

Review Article

Vitamin D Regulate the Multiple Health Outcomes: Review Update

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Abstract

Vitamin D (VD) is the oldest of all hormones has been extracted from medicinal plants several thousand years. It was documented that VD guaranteed the calcium transportation through gut from nutritional sources and had a crucial role for upkeep the bone health. The VD had a serious role for mammalian skeletal fitness. Moreover, VD has progressed into a hormone having many extra-skeletal effects by up regulating 2000 genes. In addition to VD supply has an important role in ethnic and gender differences in skin pigmentation. VD has been documented potent antioxidant, immune stimulant, as well as hepatorenal, and cardiovascular protections. In addition to the VD has a protective effect for Diabetes mellitus, obesity, respiratory failure, brain diseases and cancer, in addition to aged macular degeneration.

Keywords: Vitamin D; Function; Cancer; Antioxidant; Diabetes mellitus; Obesity; Male reproduction

Introduction

The major function of VD is to keep well bone. Most mammals get their VD prerequisites in ultraviolet contact to the skin and from nutritional source. 7-Dehydrocholesterol is the precursor of VD and has been synthesized in the skin by sun ultraviolet. It is cutaneous concentration hang on numerous environmental factors such as season variation, cloudy, time and duration of exposure [1].

Vitamin D shortage is public in the different levels of the life age, so lack of VD is familiar as one of the greatest universal public medical problem [2]. The relation between lack of VD and the augmented hazard of metabolic diseases as tumors, rheumatoid arthritis, and systemic lupus, vascular and cardiac diseases designates the rank of VD, as has a crucial rule in universal health population [3].

Structure and Synthesis of Vitamin D

The chemical construction of VD is nearly matching to cholesterol, except VD has two double bonds than cholesterol [4]. Ultraviolet solar rays, at strength (18 mc/cm²) and wave-length (290 nm to 315 nm), catalyze the 7-dehydrocholesterol into cholecalciferol (VD3) in human cutaneous tissues [5]. In a similar manner, ergosterol is utilized into ergocalciferol (VD2) in the herbal sterols [1].

Endogenously synthesized Vitamin D3 transport to the liver *via*. VD-Binding Protein (VDBP), while the dietary exogenous D2 or D3 is incorporated into micelles with bile salts and absorbed in the duodenum. VD2 and VD3 carried out in lymph through chylomicrons to the hepatic tissues. VD3 is hydroxylated in hepatic tissues to 25-hydroxy-cholecalciferol by member of cytochrome

enzymes called CYP2R1. This 25-hydroxy-cholecalciferol is utilized in the renal tissues to 1-25dihydroxy-cholecalciferol; the active form of VD (calcitriol) with another cytochrome enzyme is CYP27B1 [6].

Body Metabolism of Vitamin D

The highly rich dietary sources of VD3 are milk, cheese, fresh dairy foods, fatty fish and egg yolks. While the endogenous source of VD3 is produced in cutaneous tissues from 7-dehydrocholesterol by UV solar radiation [7]. Sun block and dress have been described to stop the change of 7-dehydrocholesterol to VD3 [8]. The nutritional sources of VD3 are presented in a little quantity since the exposure of human body to satisfactory solar UV is important management to overcome VD deficiency [3]. VD3 is carried out in the circulation with VD Binding Protein (DBP) to the hepatic tissues and hydroxylated into 25-cholecalciferol (25-(OH) VD) [7].

There is a direct relation between the concentration of 25(OH) VD in blood and tissues and dietary VD3 consumption. The serum level of, 25(OH) VD3 is a mirror indicator of VD concentration in the blood and human tissues. The half-life of 25(OH) VD3 in blood is around 60 days [9]. 25(OH) VD3 is carrying out with VDBP to the renal tissues. In the renal tissues, one of the LDL receptor super family, has a crucial rule pass the in endocytic of 25(OH) D3 for further hydroxylation into 1, 25-dihydroxyvitamin D (1,25-(OH)2VD3) which is the active form of VD [3,7,10-12]. There is direct correlation between the elevation of VDBP and the blood level of 1 to 25 dihydroxyl cholecalciferol. So VDBP levels have been reported to elevate in gestation, estradiol therapy, as well as in neonates. [13].

