Review Article
International Journal of Basic and Clinical Studies (IJBCS)
2015; 4(1): 7-17, Turkmen S, Vehapoglu A

Vitamin D

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Abstract

Vitamin D refers to a family of compounds are secosteroid (steroids with broken ring) that are derived from cholesterol. Vitamin D can be synthesized by photochemical process. We need to expose to sunlight to photosynthesize vitamin D.It has to be activated in the liver and kidney in order to have physiological effects. It has an important role in regulating body levels of calcium, phosphorus and in mineralization of bone. Immunological activities are regulated by 1,25-(OH) D, maintaining normal cell proliferation and differentiation, signaling gene response, protein synthesis, immune response, plus, cell turnover and regeneration . Vitamin D is taken to decrease the risk for autoimmune diseases, prostate, colon and breast cancer, type 1 and 2 diabetes, cognitive dysfunction and infectious disease. Vitamin D insufficiency/deficiency is a worldwide, public health problem both in developed and developing countries.

Key words: Vitamin D, Photochemical Process, Physiological Effects.

Pathophysiology

Vitamin D is the sunshine vitamin for good reason(1). Vitamin D has two major forms of vitamin D (calsiferol): vitamin D_2 (ergocalciferol), found in plants,and vitamin D_3(cholecalciferol) found in animal tissues.A lipid soluble active vitamin D,calcitriol circulates as a hormone in the blood. Calcitriol,parathyroid hormone(PTH) which are important role in regulating body levels of calcium(Ca) and phosphorus(P).

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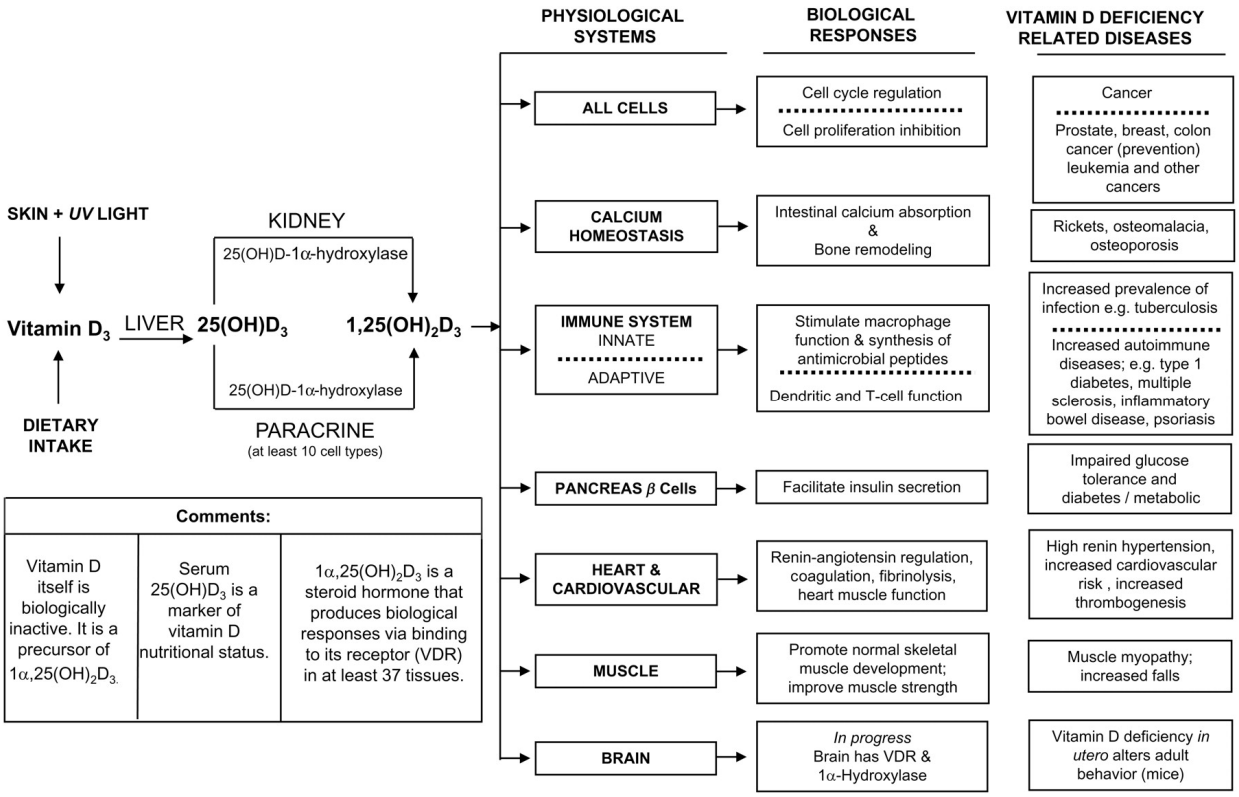

