Vitamin D Contributes to the Maintenance Forms of D

Vitamin D is a hormone precursor that contributes to the maintenance of normal levels of calcium and phosphorus in the blood. Despite its name, vitamin D is not a true vitamin, but it could best be described as a *conditional* vitamin, since human skin can create it in some circumstances. Vitamin D is also known as calciferol.

Overview

Vitamin D plays an important role in the maintenance of an intact and strong skeleton. Its primary task is to regulate the amount of calcium and phosphorus in the blood by ensuring correct intake and secretion (from intestines and urine, respectively).

Several studies show that vitamin D also regulates the growth of skin cells. Psoriasis gives shell-like skin as a result of uncontrolled cell growth. A vitamin D compound is used in the treatment of this disease.

The human body produces its own vitamin D in the skin. This process is dependent on ultraviolet radiation from sunlight. However, Vitamin D should not be excluded from the diet – this is especially important for people who do not receive sufficient sunlight.

Forms of Vitamin D

- **Vitamin D_1**: molecular compound of ergocalciferol with lumisterol, 1:1
- **Vitamin D_2**: ergocalciferol or calciferol (made from ergosterol)
- **Vitamin D_3**: cholecalciferol (made from 7-dehydrocholesterol), calcidiol, and calcitriol
- **Vitamin D_4**: 22,23-dihydroergocalciferol
- **Vitamin D_5**: sitocalciferol (made from 7-dehydrositosterol)

Vitamin D_3, also known as cholecalciferol, is a form of vitamin D that is made by the human body. It is made in the skin when 7-dehydrocholesterol reacts with UVB ultraviolet light with wavelengths 290 to 315 nm. This can be found in sunlight when the sun is high enough above the horizon for UVB to penetrate the atmosphere and is responsible for the production of cholecalciferol. Up to 20,000 IU can be made in the skin only after one minimal erythemal dose of exposure, or until the skin just begins to turn pink.

Vitamin D_2 is derived by irradiating fungi to produce ergocalciferol. Ergocalciferol does not naturally occur in the human body unless it is added by supplementation. In the rat, D_2 is more effective as a vitamin than D_3, and in the squirrel monkey and the chick, D_3 is more effective[1]. In humans, D_3 is more effective than D_2 at increasing 25-hydroxyvitamin D, the circulating reservoir of the vitamin D hormone. In certain parts of the world, particularly at higher latitudes, total vitamin D input is usually not sufficient, especially in the winter, thus the recent concern about widespread vitamin D deficiency. To help prevent this, foods such as milk may be fortified with vitamin D_2 or vitamin D_3, typically giving 100 IU per glass. Cholecalciferol is transported to the liver where it is hydroxylated to calcidiol or 25-hydroxy-vitamin D, the form of the vitamin that the body stores. A blood calcidiol level is the only way to determine vitamin D deficiency; levels should be between 40 and 60 ng/mL (100 to 150 nMol/L) for optimal health. The most active form of the vitamin is calcitriol (1,25 dihydroxy vitamin D_3), a potent hormone. Calcitriol is synthesized from calcidiol in the kidneys to perform its endocrine function of maintaining the calcium economy. Calcitriol binds to a transcription factor which then regulates gene expression of transport proteins like TRPV6 and calbindin that are involved in calcium absorption in the intestine. The general result is the maintenance of calcium and phosphorus levels in the bone and blood with the assistance of parathyroid hormone and calcitonin. A number of tissues throughout the human body also have the ability to make and regulate their own calcitriol. It is these autocrine and

paracrine functions of the vitamin D system that may explain its association with a host of chronic diseases.

Vitamin D food sources

Fortified foods are the major dietary sources of vitamin D. Prior to the fortification of milk products with vitamin D in the 1930s, rickets, commonly caused by vitamin D deficiency, was a major public health problem. In the United States milk is fortified with 10 micrograms (400 IU) of vitamin D per quart, and rickets is now uncommon there.

One cup of vitamin D fortified milk supplies about one-fourth of the official estimated adequate intake of vitamin for adults older than age 50 years. Although milk is often fortified with vitamin D, dairy products made from milk (cheese, yogurt, ice cream, etc.) are generally not. Only a few foods naturally contain significant amounts of vitamin D, including:[2]

- Fish liver oils, such as cod liver oil, 1 Tbs. (15 ml), 1,360 IU (340% Daily value)
- Fatty fish, such as:
    - Salmon, cooked, 3.5 oz, 360 IU (90% DV)
    - Mackerel, cooked, 3.5 oz, 345 IU (90% DV)
    - Sardines, canned in oil, drained, 1.75 oz, 250 IU (70% DV)
    - Tuna, canned in oil, 3 oz, 200 IU (50% DV)
    - Eel, cooked, 3.5 oz, 200 IU
- One whole egg, 20 IU (6% DV)

Vitamin D is commonly measured in micrograms (mcg). However, International Units (IU) is the unit of measurement for vitamin D that appears on food labels.

