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Vitamin D3 (Cholecalciferol): Metabolism, Functions, and Role in Disease

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Abstract:

Background: Vitamin D3 (cholecalciferol) is a fat-soluble vitamin essential for calcium homeostasis, bone metabolism, and various extra-skeletal functions. It is primarily synthesized in the skin under ultraviolet B (UVB) radiation and undergoes sequential hydroxylation in the liver and kidneys to form its active metabolite, calcitriol. Beyond its classical role in bone health, vitamin D3 has been implicated in multiple physiological processes including immune modulation, cellular proliferation, and cardiovascular regulation. Emerging evidence suggests its involvement in the pathogenesis and progression of several chronic diseases such as cardiovascular disorders, cancer, and osteoporosis.

Keywords: Vitamin D3; Cholecalciferol; UVB radiation; Calcium metabolism; Cardiovascular diseases; Osteoporosis; Cancer

Introduction:

Vitamin D is a fat-soluble vitamin that exists mainly in two forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is synthesized in the skin following exposure to ultraviolet B (UVB) radiation and is considered the most biologically active form in humans. It plays a crucial role in maintaining calcium and phosphorus homeostasis, which are essential for normal bone mineralization and skeletal integrity **(1)**.

After its synthesis in the skin or intake from dietary sources, vitamin D3 undergoes two successive hydroxylation steps. The first occurs in the liver, producing 25-hydroxyvitamin D, which is the main circulating form. The second hydroxylation takes place in the kidneys, resulting in the formation of the active metabolite 1,25-dihydroxyvitamin D (calcitriol). This active form binds to the vitamin D receptor (VDR), regulating gene expression involved in calcium absorption, immune response, and cellular proliferation **(2)**.

In addition to its classical role in bone metabolism, vitamin D3 has been increasingly recognized for its extra-skeletal effects. Deficiency of vitamin D has been associated with several chronic conditions, including cardiovascular diseases, cancer, and osteoporosis. Although observational studies suggest strong associations, the causal relationship and therapeutic implications of vitamin D supplementation remain subjects of ongoing research **(3)**.

1. Nature & Chemical structure:

There are various forms of vitamin D. The two major forms are vitamin D2, commonly known as ergocalciferol, and vitamin D3, also known as cholecalciferol (or calcitriol) **(4).**

Vitamin D2 is synthesized by plants and fungi, but not by vertebrates, and it probably plays a protective role against ultraviolet radiation.

2. Absorption and metabolism of vitamin D3:

Vitamin D3 is synthesized from 7- dehydrocholesterol in relatively large quantities in the skin of most vertebrate animals, including humans **(5).** Once produced by the skin (or ingested as food), it is hydrolyzed in the

liver in position 25, by the mitochondrial enzyme 25- hydroxylase, forming 25-hydroxycholecalciferol (25OHD or calcidiol) **(6).**

Calcidiol is then transported through the bloodstream to the proximal tubule of the kidney, where 1-alpha-hydroxylase is responsible for calcitriol (1,25- dihydroxycholecalciferol or 1,25OH)2D) synthesis. 1-alpha-hydroxylase levels are increased by parathyroid hormone (PTH), secreted by parathyroid gland. Thereafter, the so-formed calcitriol is released into the blood stream. Its ability to bind to a transporter protein, vitamin d binding protein (VDBP), enables it to reach other target districts **(7).**

The complex Vitamin D receptor (VDR)- retinoid X receptor (RXR)-vitamin D3 targets the DNA sequence VDRE (VDR responsive element). Furthermore, the VDR nuclear receptor is involved in many processes, such as proliferation and differentiation **(8).** Its presence was seen in many cells of the immune system, including monocytes, macrophages and activated T and B cells **(8).**

3.Vitamin D3 and UV radiation:

Part of vitamin D3 is synthesized in the skin during exposure to UV rays, especially to UV having a length of less than 320 nm. UV light is divided into UVC, UVB and UVA. UVC is the most energetic and shortest of the UV bands and causes skin burns and DNA damage. UVA, known as the "tanning ray", is primarily responsible for darkening skin pigmentation. Most tanning beds have a high-performance UVA, with a small percentage of UVB. UVA is less energetic than UVB, so exposure to UVA will not result in a burn. UVA penetrates more deeply into the skin as compared to UVB, due to its wavelength **(9).**

Vitamin D3 is produced under exposure to UVB radiation. It is sometimes called the "burning ray" because it is the primary cause of sunburn (erythema). Although UVB causes sunburn, it also induces special skin cells called melanocytes to produce melanin, which is protective against UV rays. The effects of UV rays on skin color are due to different mechanisms.

