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# Role of Vitamin D in human Diseases and Disorders - An Overview

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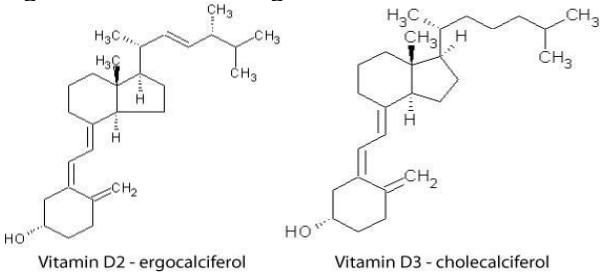
## Abstract
Vitamin D is a fat soluble vitamin and generated in human skin by ultraviolet (UV) light. Today, vitamin D is considered to be a steroidal hormone and plays a central role in bone mineralization and calcium homeostasis. The active form of the vitamin D is 1, 25-dihydroxyvitamin D [1, 25-dihydroxycholecalciferol (DHCC)] which mediatesproliferation, differentiation and various functions at the cellular level through Vitamin D receptors (VDR).Therefore, compromised vitamin D status is likely to be involved in progression or pathogenesis of various disorders. This assumption is consistent with findings from epidemiological studies that a compromised vitamin D status in humans increases the risk of autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis and type I diabetes mellitus. However, diseases like cancer, cardiovascular disorders and bone disorders are yet not focused. Thus the role of vitamin D in pathogenesis of various diseases is complex and controversial. This review briefly summarizes the role of vitamin D in development and progression of different human disorders.
**Keywords:** 1, 25-dihydroxyvitamin D, Calcium, Vitamin D receptor (VDR), Cytokines

## 1. Introduction
Vitamin D is a fat soluble vitamin, is generated in human skin by ultraviolet (UV) light[1]. Vitamin is also known as calciferols, because of their key role in calcium homeostasis and promotion of favourable health outcomes[2].The molecular structure of vitamin D is similar to steroidal hormones and therefore, it acts like pro-hormone, a substance that is precursor of various steroidal hormones. Vitamin D exists in two main forms, vitamin D2 (VD2, ergocalciferol) and vitamin D3 (VD3, cholecalciferol), differing in their side chain structure (ergocalciferol has an additional methyl group and a double bond) (Figure 1). Ergocalciferol (VD2) is formed from ergosterol and it is present in plants. Cholecalciferol (VD3) is found in animals. Ergocalciferol and cholecalciferol are sources for vitamin D activity[1].

**Figure1: Structure of ergocalciferol and cholecalciferol**

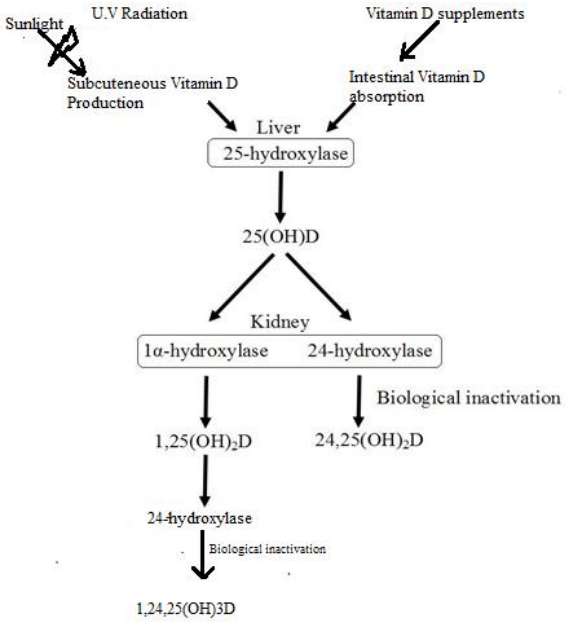



The vitamin D in endocrine system plays a central role to control bone and calcium homeostasis. The active form of the vitamin D is 1, 25-dihydroxyvitamin D [1, 25-dihydroxycholecalciferol (DHCC)], the circulating level of which is tightly regulated and acts through Vitamin D receptors (VDR) to mediate different actions on almost every tissues[3]. Vitamin D receptors are found on various immune cells and therefore it is assumed that it may modulate immune response[4]. This assumption is consistent with findings from epidemiological studies that a compromised vitamin D status in humans increases the risk of autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis as well as type I diabetes mellitus[5-11].However, diseases like cancer, cardiovascular disorders and bone disorders are yet not focused. So, this review summarizes the role of vitamin D in genesis and development of various disorders.

