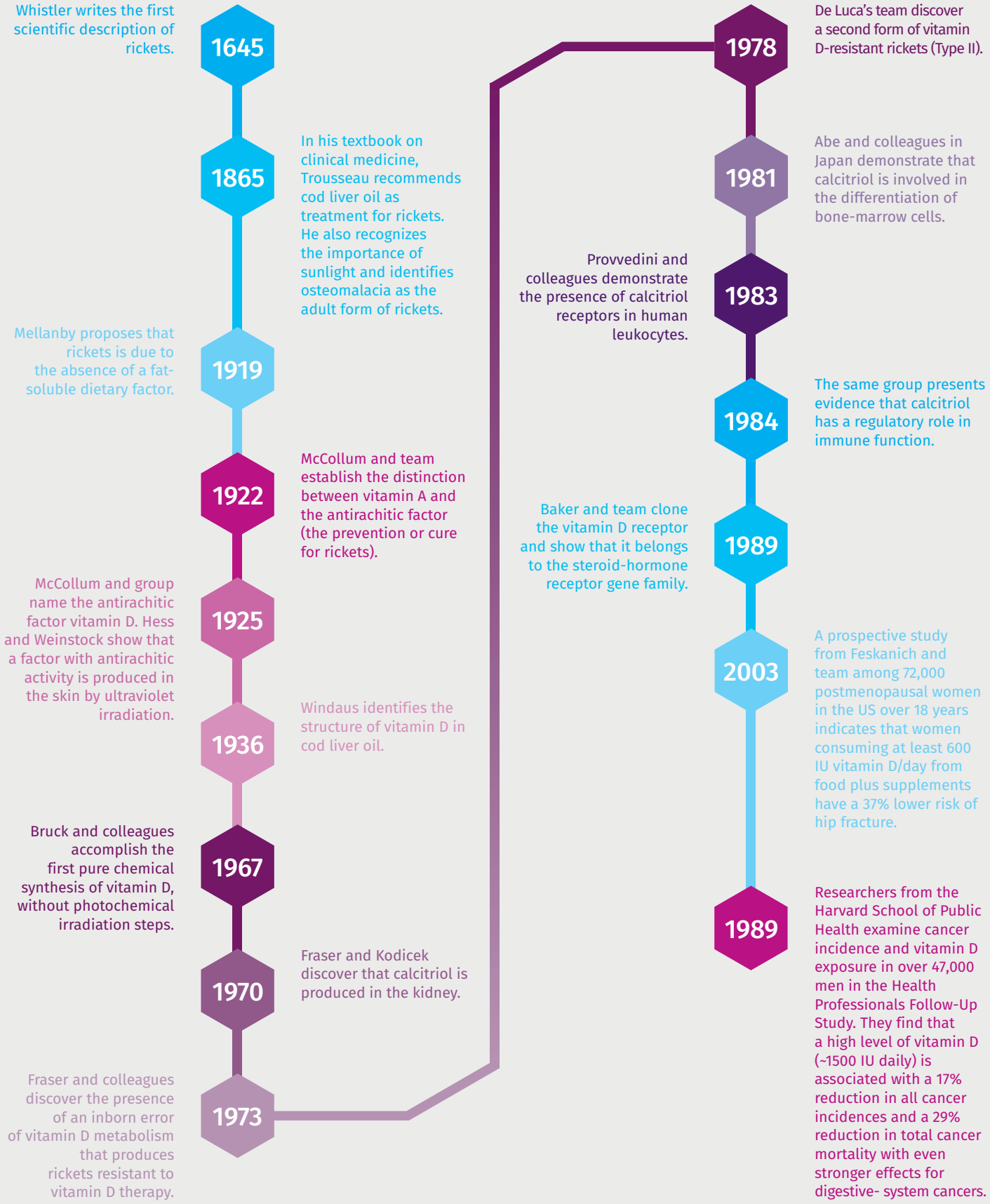
Group	Life stage	Dose/day**
Infants	0 – 12 months	400 IU (10 µg) (AI)
Children	1 – 18 years	600 IU (15 µg)
Males	19 – 50 years	600 IU (15 µg)
Females	19 – 50 years	600 IU (15 µg)
Males	51 – 70 years	600 IU (15 µg)
Females	51 – 70 years	600 IU (15 µg)
Males	>70 years	800 IU (20 µg)
Females	>70 years	800 IU (20 µg)
Pregnancy	14 – 50 years	600 IU (15 µg)
Breastfeeding	14 – 50 years	600 IU (15 µg

** European Food Safety Authority (2010)*

*** In the absence of adequate exposure to sunlight adequate intake (AI)*

If not otherwise specified, this table presents RDIs. Allowable levels of nutrients vary depending on national regulations and the final application.

History


1645
Whistler writes the first scientific description of rickets.
1865
In his textbook on clinical medicine, Trousseau recommends cod liver oil as treatment for rickets. He also recognizes the importance of sunlight and identifies osteomalacia as the adult form of rickets.
1919
Mellanby proposes that rickets is due to the absence of a fat-soluble dietary factor.
1922
McCollum and team establish the distinction between vitamin A and the antirachitic factor (the prevention or cure for rickets).
1925
McCollum and group name the antirachitic factor vitamin D. Hess and Weinstock show that a factor with antirachitic activity is produced in the skin by ultraviolet irradiation.
1936
Windaus identifies the structure of vitamin D in cod liver oil.
1967
Bruck and colleagues accomplish the first pure chemical synthesis of vitamin D, without photochemical irradiation steps.
1970
Fraser and Kodicek discover that calcitriol is produced in the kidney.
1973
Fraser and colleagues discover the presence of an inborn error of vitamin D metabolism that produces rickets resistant to vitamin D therapy.
1978
De Luca's team discover a second form of vitamin D-resistant rickets (Type II).
1981
Abe and colleagues in Japan demonstrate that calcitriol is involved in the differentiation of bone-marrow cells.
1983
Provvedini and colleagues demonstrate the presence of calcitriol receptors in human leukocytes.
1984
The same group presents evidence that calcitriol has a regulatory role in immune function.
1989
Baker and team clone the vitamin D receptor and show that it belongs to the steroid-hormone receptor gene family.
2003
A prospective study from Feskanich and team among 72,000 postmenopausal women in the US over 18 years indicates that women consuming at least 600 IU vitamin D/day from food plus supplements have a 37% lower risk of hip fracture.
1989
Researchers from the Harvard School of Public Health examine cancer incidence and vitamin D exposure in over 47,000 men in the Health Professionals Follow-Up Study. They find that a high level of vitamin D (~1500 IU daily) is associated with a 17% reduction in all cancer incidences and a 29% reduction in total cancer mortality with even stronger effects for digestive- system cancers.