Nutrition

The U.S. Dietary Reference Intake (DRI) for an Adequate Intake (AI) for a 25-year old male for Vitamin D is 5 micrograms/day (200 units/day). This rises to 15 micrograms/day (600 units/day) at 70.[3]

Diseases caused by deficiency

Vitamin D deficiency is known to cause several bone diseases, due to insufficient calcium or phosphate in the bones:

- Rickets: a childhood disease characterized by failure of growth and deformity of long bones.
- Osteoporosis: a condition characterized by fragile bones.
- Osteomalacia: a bone-thinning disorder in adults that is characterised by proximal muscle weakness and bone fragility. Osteomalacia can only occur in a mature skeleton.

Pioneering work in isolating vitamin D and determining its role in rickets was done by Edward Mellanby in 1918-1920. Vitamin D deficiency is endemic in dark skinned races living in high latitudes (see below).

Vitamin D malnutrition may possibly be linked to chronic diseases such as cancer (breast, ovarian, colon, prostate, lung and skin and probably a dozen more types), chronic pain, weakness, chronic fatigue, autoimmune diseases like multiple sclerosis and Type 1 diabetes, high blood pressure, mental illnesses (depression, seasonal affective disorder and possibly schizophrenia) heart disease, rheumatoid arthritis, psoriasis, tuberculosis, periodontal disease and inflammatory bowel disease.[4]

Who may need extra vitamin D to prevent a deficiency

Older people (age 50 and over) have a higher risk of developing vitamin D deficiency. The ability of skin to convert 7-dehydrocholesterol to pre-vitamin D_3 is decreased in older people. The kidneys, which help convert calcidiol to its active

form, sometimes do not work as well when people age. Therefore, many older people may need vitamin D supplementation.

Newborn infants who are exclusively breastfed may require vitamin D supplements. Breast milk does not contain significant levels of the vitamin, and although infants could receive this vitamin from sunlight, it is usually not recommended that small infants be exposed to sunlight in the levels required to produce a sufficient amount of vitamin D. Infant formula is generally fortified with vitamin D, so this requirement only applies to breastfed infants.

Dark-skinned people living at higher latitudes may require extra Vitamin D because their high level of skin pigmentation generally retards the absorption of UV rays. This does not pose a problem in tropical areas, where the amount of sunshine is so high that enough Vitamin D is produced despite the dark skin color. At higher latitudes, however, the decreased angle of the sun's rays, reduced daylight hours in winter, and protective clothing worn to guard against cold weather prove detrimental to the absorption of sunlight and the production of Vitamin D. Light-skinned people at higher latitudes also face these problems, but the lower amount of pigmentation in their skin allows more sunlight to be absorbed, thereby reducing the risk of Vitamin D deficiency (conversely, light-skinned people are disadvantaged in the tropics, as they are more susceptible than dark-skinned people to intense sunlight and resultant problems such as sunburn, etc.).

There is also evidence that obese people have lower levels of the circulating form of vitamin D, probably because it is deposited in body fat compartments and is less bioavailable, so obese people whose vitamin D production and/or intake is marginal or inadequate are at higher risk of deficiency.

Those who avoid or are not exposed to summer midday sunshine may also require Vitamin D supplements. In particular, recent studies have shown Australians and New Zealanders are Vitamin D deficient[5], particularly after the

successful "Slip-Slop-Slap" health campaign encouraging Australians to cover up when exposed to sunlight to prevent skin cancer. Ironically, a vitamin D deficiency may also lead to skin cancer. Still, only a few minutes of exposure (probably 6 times more in dark-skinned people) is all that is required; the production is very rapid. However, since even a few minutes of unprotected ultraviolet exposure a day increases the risk of skin cancer and causes photoaging of the skin, many dermatologists recommend supplementation of vitamin D and daily sunscreen use.

Adults taking vitamin D in vitamin pills containing 5 micrograms (200 IU) per day are not protected against vitamin D deficiency -- even though 200 IU/day is the adequate intake officially recommended up to age 50 years. Currently, the general public is advised that the safety of vitamin D intake cannot be assured beyond 50 micrograms/day (2000 IU/day). Despite a widespread recognition that current official advice to the public about vitamin D is out of date, the process for revising recommendations like the RDA has stopped, apparently for budgetary reasons. Vitamin D dietary guidelines are among the next in line for reassessment by the Food and Nutrition Board in North America.[*citation needed*]

Patients with chronic liver disease or intestinal malabsorption may require larger doses of vitamin D (up to 40,000 IU or 1 mg (1000 micrograms) daily). To maintain blood levels of calcium, therapeutic vitamin D doses are sometimes administered (up to 100,000 IU or 2.5 mg daily) to patients who have had their parathyroid glands removed (most commonly renal dialysis patients who have had tertiary hyperparathyroidism, but also patients with primary hyperparathyroidism) or who suffer with hypoparathyroidism. Long-term intake of these doses would be toxic in normal human beings.