## 2.Synthesis and metabolism of Vitamin D

Very limited dietary sources such as fish, milk, cheese and eggs contain vitamin D. Most of vitamin D is endogenously synthesised in the skin through the exposure to sunlight [2, 12].Total-body sun exposure (1 minimal erythemal dose) provides the equivalent of 250 to 500 g (10,000 to 20,000 IU) of vitamin D per day[13].Vitamin D, in the form of vitamin D2 or D3, is first metabolized to 25(OH)D through 25-hydroxylase enzymes present in the liver and then further metabolized to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] by 1-α-hydroxylase of kidney. Both 25(OH)D and 1,25$(OH)_2$D then converted into the biologically inactive form of 24,25-dihydroxyvitamin D [24,25$(OH)_2$D] and 1,24,25-trihydroxyvitamin D [1,24,25-$(OH)_3$D] by 24-hydroxylase in the kidneys and other target tissues (Figure 2)[14].

**Figure 2: A simplified diagram of vitamin D synthesis and metabolism**

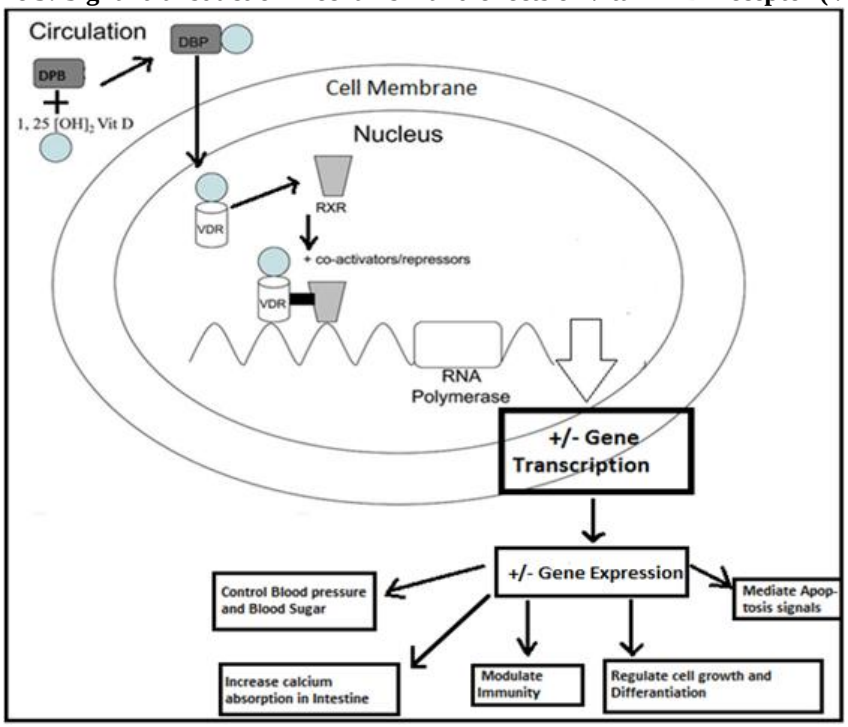



25(OH)vitamin D is considered to be the major circulating metaboliteof vitamin D and therefore serum 25(OH)D level reflects vitamin D input fromcutaneous synthesis and dietary intake. As per epidemiological studies, 25(OH) D concentration of ≥30 ng/mL are considered to be sufficient whereas 25(OH)D concentration of 20 ng/mL, is the indication of vitamin D deficiency and 25(OH)D concentration of 21-29 ng/mL, is the indication of vitamin D insufficiency [15-19]. Vitamin D deficiency is, however, accompanied by changes in PTH, calcium, phosphorus, and 1,25-dihydroxyvitamin D levels (1,25[OH]2D).

## 3. Mechanism of Vitamin D and Vitamin D Receptor (VDR)

Vitamin D is often considered as a hormone rather than a vitamin because of the fact that the active vitamin D metabolite 1,25-dihydroxyvitamin D (DHCC) circulates throughout the body, exerting its wide-ranging effects in cells that contain the vitamin D receptor (VDR). Vitamin D receptor is a type 2 nuclear receptor that is present in the nucleous of cells in most of the tissues. The VDR is present in osteoblasts, pancreatic β cells, adipose cells and immune response cells, such as macrophages, dendritic cells and activated B- and T-cells and most organs in the body, including brain, heart,lungs,liver, skin, gonads, prostate, breast, small intestine and colon[20-24]. Circulating DHCC is bound to the vitamin D binding Protein(DBP); diffuses through the cell membrane and nuclear membrane and binds to the VDR, causing a conformational change in the receptor, leading to its heterodimerization with retinoic acid X-receptor (RXR). This heterodimer with other factors, attaches to vitamin D-responsive elements on deoxyribonucleic acid (DNA), alters gene expression and resulting in expression of specific gene products[3].1,25-dihydroxyvitamin D regulates more than 200 genes, directly or indirectly, thereby influencing a wide variety of physiological processes that regulate the blood pressure, calcium level, immunity, cell growth& differentiation and apoptosis (Figure 3)[25].