The main role of melanic pigmentation is to protect from ultraviolet radiation UVB rays are not always available throughout the day: UVB are present only during midday hours at higher latitudes and only with considerable intensity in temperate latitudes and the tropics. Sun exposure before 10:00 am and after 2:00 pm has no effect on the production of vitamin D3. After UVB stimulation, it takes about 24 hours for vitamin D to reach the maximum levels in the blood. Immediately after sun exposure, 30-60 minutes are required before vitamin D3 enters the bloodstream **(10).**

4. Dietary intake of vitamin D3:

Very few foods in nature contain vitamin D: fish flesh (such as salmon, tuna, and mackerel flesh) and fish liver oils are among the best sources **(11).**

Small amounts of vitamin D are found in beef liver, cheese and egg yolks. Some mushrooms provide vitamin D2 (ergocalciferol) in variable amounts **(12).**

Mushrooms with enhanced levels of vitamin D2 from being exposed to ultraviolet light under controlled conditions are also available.

Several food sources of vitamin D are listed in **(Figure 1).**

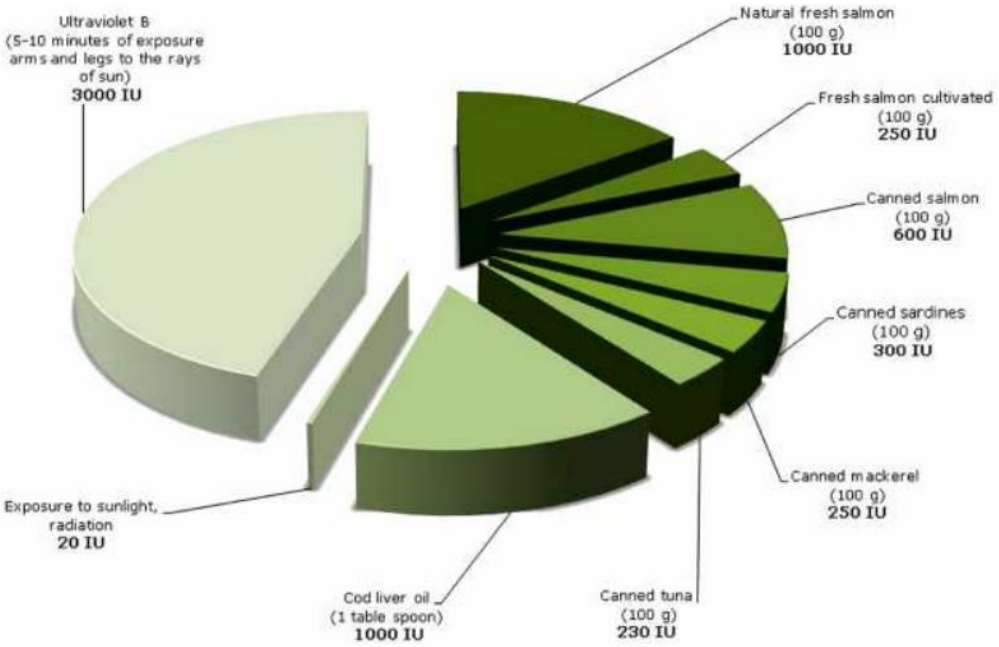

Figure 1. Foods high in vitamin D. Very few foods naturally contain vitamin D. The optimal way to intake vitamin D3 is exposure to UVB radiation. 90% of available vitamin D3 is absorbed indeed through UVB radiation and the remaining 10% comes up from dietary sources.

5. Metabolism & Function of vitamin D3:

Vitamin D3 or cholecalciferol is hydroxylated in the liver into 25-hydroxyvitamin D3 (25(OH)D) and subsequently in the kidney into 1,25-dihydroxyvitamin D3 (1,25(OH)2D), which stimulates the calcium absorption from the gut. When 1,25(OH)2D is sufficiently available, 24,25-dihydroxyvitamin D (24,25(OH)2D) is formed in the kidney, which is further catabolized. **(13).**