Oral overdose of vitamin D3

The U.S. Dietary Reference Intake Tolerable Upper Intake Level (UL) for a 25-year old male for Vitamin D is 50 micrograms/day. This is equivalent to 2000 IU/day.

Overdose is extremely rare; in fact, mild deficiencies are far more common. While the sunshine-generated quantity is self-limiting, vitamin pills were thought not to be; and this has led to widespread concern, which may well be misplaced.

In practice, the human body has enormous storage capacity for vitamin D, and in any case all common foods and correctly-formulated vitamin pills contain far too little for overdose to ever occur in normal circumstances and normal doses. Indeed, Stoss therapy involves taking a dose over a thousand times the daily RDA once every few months, and even then often fails to normalise vitamin D3 levels in the body. However, oral overdose *has* been recorded due to manufacturing and industrial accidents and leads to hypercalcaemia and atherosclerosis and ultimately death.

The exact long-term safe dose is not entirely known, but intakes of up to 2000 IU (10x the RDA) are believed to be safe, and some researchers believe that 10,000 IU does not lead to long term overdose. It seems that there are chemical processes that destroy excess vitamin D, even when taken orally, although these processes have not been identified (in experiments blood levels of vitamin D do not continue to increase over many months at these doses as presumably would be needed for toxicity to occur.)

Note that although normal food and pill vitamin D concentration levels are too low to be toxic, cod-liver oil, if taken in multiples of the normal dose, could reach poisonous levels because of the high vitamin A content in cod-liver oil -- not the vitamin D.

Vitamin D in cancer prevention and recovery

Recent research suggests that cancer patients who have their surgery/treatment in the summer - and therefore get more vitamin D - have a much better chance of surviving the disease than those who have their treatment in the winter when they are exposed to less sunlight. [6]

In 2005, U.S. scientists released a study, published in the American Journal of Public Health, which seems to demonstrate a beneficial corelation between Vitamin D intake and prevention of cancer. Drawing from their review of 63 old studies, the scientists claimed that taking 1,000 international units (IU) - or 25 micrograms - of the vitamin daily could lower an individual's cancer risk by 50% in colon cancer, and by 30% in breast and ovarian cancer[7]. Cancer experts, however, say that much further research is needed to provide concrete proof about Vitamin D's ability to prevent cancer.

Human skin production of vitamin D

Vitamin D_3 is produced in the skin by conversion of 7-dehydrocholesterol by UVB. Human skin exposed to sunlight can, under the right conditions, produce quantities as large as 20,000 IU in just a few minutes without any apparent toxicity. This is easily enough to avoid deficiency and builds up the body's stores.

Exposure to sunlight also destroys vitamin D, so long term exposure to sunlight cannot cause toxicity, as levels are self-adjusting.

However merely being exposed to sunlight does not automatically mean that vitamin D is produced, only the UVB in sunlight triggers vitamin D production, but UVB mainly reaches ground level when the sun is high in the sky. This occurs a few hours around solar midday (1 pm summertime). At higher latitudes, the sun is only high enough in the sky in summer. For example, in the United States, those living north of a line from San Francisco to Philadelphia (about 40 degrees of latitude) will not be able to produce it in significant quantities for 3 to 6 months a year.

Therefore from the end of summertime to the following spring humans run on stores which gradually deplete. By some estimates 10-20% of the population become at least mildly deficient by the end of winter, and deficiency is high even in very sunny countries like India. People who never go out in the midday sun become deficient even on supplementation at 100% of the RDA.

In addition, suntan lotion blocks production. Deficiencies are now much more common in Australia, which had a very successful 'slip slop slap' campaign, though most of the deficient people have dark skin, cover up when outdoors or are confined indoors (e.g. elderly preople or those with a disability or serious illness). This campaign has also taken place in New Zealand. Melanin screens UVB light so dark skin is much less efficient at generating vitamin D. It would therefore be expected that people with darker skin would suffer from deficiencies more frequently, especially if they live at higher latitudes or have an urban lifestyle, and there is much evidence that this is the case. Vitamin D deficiency and osteomalacia are known to be endemic in dark-skinned populations in the UK (particularly those from South Asia).

Vitamin D_3 synthesis mechanism

Vitamin D_3 is synthesized from 7-dehydrocholesterol, a derivative of cholesterol, which is then photolyzed by ultraviolet light in 6-electron conrotatory electrocyclic reaction. The product is Previtamin D_3. Previtamin D_3 then spontaneously isomerizes to Vitamin D_3 in a antarafacial hydride [1,7]Sigmatropic shift Vitamin D_3 (cholecalciferol) is then hydroxylated in the liver to 25-hydroxycholecalciferol (calcidiol) and stored until it is needed. 25-hydroxycholecalciferol is further hydroxylated in the kidneys to the main biologically active form 1,25-dihydroxycholecalciferol (calcitriol) in a tightly regulated fashion. Calcitriol is represented below right (hydroxilated Carbon 1 is on the lower ring at right, hydroxylated Carbon 25 is at the upper right end).

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