**Figure 3: Signal transduction mechanism and effects of Vitamin D Receptor (VDR)**

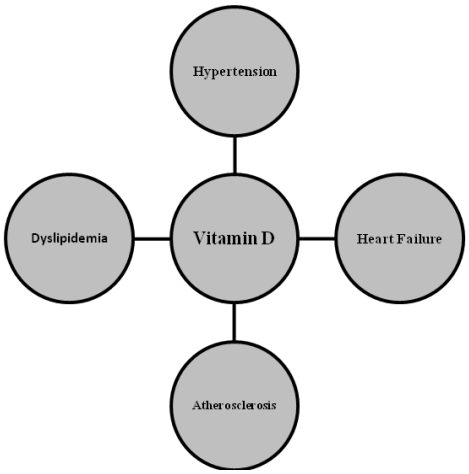



Expression and activation of VDR are necessary for the effects of vitamin D. Alterations of the VDR gene could lead to defects on gene activation, affecting calcium metabolism, cell proliferation and immune functions. Several genetic variations called polymorphism have been identified in the VDR which might be linked to various diseases[3].

## 4. Cardiovascular diseases

Today, cardiovascular diseases are first leading cause of death in the world. Vitamin D appears to play an important role in maintaining normal cardiovascular activity through its ability to modulate BP, prevent calcification of the heart and blood vessels, support normal cardiovascular contractility and reduce the risk of thrombosis. Evidence from animal and human studies illustrates that vitamin D decreases systemic inflammatory mediators of vascular disease and imbues immune cells with anti-inflammatory properties[26-27]. Epidemiologic evidence shows that there is a strong association between vitamin D deficiency and several cardiovascular diseases[28]. As per recent data, 25-hydroxyvitaminD deficiency is considered to be a novel risk factor for cardiovascular diseases like hypertension, dyslipidemia, atherosclerosis and heart failure (Figure 4)[29-31] and also related to other major CV-risk factors like obesity, type 2 diabetes and chronic kidney disease[32].

**Figure 4: Association of cardiovascular diseases with Vitamin D**



Out of all cardiovascular diseases, hypertension is considered to be a silent killer. Possible mechanisms for this association of vitamin D and blood pressure include the inverse association of vitamin D levels with the rennin angiotensin-aldosterone system (RAAS) activity, the effect of improving endothelial function and the prevention of secondary hyperparathyroidism[33]. High parathyroid hormone (PTH) level reflects vitamin D deficiency status and it might be related with High Blood Pressure[34-35].

Cardiac Heart failure (HF) is characterized by disordered heart structure and function that interferes with normal filling or ejection.Imbalance between pro-inflammatory and anti-inflammatory cytokines have important role in progression of cardiac heart failure. Thehigherconcentration of pro-inflammatory cytokines, such as tumor necrosisfactor α (TNF-α) and interleukin 6 (IL-6) was found in patients with HF[36-37].TNF-α may contribute to the pathogenesis and the progression of CHF[38]. Experimental studies have shown that the vitamin D hormone calcitriol can suppress the release of TNF-α and up-regulates the synthesis of the anti-inflammatory cytokine interleukin 10 (IL-10). These all together retard the progression of HF. So, low vitamin D status may contribute to the pathogenesis and symptoms of HF[39].

