

Vitamin D in a Nutshell

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Abstract

This review comprises the synthesis, function, measurement and also the recommendations of Vitamin D and its derivatives. In light of the evidence provided by clinical trials, deficient vitamin D levels were found to be correlated with higher incidences of rickets, skeletal disorders, diabetes, obesity, cardio vascular disorders, asthma, depression, schizophrenia and immune disorders. Vitamin D supplementation which is available at low cost and with a wide therapeutic window, should be implemented to the population and should be monitored only in patients with a high risk of kidney and liver diseases, hyperparathyroidism, sarcoidosis, tuberculosis and histoplasmosis.

Keywords: Vitamin D function, Vitamin D deficiency, Vitamin D sources

Kısaca D Vitamini

Öz

Bu derleme D Vitamini ve türevlerinin sentezi, fonksiyonu, ölçümü ve önerilen D vitamin kullanım dozlarını incelemektedir. Klinik deney bulgularının ışığı altında D vitamin eksikliği raşitizm, kas-kemik bozuklukları, diyabet, obezite, kardiyovasküler bozukluklar, astım, depresyon, şizofreni ve bağışıklık sistemi bozuklukları ile alakalı bulunmuştur. D vitamini takviyeleri düşük maliyetli olup oldukça geniş bir terapötik alan etkinliğine sahip

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olduğundan toplumca kullanımı özendirilmelidir. D vitamini kullanımına bağlı gelişebilecek toksite ve yan etkilerin önüne geçilmesi için doz takibinin karaciğer ve böbrek hastalıkları açısından riskli gruplarda ve hiperparatiroidizm, sarkoidoz, tüberküloz ve histoplazmoz durumlarında yapılması etkili ve yeterlidir.

Anahtar Sözcükler: D Vitamini işlevi, D Vitamini eksikliği, D Vitamini kaynakları

Introduction

Types of Vitamin D and Their Synthesis

The fat-soluble vitamin D can be categorized into 5 subclasses (D₂-D₅) due to its structural types and sources. Though the active form found in the human body is D₃, vitamin D is generally used to describe both D₃ and D₂ in the literature. Vitamin D₅, also known as sitocalciferol, derived from 7-dehydrosterol, is the least toxic form of artificially produced form of D₃. On the other hand, D₄, also known as 22, 23-hydroergocalciferol with a methyl group in the side chain is originated from mushrooms. Vitamin D₂, also known as ergocalciferol, is a secosteroid form of cholesterol produced by algae, yeasts, plants, fungus and invertebrates. Vitamin D₂ differs from D₃ not only by the nutritional sources, but also by its structural properties as D₂ which has a double bond between C₂₂ and C₂₃ and a methyl group at C₂₄ in the side chain¹. D₂ also has a closed formula of C₂₈H₄₄O. On the other hand Vitamin D₃, which is also known as **cholecalciferol**, has a closed formula of C₂₇H₄₄O. Vitamin D₃ is derived from animal based sources such as cod liver oil, fish oil, fish roe, beef and dairy products². Aside from its nutritional diversity, D₃ has dermal synthesis from 7-dehydrocholesterol which is a derivate of cholesterol. Exposure to sunlight at the 290–315 nm UVB range, results in the high-energy photons to be absorbed in the conjugated 6,7-diene in the B-ring of ergosterol and 7-dehydrocholesterol, resulting in the ring being opened at C₉ and C₁₀ with the formation of pre vitamin D₃. From the site of synthesis in the epidermis, pre vitamin D diffuses through the blood with 85% of it carried to the liver by a specific transport protein, called vitamin D binding protein (DPB)⁴. The remaining 15% of the vitamin D is carried by albumin. Even though the mass content of vitamin D shows high affinity to

albumin, polyunsaturated fatty acid content of albumin can decrease this attraction⁵. It was also shown that differences between D_3 and D_2 in their side chains, affect their affinities in DBP binding in favor of D_3 . Thus D_2 shows a faster clearance from circulation, and a limited conversion, whereas the side chains feature an increased stability, thus altering catabolism and clearance to D_3 ⁶. In this stage, D_2 and D_3 are considered to be prohormones with no activity other than pre-vitamins. Their active forms require a 3 step enzymatic reaction⁶ that initiates in liver. The 25-hydroxylase enzyme, which is found in both microsomal and mitochondrial fractions, solely CYP27A1, is a mitochondrial enzyme, which only functions in the hydroxylation of D_3 .

