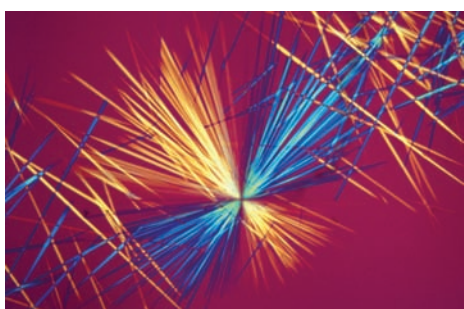


Vitamin D



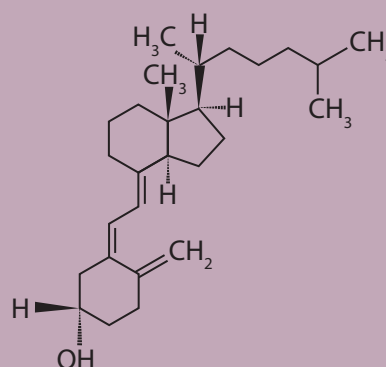
Vitamin D crystals in polarised light

Synonyms

Calciferol; antirachitic factor; "sunshine" vitamin

Chemistry

Vitamin D is a generic term and indicates a molecule of the general structure shown for rings A, B, C, and D with differing side chain structures. The A, B, C, and D ring structure is derived from the cyclopentanoperhydrophenanthrene ring structure for steroids. Technically, vitamin D is classified as a seco-steroid. Seco-steroids are those in which one of the rings has been broken; in vitamin D, the 9,10 carbon-carbon bond of ring B is broken.



Molecular formula of vitamin D₃ (cholecalciferol)

Introduction

Vitamin D is the general name given to a group of fat-soluble compounds that are essential for maintaining the mineral balance in the body. The chemical structure of vitamin D was identified in the 1930s. The main forms are vitamin D₂ (ergocalciferol: found in plants, yeasts and fungi) and vitamin D₃ (cholecalciferol: of animal origin).

As cholecalciferol is synthesised in the skin by the action of ultraviolet light on 7-dehydrocholesterol, a cholesterol derivative, vitamin D does not fit the classical definition of a vitamin. Nevertheless, because of the numerous factors that influence its synthesis, such as latitude, season, air pollution, area of skin exposed, pigmentation, age, etc., vitamin D is recognized as an essential dietary nutrient.

Functions

Following absorption or endogenous synthesis, the vitamin has to be metabolised before it can perform its biological functions. Calciferol is transformed in the liver to 25-hydroxycholecalciferol (25(OH)D, calcidiol). This is the major circulating form, which is metabolised in the kidney to the active forms as required. The most important of these is 1,25-dihydroxy-cholecalciferol (1,25(OH)₂D, calcitriol) because it is responsible for most of the biological functions. The formation of 1,25(OH)₂D, which is considered a hormone, 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 level of parathyroid hormone, calcium and phosphorus.

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 50 genes in a wide variety of tissues.

Vitamin D is essential for the control of normal calcium and phosphate blood levels. It is known to be required for the absorption of calcium and phosphate in the small intestine, their mobilisation from the bones, and their reabsorption in the kidneys. Through these three functions it plays an important role for the proper functioning of muscles, nerves and blood clotting and for normal bone formation and mineralisation.

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

Main functions in a nutshell:

- Regulation of calcium and phosphate blood levels
- Bone mineralisation
- Control of cell proliferation and differentiation
- Modulation of immune system

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. Plants are poor sources, with fruit and nuts containing no vitamin D at all. The amount of vitamin D in human milk is insufficient to cover infant needs.

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 incorporated into the chylomicron fraction and absorbed through the lymphatic system. Vitamin D is stored in adipose tissue. It has to be metabolised to become active.

Measurement

Vitamin D status is best determined by the serum 25(OH)D concentration because this reflects dietary sources as well as vitamin D production by UV light in the skin. Usual serum 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).

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.

Vitamin D content of foods

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

(Souci, Fachmann, Kraut)

Interactions

Positive interactions

Women taking oral contraceptives have been found to have slightly elevated blood levels of 1,25(OH)₂D.

Negative interactions

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. Corticosteroid hormones, anticonvulsant drugs and alcohol can affect the absorption of calcium by reducing the 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.

Deficiency

Among the first symptoms of marginal vitamin D deficiency are reduced serum levels of calcium and an increase in parathyroid hormone (PTH) production. Serum alkaline phosphatase is elevated in vitamin D deficiency states. This can be accompanied by muscle weakness and tetany, as well as an increased risk of infection. Children may show unspecific symptoms, such as restlessness, irritability, excessive sweating and impaired appetite. Marginal hypovitaminosis D may contribute to bone brittleness in the elderly. Vitamin D deficiency can also cause hearing loss.

The most widely recognised manifestations of severe vitamin D deficiency are rickets in children and osteomalacia in adults. Both are characterised by loss of mineral from the bones. This results in skeletal deformities such as bowed legs in children. The ends of the long bones in both the arms and legs are affected, and their growth may be retarded. Rickets also results in

inadequate mineralisation of tooth enamel and dentin.

Osteoporosis, a disorder of older age in which there is loss of bone, not just demineralisation, has also been associated with less obvious states of deficiency.