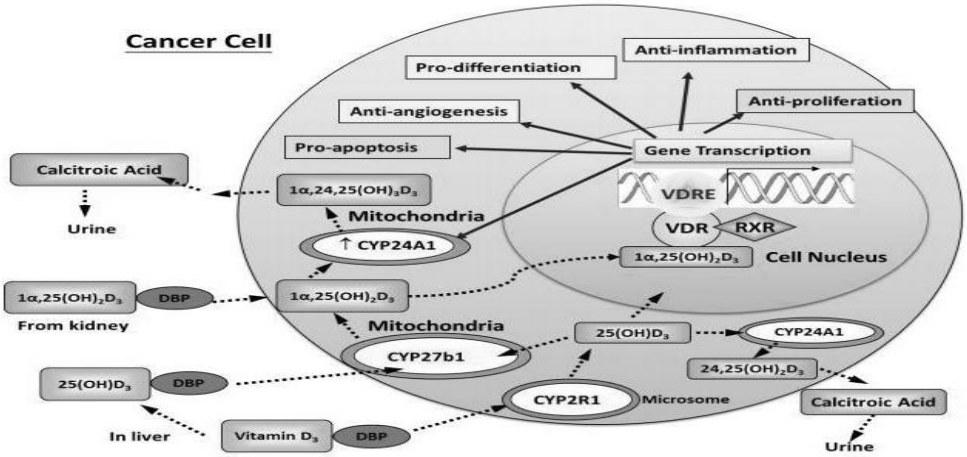
Cardiac action potentials are generated by the movement of calcium through calcium channels in nodal tissue. Intracellular calcium modulates the activity of sodium channels-- which transmit these action potentials throughout the myocardial tissue—to keep the heart rate under control[40]. In a recent report, the correction of vitamin D deficiency and hypocalcemia resulted in control of incessant ventricular tachycardia andcardiomyopathy[41].

Atherosclerosis is characterised by intimal lesions called as atheromas (atherosclerotic plaques) that protrude into vessel lumen.Vitamin D might have protective effect against atherosclerosis but excess vitamin D will pro-athrogenic.Colecalciferol i.e. vitamin D3metabolised to1,25-dihydroxyvitaminD3 [1,25(OH)2D3]. Itswell known that the abnormally high level of 1,25-dihydroxyvitaminD3contribute to the pathogenesis of atherosclerosis.It inhibits the transcription of PTHrelated peptide and stimulating the expression of osteopontin leading to increased blood calcium level and promoting calcification of atherosclerotic plaque[42]. Moreover, it dose-dependently activates p38 mitogen-activated protein (MAP)-kinase[43]and phosphatidyl-inositol (PI)-kinase[44-47].Once activated, these signal transducers, in concert with cytokines and growth factors, induce smooth muscle cell dedifferentiation& migration and increase oxidative stress, thereby leading to the structural disintegration and stiffening of the arterial wall[48].

## 5. Cancer

Over the past few decades,incidence of cancer in worldwide is going to be increased tremendously and it is associated with high rate of morbidity and mortality. Researchers have found that vitamin D and its active metabolite, 1,25(OH)2D exert various actions through VDR that may be useful for the prevention or treatment of various cancers[49].TheVDRis believed to be involved in detoxification of exogenous and endogenouscarcinogenic substances and thereby help to prevent or decrease the progression of cancer[50].The local production of 1,25(OH)2D in non-calcium regulating tissues such as the colon, prostate, and breast is thought to be for the purpose of regulating up to 200 genes, which helps to control cell growth and cellular differentiation and may be responsible for decreasing the risk of the cells being transformed into a malignant state.1,25-dihydroxyvitaminD has been found to exert various anti-cancer actions, including anti-proliferation, anti-inflammation, pro-differentiation, pro-apoptosis and anti-angiogenesisin a tissue- and cell-specific manner(Figure-5).There is a negative correlation has been found between 1,25(OH)2D3 level and progression of some cancers like breast, prostate and colon cancers[3].

**Figure 5: The genomic anti-cancer actions of 1α, 25(OH)2D3**




Skin cancer is the most common cancer afflicting mankind. Vitamin D3 is synthesized via initial conversation of 7-dehydrocholesterol upon UVirradiation of the skin[51-54]. The skin cancer is mainly due to U.V. Radiation with a spectrum

between 280-320 nm[55]. UV wavelengths longerthan 320 nm (UVA), the major component of sunlight, can cause oxidative DNA damage that ispotentially mutagenic[56].Therefore, Sun avoidance may reduce the risk of developing skin cancer via the vitamin Dsignalling mechanisms[57].In colorectal cancer,1,25(OH)2D3 significantly increases the expression and activity of alkaline phosphatase, a marker of colonic differentiation[58]. Mammographic breast density is strongly related to breast cancer risk [59-60]. The study carried out by Yan Cui and Thomas Rohan revealed that breast density is inversely associated with dietary calcium and vitamin D intake.