CYP2R1, identified in the microsomal fraction, carries out hydroxylation and produces 25-hydroxylates of both D_2 and D_3 ¹. Prohormones of 25(OH) D_3 and 25(OH) D_2 are transported from the liver to the kidneys via circulation mainly by D vitamin Binding Protein (DBP), also known as group specific component (GC), a hepatocytes originated protein⁷ and by other lipophilic proteins such as specific globulins (ex: albumin). Even though these steroid hormones can diffuse through the cellular membrane of kidneys, receptor mediated endocytosis protein called megalin facilitates the uptaking process by reabsorbing the vitamin and its ligand from the proximal tubules surface to luminal sites^{8,9}. In the mitochondria of the epithelial cells found in proximal tubules of the liver; by the reactions of 1 α -hydroxylation or 24-hydroxylation of cytochrome P450 mixed-function oxidase enzymes, either the active form, 1,25 dehydroxycholecalciferol or relatively inactive form of the vitamin as 24, 25 dehydroxyvitamin are generated⁹.

Seasonal Changes Effects on Vitamin D Synthesis

As our knowledge of vitamin D synthesis increases, the aspects for regulating vitamin D levels vary. One method for increasing vitamin D is through sun exposure. Studies show that inadequate exposure to the sun and Vitamin D intake, can cause vitamin D insufficiency, while the conversion of 7-dehydrocholesterol to previtamin D_3 is limited to 15% in the skin. In an Australian study, it has been showed that only 3.9% of the difference in vitamin

levels depend on the latitude¹⁰. Not only the 290 to 315 nm length of the UVB, but also the zenith angle (The angle formed between the sun's rays and the horizontal surface) of the sun affect the rate of synthesis. Generally, in higher latitudes than 33° and shorter distances from the equator, less UVB reaches the cutaneous naked skin, leading to less Vitamin D synthesis. While there is no absorption for all kinds of UVB radiation through glass, it should be kept in mind that as long as UVB has no direct contact with bare and naked skin, vitamin D₃ will not be produced¹¹. Studies in the North (34 degrees N and 18 degrees N) populations, display that vitamin D synthesis occurs during 6 months of the year, from November through February^{12,13}. In Turkey, with 39°N Latitude and 35°E Longitude, research show that Vitamin D synthesis is only possible during April to November. This eight-month long illumination cannot prevent Vitamin D insufficiency. Throughout the year 59% of the population is shown to have insufficiency with a level of 13.9µ/l in general and 19.7 µ/l in the summer season. The rate reaches to 94% during the winter period¹⁴.

Measurements of Vitamin D Levels

Measurements of 25(OH) D levels are essential for clinically evaluating the disorders related to bone diseases and the health status of patients. In the early 70s, an assay measuring both the 25(OH)D₂ and 25(OH)D₃ through competitive binding of DBP was introduced by another assay technique; sialic acid chromatography¹⁵. In late 70s, High Performance Liquid Chromatography assays (HPLC) using UV absorption assay was developed¹⁶. Because eliminating the interfering lipid molecules and D vitamin derived metabolites required advanced technology, search for alternative methods continue. Even though RIA (Diasorin) which requires no pre-analytic elimination has been in use since the late 80s, HPLC assays are considered to be the gold standard. Liquid Chromatography combined with Mass spectrometry (LC-MS/MS) are also being used in reference laboratories with a trend revealing a switch in favor of LC-MS¹⁶. In a study comparing the standard deviations of the techniques of Immunoassays DiaSorin Liaison, IDS ISYS, Abbott Architect and the Siemens ADVIA Centaur suggest that both methods show accordance¹⁷.

In order to compare and validate the levels of Vitamin D₂ and D₃ pre analytical studies are also carried for sampling types, amounts, centrifugation and storage conditions. The results showed that the stability of Vitamin D was unchanged up to 4 hours at room temperature or 24 hours at 2-8° C. At lower temperatures, Vitamin D was unchanged or slightly unchanged (up to a 10% decrease in the level) being stored at -20° C for 24 hours, 7 days or at -80°C for 3 months^{18,19}.

Sources of Vitamin D

Even though the synthesis of Vitamin D is common in animals and plants, the sufficient amount contained in daily food types are limited. The main animal sources of vitamin D can be listed as; fatty fish (salmon, tuna, sardines, mackerel) and fish liver oil. In the study of Mattila et al. even though the highest content of D₃ was found in liver of beef meat, the content was not greater than 0.0–9.0 µg/kg²⁰. Following meat, dairy products such as eggs and offal can also be included, even though their content is not as high as seafood²¹. The level of Vitamin D can be elevated by exposure to UV light in plants and fungi as well. Some plants and fungi (eg. mushrooms) may include Vitamin D₂ naturally. Foods fortified with Vitamin D₃ such as dairy products, have been in use in several countries. Vitamin D supplemented foods are added voluntary in USA and United Arab Emirates or by law in Canada². When compared, nearly all milk consumed in the USA is fortified with 100IU of vitamin D per cup, whereas the fortification amount of milk in Canada is limited to 35–40 IU/100 mL. Margarine, cheese, yogurt, crema, orange juice and cereals are other samples of fortified products.