Groups at risk of deficiency:

- Infants who are exclusively breast fed are at high risk of vitamin D deficiency, because human milk is a poor source of vitamin D. In addition, in premature and low-birth-weight infants, liver and kidney function may be inadequate for optimal vitamin D metabolism.
- The elderly have a reduced capacity to synthesise vitamin D in the skin by exposure to sunlight.
- People with diseases affecting the liver, kidneys, the thyroid gland or fat absorption, as well as vegetarians, alcoholics and epileptics on long-term anticonvulsant therapy have a greater risk of deficiency, as do people who are house-bound.
- Dark-skinned people produce less vitamin D from sunlight and are at risk of deficiency when living far from the equator.
- Populations living at latitudes of around 40 degrees north or south are exposed to insufficient levels of sunlight to cover vitamin D requirements through endogenous production, especially during winter months.

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

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

Disease prevention and 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 are used in the treatment of psoriasis.

Vitamin D is 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 (multiple sclerosis, insulin-dependent diabetes mellitus, rheumatoid arthritis) may be decreased by adequate vitamin D intake.

Vitamin D plays an important role in the prevention of osteoporosis because vitamin D insufficiency can be an important contributing factor in this disease. A prospective study among 72,000 postmenopausal women over 18 years indicated that women consuming at least 600 IU vitamin D/day from food plus supplements had a 37% lower risk of hip fracture. Evidence from most clinical trials suggests that vitamin D supplementation slows bone density losses and decreases the risk of osteoporotic fracture in men and women.

Various surveys and studies suggest that poor vitamin D intake or status is associated with an increased risk of colon, breast and prostate cancer.

Recommended Dietary Allowance (RDA)

Establishing an RDA for vitamin D is difficult because vitamin D can be endogenously produced in the body through exposure to sunlight. Healthy people regularly exposed to the sun have no dietary requirement for vitamin D, under appropriate conditions. As this is rarely the case in temperate zones, however, a dietary supply is needed.

In 1997, the Food and Nutrition Board based adequate intake levels (AI) on the assumption that no vitamin D is produced by UV light in the skin. An AI of 5 µg (200 IU)/day is recommended for infants, children and adults (ages 19-50 years). For the elderly, higher intakes are recommended to maintain normal calcium metabolism and maximise bone health. In other countries, adult recommendations range from 2.5 µg (100 IU) to 10 µg (400 IU).

Safety

Hypervitaminosis D is a potentially serious problem as it can cause permanent kidney damage, growth retardation, calcification of soft tissues and death. Mild symptoms of intoxication are nausea, weakness, constipation and irritability. In general, the toxic dose for adults is around 1.25 mg (50,000 IU) per day. However, certain individuals have an increased sensitivity to vitamin D and present with toxic symptoms after 50 µg (2,000 IU) per day. Hypervitaminosis D is not associated with overexposure to the sun because a regulating mechanism prevents overproduction of vitamin D.

The Food and Nutrition Board (FNB) and the EU Scientific Committee on Food have set the tolerable upper intake level (UL) for vitamin D at 50 µg/day for adolescents and adults.



Supplements and food fortification

Monopreparations of vitamin D and related compounds are available as tablets, capsules, oily solutions and injections. Vitamin D is also incorporated in combinations 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.

Current recommendations in the USA

RDA*

Infants		5 µg (AI)
Children	1-18 years	5 µg (AI)
Males	19-50 years	5 µg (AI)
Females	19-50 years	5 µg (AI)
Males	51- 70 years	10 µg (AI)
Females	51-70 years	10 µg (AI)
Males	> 70 years	15 µg (AI)
Females	> 70 years	15 µg (AI)
Pregnancy		5 µg (AI)
Lactation		5 µg (AI)

*The Dietary Reference Intakes (DRIs) are actually a set of four reference values: Estimated Average Requirements (EAR), Recommended Dietary Allowances (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Levels, (UL) that have replaced the 1989 Recommended Dietary

Allowances (RDAs). The RDA was established as a nutritional norm for planning and assessing dietary intake, and represents intake levels of essential nutrients considered to meet adequately the known needs of practically all healthy people

Industrial 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. Starting material for the production of calcitriol is the cholesterol derivative pregnenolone.

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 recognises 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 coworkers establish the distinction between vitamin A and the antirachitic factor.
- 1925** McCollum and coworkers 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.
- 1937** Schenck obtains crystallised vitamin D₃ by activation of 7-dehydro-cholesterol.
- 1968** Haussler and colleagues report the presence of an active metabolite of vitamin D in the intestinal mucosa of chicks.
- 1969** Haussler and Norman discover calcitriol receptors in chick intestine.
- 1970** Fraser and Kodicek discover that calcitriol is produced in the kidney.
- 1971** Norman and coworkers identify the structure of calcitriol.
- 1973** Fraser and associates discover the presence of an inborn error of vitamin D metabolism that produces rickets resistant to vitamin D therapy.
- 1978** De Luca's group discovers 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.
- 1986** Morimoto and associates suggest that calcitriol may be useful in the treatment of psoriasis.

- 1989** Baker and associates show that the vitamin D receptor belongs to the steroid-receptor gene family.
- 1994** The U.S. Food and Drug Administration approves a vitamin D-based topical treatment for psoriasis, called calcipotriol.
- 2003** A prospective study from Feskanich and coworkers among 72,000 postmenopausal women in the U.S. over 18 years indicated that women consuming at least 600 IU vitamin D/day from food plus supplements had a 37% lower risk of hip fracture.
- 2006** Researchers from the Harvard School of Public Health examined cancer incidence and vitamin D exposure in over 47,000 men in the Health Professionals Follow-Up Study. They found that a high level of vitamin D (~1500 IU daily) was 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.



Sir Edward Mellanby



Elmer V. McCollum



Adolf Windaus