Fig Experimental Biology and Medicine

Vitamin D is an essential component of bone and mineral metabolism in both children and adults. It is required to accelerate calcium absorption in the intestine and is essential for normal growth-plate calcification and bone mineralization (2). It plays a significant role in the homeostasis of calcium and phosphorus and is vital for bone mineralization, skeletal growth, bone health. The main sources of vitamin D are sunlight, supplement, and <10% is derived from dietary sources, fatty fishes (e.g., salmon and tuna), eggs,milk , some other diary products including yogurt , some cheeses, cereals, some juices and vitamin D-fortified products.Vitamin D deficiency causes poor mineralization of the collagen matrix in young children's bones leading to growth retardation and bone deformities known as rickets (3). In adults, vitamin D deficiency induces secondary hyperparathyroidism, which causes a loss of matrix and minerals, thus increasing the risk of osteoporosis and fractures. In addition, the poor mineralization of newly laid down bone matrix in adult bone results in the painful bone disease of osteomalacia (4).

Vitamin D Metabolism

Over the last 2 decades, our understanding of vitamin D synthesis and its functions has increased markedly. The main source

of vitamin D is synthesis in the skin from 7-dihydroxycholesterol upon influence of sunlight UVB (ultraviolet B; 290–315 nm) irradiation (5).Skin pigment, sunscreen use, aging, time of day, season and latitude dramatically affect vitamin D synthesis. Vitamin D from cutaneous synthesis or dietary/supplemental intake is bound to the vitamin D binding protein and transported to the liver, where it is hydroxylated on C-25 by the cytochrome P450 enzyme (CYP2R) (6). In addition, 25-hydroxyvitamin D [25(OH)D] is the main circulating metabolite of vitamin D (Calcidiol) . In the kidneys, a second hydroxylation at the C1-position by the cytochrome P450 [25(OH)D-1α-hydroxylase; CYP27B1] occurs(7).This results in the production of 1,25-dihydroxyvitamin D [$1,25(OH)_2D_3$], the biologically active metabolite of vitamin(calcitriol) .The concentration of $1,25(OH)_2D_3$ in the blood is regulated via a feedback mechanism by $1,25(OH)_2D_3$ itself (via an induction of the 25(OH)D–24-hydroxylase; CYP24A1), as well as by parathyroid hormone, calcium, fibroblast growth factor 23, and various cytokines such as interferon γ and tumor necrosis factor α (8). The genomic action of $1,25(OH)_2D_3$ are modulated through the vitamin D receptor(VDR), transcription factor belonging to the steroid/hormone receptor family.$1,25(OH)_2$ D_3 acts by binding to the nuclear VDR cells.The VDR is broadly throughout the body. The VDR is found in the endocrine glands (pituitary, pancreas, parathyroid, gonads, and placenta) and in cardiovascular tissues such as endothelial cells, vascular smooth muscle cells, and cardiomyocytes (9). Vitamin D increases the efficiency of intestinal calcium absorption to 30-40% and phosphorus absorption to approximately 80%. Renal production of $1,25(OH)_2$ D_3 occurs in response to decreased levels of circulating calcium, which stimulates the production of parathyroid hormone. Optimal intestinal calcium absorption is necessary for the protection of bone and the prevention of osteoporosis. Ca absorption can be represented as the sum of a saturable pathway and a non-saturable pathway that is primarily dependent upon luminal Ca concentration.The absorption of calcium occurs primarily in the small intestine via an active trans-cellular process on the one hand, regulated by active vitamin D (1.25 $(OH)_2D_3$, and via para-cellular diffusion on the other hand, the latter being largely vitamin D independent (10). The active transport is a process that can become saturated and is particularly important in the event of limited calcium intake.This results in an upregulation of the production of active vitamin D.As the fractional calcium absorption is significantly determined by active vitamin D, vitamin D deficiency will also result in decreased calcium absorption (11). In conditions of vitamin D deficiency, low ionized calcium levels stimulate PTH secretion, which increases calcium reabsorption in renal tubules and increases 1α-hydroxylase activity, which causes increased $1,25(OH)_2D_3$ synthesis.Increased PTH levels cause phosphorus loss in urine. Decreased levels of phosphorus and calcium result in decreased bone mineralization (12).Vitamin D due to inadequate dietary intake, and the fact that