In dissimilarity, the making 1 to 25 dihydroxyl cholecalciferol is firmly controlled, by calcium and phosphorous concentrations in the plasma and with the support of parathyroid hormone. This is documented in the rats administrated a high dose of VD3, the blood levels of 1 to 25 dihydroxyl cholecalciferol was elevated [14,15].

The active VD both 25(OH) VD3 and 1, 25(OH) 2VD3 are catabolized by 24 hydroxylase (CYP24) gene, a member of family cytochrome P450 enzymes, can hydroxylate both 25 hydroxyl cholecalciferol and 1 to 25 dihydroxyl cholecalciferol [7,8]. The VD rank is evaluated by determining the plasma concentrations of 25-OHVD3, which is correlated with skeleton health, blood total calcium

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concentrations, and parathyroid hormone production [3,11,16].

Vitamin D Serum Markers

The hypervitaminosis VD [9].

The blood concentrations of 25(OH) VD is elevated 2 to 15 times compared with controls patients with highly elevated serum calcium level and markedly decreased serum PTH. On the other hand, PTH is raised and calcium serum level is decreased in VD insufficiency patients which are a gold marker for diagnosis VD disorders.

Disorders in Vitamin D Metabolism

Severe infantile hypercalcemia has been reported in a patient with genetic defect in CYP24A1 [2,8,17]. The main source of Fibroblast Growth Factor (FGF23) is the bone. The FGF23 decreases blood phosphorous level by decreasing the phosphorous absorption in the renal tubules and gut by decreasing 1, 25-dihydroxyvitamin VD blood concentrations [18]. So, over activity of Fibroblast Growth Factor (FGF23) is recommended to be a public pathogenic pathway of reducing the blood circulating phosphorous, decrease blood level of calcitriol, and rickets/osteomalacia [12].

Sarcoidosis is disorders in patients characterized by the elevation of calcitriol and hypercalcemia as a result of the presence 1 α (OH)ase in the monocytes and macrophages [16,19]. In addition, the catabolism of the calcitriol could be reduced.

Chronic Kidney Disease (CKD) is observed with reduced The VD metabolism through different pathway [4]. The renal tissues damage and reduced the renal function result in deficient in the production 1 α (OH)ase and subsequent marked decrease in the active VD, Calcitriol [20].

Idiopathic Infantile Hypercalcemia (IIH) and Williams's syndrome are two situations related with inheritance hypercalcemia in embryonic stage [21-24].

Vitamin D Receptors

Vitamin D Receptor (VDR) is extensive distributed in different organs and tissues clarifies the pleotropic action of VD [25]. By interrelating with the VDR and Calcitriol resulted in control the function of around 2000 genes [5,26].

Vitamin D uses its action by interacting with VDR and a transcription factor which is one of nuclear hormone receptor group [11]. When stimulated, the VDR orders gene expression and excites intracellular signaling phenomena. The VDR is universally present in a varied of hepatic and renal tissues, testicular tissues including human brain [27-32]. There are extensive of VDR in the genome supportive the frequent and pleiotropic actions that have been accredited to VD [33,34].

Function of Vitamin D

The major, hormonal actions of VD in all mammals, counting humans, is related to mineral metabolism and skeletal health, as well as, to maintain blood calcium and phosphorus levels in a variety that maintain cellular metabolism, neuromuscular work, and bone ossification [15]. VD improves bowel calcium and phosphorus absorption, excites osteoclast growth and calcium deposition in the bone and endorses bone density [25]. The primary mark for the function of VD consumption for human health originated from initial studies on rickets and osteomalacia [4]. Where severe VD lack caused market skeletal deformity and hypocalcemia and classically disturbs patients with blood VD concentrations lower 8 ng/mL [35].