Functions and Importance of Vitamin D

Calciferol, the other name of the active 1,25 dehydroxycholecalciferol prohormone, through electro-chemical gradient regulated channels and by upregulating the expression of calcium binding proteins in the brush membrane borders of intestine, plays a role in calcium uptake. In a similar manner,

phosphorus absorption in the ileum is regulated. Vitamin D receptors, by upregulating the expression of receptor activator of nuclear factor kB ligand, (RANKL) controls the turnover rate of osteoclasts¹⁵. In the kidneys, vitamin D prevents calcium loss while in bones, up regulates calcium resorption. In the parathyroid glands, vitamin D inhibits parathyroid hormone synthesis and release, which plays a role in the prevention of rickets and osteomalacia¹. Epidemiologic evidence suggest that vitamin D and its analogs suppresses tumor development especially in the colon and breasts. Vitamin D receptors can be found in the tissues of organs such as the brain, prostate, and muscle ²¹, A lack of Vitamin D is found to correlate with cardiovascular, immune diseases, schizophrenia, obesity and diabetes²².

Vitamin D Deficiency, Prevention and Treatment

Globally, Vitamin D deficiency is currently implicated as an epidemic in both adults and pediatrics²³. According to surveys in the USA, Canada and European countries, Vitamin D deficiency occurs at a rate of 30 to 50% ²⁴. In England, one study has shown over 50% of the population has Vitamin D deficiency, of which 16% has insufficient levels. In another study in Ankara, Turkey, Vitamin D deficiency was observed in 51.8% of the population of which 20.7% were found to be insufficient²⁵. The two main causes of Vitamin D deficiency are due both to a lack of sun exposure, and inadequate intake of foods containing vitamin D. Fortified foods with vitamin D and supplements play an important role in the prevention and treatment of Vitamin D deficiency/insufficiency.

Many studies have been carried out to show Vitamin D insufficiency/ deficiency based on the metabolism of calcium and its interactions with serum parathyroid hormone (PTH) and 25 (OH) D levels. Based on the Endocrine Society Clinical Practice Guideline; vitamin D deficiency is determined as serum 25 (OH) D level of <20 ng/ml, and insufficiency to be between 21 and 29 ng/ml. Sufficient levels of 25 (OH) D is >30 ng/ml²³.

Daily Recommendation

The The daily vitamin D intake recommendations according to the Institute of Medicine (**IOM**) to prevent vitamin D deficiency are as follows: birth to 12 months, 400 IU. 1-70 years 600IU/day and 800 IU/day for age 70 and over ²³. However, recommendations from IOM are not sufficient for the Endocrine Society to evaluate serum 25(OH) D level greater than 30 ng/ml. The Endocrine Society Practice guideline recommends the following levels of daily intake for D vitamin supplementation: for the first year in infants 400-1000 IU (up to 2000 IU). Between ages 1-18, 600-1000 IU per day (up to 4000 IU). Over 18 years old, 1500-2000 IU (up to 10,000 IU). In obese individuals, those with malabsorption syndrome, individuals using glucocorticoid or antiepileptic drugs, higher Vitamin D doses may be required. In obese patients, patients with malabsorption syndrome and patients who use medications that affect vitamin D metabolism, high dose vitamin D treatment with at least 6000-10,000 IU / day and maintenance treatment at 3000-6000 IU / day is recommended.

The strategy of administering doses of 50,000 IU D twice monthly could prevent vitamin D deficiency/insufficiency without any toxic effect and recurrences, for up to 6 years.

A recently published study showed that 50,000 IU Vitamin D intake every two weeks or equivalent 3000 IU / day intake in adults, sustain blood levels of 25 (OH) D between 40 and 60 ng / mL without any toxicity ^{26,27}. In Turkey, the prevalence of nutritional rickets is found at a rate of 1.7%-19% in children, with vitamin D₃ insufficiency and as 80.2% in fertile woman. Under the prevention program, the Turkish Ministry of Health has been providing 400IU/daily dose of Vitamin D distribution to infants from birth to 12 months²⁸.

Result

Vitamin D applications are low cost and effective therapeutic agents that will be used in the prevention of rickets, obesity and in cardiovascular diseases. To avoid any possible toxicity and side effects that may occur due to the use of vitamin D supplements, it is more effective to perform dose follow-up test only in risky groups in terms of liver and kidney diseases patients of hyperparathyroidism, sarcoidosis, tuberculosis and histoplasmosis.

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