solar UVB is absorbed by atmospheric ozone leading to marked variation in surface intensity with latitude and time of year. The ability to synthesize vitamin D is affected by latitude, rotation of earth about the season and its own axis (day and night)- time of day(13). For high latitude locations (>35N), the data obviates the need for increased sun exposure for maintaining vitamin D sufficiency during winter. This means it is necessary to measure high latitude (>35N) vitamin D UV irradiance to understand appropriate wintertime sun exposure for high latitude populations(14).For example living in Istanbul (40°58'N latitude) essentially no vitamin D can be produced in the skin from November through February. Vitamin D production does not occur before 9 AM and ceases after 4 PM even in the summer.Atmospheric pollution attenuates solar radiation.Dress code, skin pigmentation, and application of sun protection factor (SPF) of 15 reduces the UVB penetration into epidermis by >95%, thereby limiting the production of vitamin D by the skin (15). The risk factors for vitamin D insufficiency/deficiency in the pediatric population are season, insufficient time spent outdoors, ethnicity (non-white), older age, more advanced stage of puberty, obesity, low milk consumption, low socioeconomic status(16).It has been recognized for more than 15-20 years that living at higher latitudes increases risk of developing and dying of a variety of cancers including colorectal cancer, breast cancer, prostate cancer(17,18). Women who had the most sun exposure as teenagers and young adults reduce their risk of developing breast cancer later in the life by 50-60% (19). 25(OH) D is the major circulating form of vitamin D, and its levels are the best available indicator of total body vitamin D status. The half-life of 25(OH) D is 2 to 3 weeks, much longer than that of the active metabolite, 1,25(OH) D, which has a half-life of only 4 hours (20).The definition of vitamin D deficiency has been controversial, however, most clinicians and researchers agree on the following stratifications based on the serum concentration of $25(OH)_2$ D: deficiency, <50.0 nmol/L or <20.0 ng/mL; insufficiency, 50.0-74.9 nmol/L or 20.0-29.9 ng/mL; and sufficiency, ≥75.0 nmol/L or ≥30.0 ng/mL (21,22). The European Society for Pediatric Gastroenterology, Hepatology and Nutrition has highlighted the difficulty in defining a cut-point for vitamin D deficiency but recommends 25(OH)D>50 nmol/L as indicative of sufficiency and <25 nmol/L as indicative of severe deficiency(23).

The 25(OH)D measurements of the vitamin D assays were based on $25(OH)D_2$ and $25(OH)D_3$ detection. Common Assays available for measurement of serum 25(OH) D, are immunoassay methods (CLIA,RIA and EIA methods) and liquid chromatography-based methods.Immunoassay methods also measure competitive protein-binding assays 25(OH)D (24). They generally overestimate the vitamin D level by approximately 10% to 20% (24). Tandem mass spectrometry (LC-MS/MS) have been reported as the reference standard for vitamin D assays (25).

Vitamin D deficiency

Vitamin D deficiency is risk of the world's population.More recent data from molecular experiments and epidemiological studies has provided evidence that vitamin D has a broad spectrum of actions. Vitamin D deficiency also has other serious consequences on overall health and well-being. Osteoporosis and primary hyperparathyroidism are the two most common bone and mineral disorders whose clinical expression is often influenced by the prevailing vitamin D and calcium nutritional status (26). Vitamin D deficiency affects not only musculoskeletal health but also a potentially wide range of acute and chronic diseases (27).Vitamin D deficiency causes muscle weakness, increasing the risk of falling and fractures. (28). There is mounting scientific evidence that implicates vitamin D deficiency with an increased risk of type 1 and 2 diabetes mellitus, infectious disease, autoimmune disease, multiple sclerosis, rheumatoid arthritis, asthma, cardiovascular heart disease, and many common deadly cancers, neurocognitive dysfunction and mental illness in pediatric and adults (29-31).

Vitamin D and VDR

The functions of vitamin D are characterized as genomic, mediated through the VDR transcriptional effects inside the cell nucleus, and non-genomic, when the VDR induces rapid signaling,situated on the cell membrane and/or cytoplasm 32. VDR gene polymorphisms and the risks for various breast and ovarian cancers have been reported in many epidemiological studies.A meta-analysis to assess the associations between VDR polymorphisms (Cdx-2, FokI, BsmI, ApaI, and TaqI) and the risks for reproductive cancers . Results indicate that the FokI polymorphism was related to increased risks for breast and ovarian cancers, whereas the BsmI polymorphism was associated with a decreased risk for developing cancers. A comprehensive meta-analysis indicated that the FokI and BsmI VDR gene polymorphisms may be significantly associated with gynecological cancers.(33) VDR within the muscle suggested a significant role for vitamin D in muscle tissue function. Research has suggested vitamin D to have a significant effect on muscle weakness, pain, balance, and fractures in the aging population.There are few studies to date that have examined the relationship between vitamin D status and performance, therefore, We should focus on the bodily roles of vitamin D, recommended 25(OH)D levels, vitamin D intake guidelines and risk factors for vitamin D insufficiency in athletes. (34)