The dynamic active VD, control the transcription of a great number of genes by binding VDR.

Vitamin D and immune system

Primary indications VD has a significant role in innate immunity in tuberculosis patient treated with VD [19]. Also, VD has been approved to stimuli macrophages function, in controlling *Mycobacterium tuberculosis* infection [36,37]. Besides, macrophages treated with VD and *M. tuberculosis* showed a promise expression of the CYP27B1 and the VD receptor after identifying the microorganism by specific receptors, resulting in augment immune response [38,39].

Several documents studying the role of VD on immune system regulation. There is direct correlation between the presence of VDR and up regulation of T- and B cells [40-43]. Also, the active VD has been approved to regulate B cell function, counting plasma-cell generation, and upgrade the apoptosis of immunoglobulin making cells [3].

Autoimmune diseases are categorized by a dysregulation of immune response, producing auto-antigen, ultimately resulting in damage of the body organ [44]. Frequent epidemiological revisions approved the relations between VD shortage and a developed of autoimmune diseases, as, Multiple Sclerosis (MS) Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis (RA) and Inflammatory Bowel Disease (IBD) [45].

Recently, VD is promising antibacterial as well as approved to improve sensitivity to antimicrobial multidrug-resistance against infectious diseases such as tuberculosis, *H. pylori* infections [46]. Moreover, the anti-inflammatory response of VD has been investigated through down regulation the proinflammatory markers, IL-1 β , IL-6, TNF and Up regulation the anti-inflammatory cytokines, IL-10 and IL-12 [30-32,34].

Vitamin D and diabetes mellitus

Type 1 Diabetes Mellitus (T1D) typically caused by self-antigen destruction of β -cells making insulin, and frequent onset in juvenile or youth. There is suggestion that normal VD levels juvenile are a defensive aspect against the incidence of juvenile diabetes [47].

The VD encouraged intracellular Ca²⁺ signals and control insulin release from Islets β -cells [48]. Moreover, reduction the VD level is measured a risk issue for obesity and Type -II diabetes [49]. Recently, the treatment of pre-diabetic patient and had VD serum level deficiency (<12 ng/ml) with VD supplementation was reduced risk of Type II diabetes compared with control [50].

Vitamin D and obesity

VD has been documented to regulate adipocytes and regulate the obesity by enhancing different Ca²⁺ signaling pathways, and a constant elevate intracellular Ca²⁺ resulting in stimulation of the Ca²⁺ dependent molecules and preserving the standard stages of apoptosis in fatty tissue [48,51]. Recently, the obese patient showed down regulation the expression the active form of VD (CYP27B) which associated with up regulation the proinflammatory genes expression IL-1 β , IL-6 and IL-8 [52]. Additionally, numerous studies presented that blood VD concentrations are contrariwise associated with body weight, fat load or body fat percent and waist boundary [53].

Vitamin D and brain function

Schizophrenia is a debilitating neuropsychiatric disorder. It has been approved that the heredities and ecological stimuli raise the

danger for schizophrenia. VD has been labeled as a neuroactive steroid hormone complicated in brain growth and function [54]. VD₃ reportedly reduced neuronal damage induced by H₂O₂ in the ventral mesencephalic neuronal culture [55,56]. Moreover, up regulation of neurotrophic factors, has been attributed to VD induced neuro protection [57,58]. In conclusion, VD exerts its Neuro-protection *via* antioxidative actions.

The VDR is articulated in dopaminergic neurons in human and rat hippocampus and prefrontal cortex that regions implicated in schizophrenia [59,60]. In conclusion the presence of VD deficiency has a role in the expansion of neuropsychiatric disease [61,62]. Recently, concluded the expression of 25-OHVD and VD related molecules, VD receptors and VD binding proteins have a crucial role in regulation and maintained the brain function [63].

Vitamin D and cardiovascular diseases

VD insufficiency is recognized in the ageing as a possible danger influence for cardiovascular disease progress [64,65].