The vitamin D metabolites are bound in the circulation to vitamin D binding protein which has a high affinity to 25(OH)D, 24,25(OH)2D and 1,25(OH)2D and has a high homology to albumin. The active metabolite 1,25(OH)2D enters the cell and binds to the vitamin D receptor. This complex forms a heterodimer with the retinoid receptor and binds to a vitamin D responsive element on a responsive gene, such as that of osteocalcin, calcium binding protein or 24-hydroxylase **(2).** This is followed by transcription and translation and proteins are formed such as the calcium binding protein or osteocalcin. The classic effect of 1,25(OH)2D on active calcium transport occurs in the intestinal cell. Calcium enters the cell through membrane proteins. In the intestinal cell, 1,25(OH)2D binds to the vitamin D receptor and the calcium binding protein is synthesized and this regulates the active transport through the cell. The calcium is transported to the extracellular fluid by an ATP-dependent mechanism. There also is passive transport through paracellular diffusion of calcium.

6. Role of Vitamin D3 in different diseases:

6.1. Vitamin D and atherosclerosis:

Several lines of evidence suggest that vitamin D also influences vascular structure and function. Vascular smooth muscle cells and endothelial cells express 1-α-hydroxylase **(14, 15),** and activated vitamin D can, in turn, modulate the growth of both cell types **(14, 16).**

Functional changes induced by vitamin D include the activation of vasodilatory and antithrombotic gene programs. For instance, coronary vascular smooth muscle cells exposed to 1,25-OH D have reduced expression of thrombogenic genes and increased expression of fibrinolytic and vasodilatory genes **(17).**

6.2. Vitamin D and cardiovascular diseases:

Whether the consistent association of low vitamin D levels with cardiovascular events in observational studies reflects a causal relation has substantial implications. Vitamin D deficiency is extremely common, particularly in developed countries, where prevalence estimates range from one-third to one-half of adults depending on the definition **(18).**

The compelling experimental evidence linking vitamin D metabolism and cardiovascular function supports the possibility of a causal relationship. However, genetic models in animals may not faithfully reflect vitamin D deficiency in humans. Moreover, findings from observational studies of nutritional deficiencies are susceptible to residual confounding and/or reverse causality. Thus, individuals with vitamin D deficiency might be more likely to have chronic illness or underlying risk factors for future cardiovascular disease that are not readily captured by multivariable adjustment. This could be the result of functional limitations that lead to dietary alterations or reduction in outdoor activities.

Most existing randomized clinical trials of vitamin D supplementation were designed to examine skeletal endpoints, though several have included secondary ascertainment for cardiovascular events. The largest example is the Women's Health Initiative, which randomized >36,000 women to 400 IU of vitamin D3 and 1,000 mg/day of calcium carbonate versus placebo **(19).** This trial found no evidence that active supplementation reduced the risk of coronary events or stroke (HR 1.04, 95% CI 0.92–1.18).

A British trial randomized 2,686 older individuals to 100,000 IU of vitamin D every four months or placebo for fracture prevention **(20).**

In a post hoc analysis, the authors noted a nonsignificant reduction in cardiovascular mortality (relative risk 0.84, 95% CI 0.65–1.10). Other supplementation trials that have included cardiovascular events as a "safety endpoint" have not reported any significant reduction or increase in incidence, but these results are based on small numbers of events **(21, 22).**

6.3. Vitamin D and Cancer:

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast cancer and are more likely to die from cancer, as compared with people living at lower latitudes **(23).** The sunlight hypothesis (assuming that sunlight is a surrogate for vitamin D circulating levels) has been proposed to explain the higher risk for several types of cancer **(24)** including colorectal cancer (CRC) **(25),** prostate cancer (PCa) **(26)** and breast cancer (BCa) **(27).** The evidence is stronger for CRC: circulating 25OHD levels and vitamin D intake are indeed inversely associated with CRC incidence and recurrence **(28).**

6.4. Vitamin D and Osteoporosis:

Although osteoporosis is a multifactorial disease, vitamin D deficiency can be an important contributing factor. Without sufficient vitamin D levels, calcium absorption cannot be maximized and the resulting elevation in PTH secretion by the parathyroid glands results in increased bone resorption, which may lead to osteoporotic fracture. The results of most clinical trials suggest that vitamin D supplementation can slow bone density loss or decrease the risk of osteoporotic fractures in men and women who are unlikely to assume enough vitamin D **(29).**

Approximately 33% of women aged 60-70 years and 66% of those aged 80 years or older have osteoporosis **(29, 30).** Since bone loss occurs without symptoms, osteoporosis is often considered a 'silent disease'.

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