Vitamin D and muscloskeletal health

Low vitamin D status has been linked to poor performance in neurocognitive testing in elderly. Vitamin D deficiency has been associated with muscle weakness, depression, Alzheimer's disease, multiple sclerosis and a lower motor neuron-induced muscle atrophy(35). Prevalence of vitamin D insufficiency/deficiency between childhood and adult-onset demyelinating disease, suggesting age at

disease onset is irrelevant to vitamin D status in demyelinating disease. Both race and obesity are independent factors associated with vitamin D insufficiency/deficiency, regardless of age of disease onset. Obesity, independent of gender, is significantly higher in children compared to adult patients diagnosed with multiple sclerosis and may have a role in the development of childhood-onset demyelinating disease(36). Does Vitamin D supplementation have a significant effect on muscle strength? Vitamin D supplementation does not have a significant effect on muscle strength in adults with baseline 25(OH)D>25 nmol/L. However, a limited number of studies demonstrated an increase in proximal muscle strength in adults with vitamin D deficiency (37) Vitamin D deficiency may be associated with an increased risk of statin-related symptomatic myalgia in statin-treated patients. Vitamin D plasma concentrations were significantly lower in patients with statin-associated myalgia compared with patients not manifesting this side effect.The meta-analysis provides evidence that ,low vitamin D levels are associated with myalgia in patients on statin therapy (38). The importance of vitamin D for musculoskeletal health has long been recognized, and awareness of significant extra-skeletal effects in health and disease is rapidly emerging. Report at least one statistically significant worse outcome in patients with low vitamin D status.(39)

Vitamin D andosteoporosis

If Vitamin D and Ca be inadequacy,It will due to concerns about ageing populations, associations with osteoporosis high prevalence. In osteoporotic populations, the prevalence of 25(OH) vitamin D concentration <12 ng/ml ranged from 12.5% to 76%, while prevalence rates reached 50% to 70% of patients with a history of fracture(s) .In post-menopausal women, the prevalence of 25(OH) vitamin D concentrations < 20 ng/ml ranged from 1.6% to 86% for community-living and institutionalized women, respectively. The most common factors associated with inadequate vitamin D levels included limited sun exposure, lack of dietary vitamin D intake, nursing home environment, wintertime, and increasing age (over 70 years). The prevalence of inadequate vitamin D levels appears to be high in post-menopausal women, especially in those with osteoporosis and history of fracture. (40)

Vitamin D and bowel disease,cancer

Low serum 25(OH) D levels have been repeatedly reported in inflammatory bowel diseases together with a relationship between vitamin D status and disease activity. . Vitamin D and VDR are known to interact with different players of the immune homeostasis by controlling cell proliferation, antigen receptor signalling, and intestinal barrier function. 1,25(OH) D is implicated in nucleotide-binding oligomerization domain proteins-NOD2-mediated expression of defensin-β2

(HBD2), the latter known to play a crucial role in the pathogenesis of Crohn's disease inflammatory bowel disease - (IBD1 gene), and several genetic variants of the VDR have been identified as Crohn's disease candidate susceptibility genes. From animal models we have learned that deletion of the VDR gene was associated with a more severe disease.(41) Vitamin D deficiency and dysfunction of VDR, also correlate with colon cancer. Moreover, leptin, a 16-kDa polypeptide, participates in the regulation of food intake and is associated with other environmental factors affecting colon cancer through the leptin receptor. Altered levels of serum leptin and patterns of expression of its receptor (LPR) may be observed in human colon tumours. In vitro and in vivo studies have indicated that consuming probiotic non-pathogenic lactic acid bacteria have beneficial effects on colon cancer. Probiotics, inflammation and vitamin D/VDR have been correlated with leptin and its receptor and are also with colon cancer.(42)

Vitamin D and metabolic syndrome

Among children and adolescents, metabolic syndrome (MetS) is more common than previously believed.Hence, any information on the relation between vitamin
D insufficiency/deficiency and insulin resistance (IR) in this population with risk of developing MetS is of great importance (43). Vitamin D deficiency risk factors of metabolic syndrome which affect cardiovascular system, increase IR and obesity, stimulate rennin-angiotensin-aldosterone system that cause hypertension. VDR expressed ubiquitously in almost all body cells such as immune, vascular and myocardial cells, pancreatic beta cells, neurons and osteoblasts suggests an involvement of vitamin D mediated effects on metabolic syndrome (44).