Study on the probable that VD has a defend role against Cardiovascular Diseases (CVD) has been studied lately [66,67]. Also VD modulates the cardiac damage procedures results from cytokines mediators and avoids plaque and thrombosis development [68,69]. Also reported that VD has a defensive outcome on blood vessels against oxidative stress damage induced by dextrose toxicity. Moreover, VD treatment has been approved to protect the myocardial ischemia and reduced the injury through the anti-inflammatory action of VD [70].

Vitamin D and antioxidant activities

Numerous investigations have revealed that VD owns an antioxidant action. VD has been established as a membrane antioxidant that reserved iron caused lipid oxidation of nervous tissues [71]. Treatment with VD₃ repressed the raised lipid oxidation detected in VD₃ lacking rats [72]. VD₃ is initiated to reduce endotoxemia through control of cellular oxidative stress [73]. Moreover, VD reduced INO saction and diminished reactive oxygen effect in rat astrocytes and keratocytes [74-76]. Furthermore, VD is documented to decrease reactive oxygen by enhancing antioxidant molecules, counting reduced glutathione, glutathione peroxidase, and catalase and superoxide dismutase in cultured liver [30-32,34,77].

Vitamin D and cancer

Greatest of epidemiological investigation concluded that continuing sun contact is linked with decreased risk of colorectal (CRC), breast, and prostate cancer [65,78-80]. Meanwhile, other studies reported that in prostate cancer and non-Hodgkin's lymphoma, no associations were found [81-83]. Moreover, it is reported that sunlight and VD is a defensive aspect for CRC, prostate, and breast cancer [84]. Several others reported are verse relation between CRC death and contact to sunlight and VD supplementation [85-89].

In vitro, active VD prevents the development of cancer melanoma tissues culture by controlling cell division, differentiation and cell death, with anti-cancer effect [90,91]. In conclusion the sunlight potentiates the VD regulating ways, and variation of the immune system, and the degradation of folic acid, as well as inhibit proliferation, induces differentiation and inhibit angiogenesis might play a role in reduced cancer [1,92,93]. Recently, several studies have been approved that the VD₃ supplementation protect and improve survival rate and reduced the incidence of relapse in cancer patients [94,95].

Vitamin D and male reproductive system

VD is recent known as a signaling molecule other than is a controller of bone fitness and calcium blood levels [30,96]. The newly recognized mark aspect of VD is male generative function. The VDR and the VD processing enzyme development revisions have been documented the attendance of the VD molecular system in the male reproductive organs, testes and spermatozoa. Conclusion that both universal and resident VD have a crucial role in male reproductive function. Yet, the present question which cell the key VD goal in the testis. Where, the VD is significant for sex hormone manufacture and function of spermatozoa [1,30].

VDR and the VD processing enzymes, including CYP27B1 and CYP24A1, were articulated in a significant ratio in the sperm of standard men's in comparison with sperm from infertile men's, concluding a association between VD and excellent semen quality [97,98]. In precise, CYP24A1 is an appropriate indicator for semen superiority [72,98,99]. In addition to, CYP24A1 is an indicator of VD motivation the process of spermatogenesis transcription [100].

Moreover, several information available to arrange that VD is a robust controller and elaborate in the regulation of synthesis the steroid sex hormones in human Leydig cells [101,102]. Meanwhile, concluded that there are not enough marks for a stimulatory action of VD on testicular testosterone manufacture [103].

Conclusion

In Conclusion, VD is hormone has receptors all over the body. VD is not only very important bone growing by conserving bone mineral density, but has possible assistances in cardiovascular health, modulation of the immune system, regeneration antioxidant system, as well as hepatorenal and brain function. Recently, VD has a protective effect in Diabetes mellitus, obesity, rheumatoid arthritis, Crohn's disease and multiple sclerosis, cancer. The reviewed evidence suggests some effects of VD in the regulation of male fertility potential and has crucial role for ideal male reproductive function.

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