Vitamin D and thyroid disease

Vitamin D reduction and autoimmune thyroid disease (AITD),which includes Graves' disease and Hashimoto thyroiditis,is still controversial.AITD patients had lower levels of 25(OH)D and were more likely to be deficient in 25(OH)D (45). Graves' disease in low vitamin D status may increase the risk of Graves disease.The meta-regression found had the definite influence on heterogeneity (46).

Vitamin D and diabetes

Data from epidemiological and association studies clearly indicate a correlation between vitamin D deficiency and a higher prevalence of both forms of diabetes. In animal models,vitamin D deficiency predisposes to type 1 (T1D) and 2 diabetes, whereas high doses of vitamin D or its active hormonal form, 1,25(OH)D, prevent disease(47). In the meta-analysis serum 25(OH)D in T1D was lower than in healthy controls (48). The higher risk of nephropathy in vitamin D deficient diabetic patients had been showed in meta-analysis (49).

Vitamin D and infection diseases

Vitamin D is postulated to have antimicrobial properties, reduce inflammation, and has been implicated in respiratory health. Serum 25(OH)D has been associated with risk and severity of respiratory tract infections (50).It is more likely that low body vitamin D levels increase the risk of active tuberculosis (51) Is risk factors associated with hypovitaminosis D in adult patients infected with HIV/aids? Lower values were associated with the use of antiretroviral medication , overweight and obesity (52). A number of observational studies have found an association between low vitamin D levels and risk of sepsis.Vitamin D deficiency were associated with an increased susceptibility of sepsis(53).Vitamin D is a direct and indirect regulator of T cells. The mechanisms by which vitamin D directly regulates T cells are reviewed and new primary data on the effects of 1,25(OH)D on human invariant natural killer T cells is presented. The in vivo effects of vitamin D on murine T cells include inhibition of T cell proliferation, inhibition of IFN-γ, IL-17 and induction of IL-4.Together the data support the late effects of vitamin D on diseases like inflammatory bowel disease and multiple sclerosis where reducing IL-17 and IFN-γ, while inducing IL-4 and IL-10, would be beneficial(54).

Vitamin D and other effects

The children with asthma and healthy children with low vitamin D levels had frequent Respiratory tract infections, leading to more emergency unit admissions and to more use of health services owing to more hospitalizations. A higher frequency of asthma attacks, more severe asthmatic episodes and greater difficulty in asthma control were observed in asthmatic children with low vitamin D levels. Evidently, that relationship being influenced by multiple factors other than vitamin D (55).Turkey receives a high level of sunlight, and vitamin D deficiency was thus thought to be unusual here; however, the reported prevalence of hypovitaminosis D is 40-65% in children and adolescents (56).Growing pains are the most common form of nonspecific, recurrent leg pains in childhood, and are frequent causes for pediatric outpatient visits. Vitamin D supplementation significantly increased the 25(OH)D levels and caused a significant reduction in pain intensity in children with growing pains. Monitoring 25(OH)D levels and, when indicated, supplementing nutritional calcium and oral vitamin D could help to resolve growing pains (57).Vitamin D may interact Kidney hormones such as renin and erythropoietin .The administration of analogues of vitamin D has been associated with an improvement of anaemia and reduction in erythrocyte-stimulating agents (ESA) requirements. Vitamin D deficiency could contribute to an inappropriately activated or unsuppressed renin-angiotensin-aldesteron system (RAS) as a mechanism for progression of Chronic Kidney Disease (CKD) and/or cardiovascular disease.Experimental data on the anti-RAS and anti-inflammatory effects treatment

with active vitamin D analogues suggest a therapeutic option particularly in proteinuric CKD patients (58). 1,25(OH)D and calcium have been shown to promote epidermal keratinocyte differentiation and prevent proliferation. These prodifferentiation and antiproliferative effects of 1,25(OH)D have led to its clinical use in the treatment of psoriasis. While the actions of calcium and the VDR signaling pathways on epidermal keratinocyte differentiation are redundant, their effects on the hair follicle are not (59). Vitamin D supplementation and depressive disorder based on meta-analysis,no significant reduction in depression was seen aftervitamin D supplementation (60).

Intoksication

Vitamin D toxicity also known as hyper vitaminosis D was previously believed to be rare. Fat soluble vitamins like Vitamin D, due to their ability to accumulate in the body, have a higher potential for toxicity than water soluble vitamins. The main clinical consequence of vitamin D toxicity is hypercalcemia. Physicians need to consider the risk of medication errors while prescribing vitamin D therapy(61).

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