Prostate cancer is the most commonly diagnosed malignancy in men[61].In the United States, it is the second most commoncause of death caused by cancer in men.In prostate gland cancer, the proliferation of tumor-cells is stimulated by Prostaglandins (PGs). As we know, the PGs are synthesised through cyclooxygenase-2(COX-2) enzyme and degraded by 15-prostaglandin dehydrogenase (15-PGDH) enzyme. 1,25-dihydroxyvitamin D3 (Calcitriol)significantlydecreases the expression of COX-2 gene, while increasing that of 15-PGDH enzyme and thereby reducesthe levels of PGs; exerting tumor-suppressor effects[62].

## 6. Bone related diseases

Vitamin D is important for normal development and maintenance of the bone. Vitamin D, PTH, and Ca levels are interrelated to each other to maintain normal calcium homeostasis in the body. Dietary calcium intake influences the PTHlevel, which influences the turnoverof vitamin D metabolites [63].

The insufficient amount of calcium in the diet leads to low level of calcium in the serum.this in turn stimulate the conversion on vitamin D to its active metabolite 1,25(OH)2D. This 1,25(OH)2Dinteracts with its receptor in osteoblasts and induces the expression of receptor activator of nuclear factor-κB (NF-κB) ligand, which interacts with its receptor on preosteoclasts, inducing them to become mature osteoclasts[64,65].The net effect is to enhance mobilization of calcium from the bone to maintain serum calcium concentrations in the normal range. Vitamin D deficiency results in decreased concentrations of ionized calcium, which are immediately recognized by the calcium sensor in the parathyroid glands[66] and increased expression, production, and secretion of PTH. Parathyroid hormone increases the tubular re-absorption of calcium in the kidneyand enhance the production of 1,25(OH)2D and thus maintains the normal calcium level in blood.

Osteomalacia is an end-stage bone disease caused by chronic and severe vitamin D depletion occurs due to any reason[67].Either calcium or vitamin D insufficiency leads to prolonged secondary hyperparathyroidism causing net loss of cortical bone on the endossurfaceand thisresults into cortical porosity and thinning of cortical bone. Thisloss of cortical bone is irreversible[68].An absolute deficiency of vitamin D, however, leads toan increasing amount of unmineralized osteoid in the bones. As a result, weight-bearing bones begin to bend and the patientexperiences vague pains in the limbs[69].

Bone “density” (bone mass/bone volume) declines with age from the menopause in women and from about age 55 in men. This fall in bone density (osteoporosis) weakens the bones and leads to a progressive rise in fracture rates, particularly in women[70]. Vitamin D deficiency can be an important risk factor for osteoporosis[71]. Vitamin D deficiency adversely affects calcium metabolism, osteoblastic activity, matrix ossification, bone remodeling, and bone density[72]. Low 25-hydroxyvitamin D (25OHD) associated with secondary hyperparathyroidism and increased bone turnover. Some studies suggest that a low serum 25OHD level is associated with low BMD[73-74] in postmenopausal womenwith osteoporosis.

## 7. Autoimmune diseases

Autoimmune diseases occur when there is disturbance of body’s immune system, thereby allowing the immune system to breakdown and attack body’s own healthy cells and tissues.1,25(OH)2D is a very effective modulator of the immune system as macrophages, Band T-lymphocytes contains VDR[75]. The immune-regulatory role of vitamin D affects both the innate and adaptive immune systems[76].The most common autoimmune diseases, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, and Crohn’s disease, have all been successfully prevented in the animal models if they are pre-treated with 1,25(OH)2D3 [2,4,77-80].

Multiple sclerosis(MS) is an autoimmune disease in which the body makes auto-antibodies against the myelin sheaths surrounding neuron axons, destroying the nerve insulation and thus nerve transmission.As per epidemiological data, poor dietary vitamin D links with incidence of MS[81].Cytokines are proteins used as a source ofcommunication between immune system cells and cells ofother organ systems. Most importantly, cytokines canconsiderably enhance or attenuate an inflammatory response.Cytokines are typically out of balance in patientswith autoimmune disease, with pro-inflammatory cytokineshigh and anti-inflammatory cytokines low. Thus,compared with a healthy person, MS patients have increasedlevels of inflammatory cytokines (eg, interleukin-2, TNF-α, and interferon-γ), as well lower levels of some anti-inflammatory cytokines[82-85].

Inflammatory bowel diseases (IBD) are immune-mediated diseases of unknown etiology affecting the gastrointestinal (GI) tract. Evidence shows that the environment contributes to IBD development, and vitamin D might be one of the environmental factors affecting IBD[86]. Cantorna *et al.*[87]showed that vitamin D deficiency plays a role in the pathogenesis of IBD and supplementation of 1,25-(OH)2D3, an active metabolite of vitamin D3, prevents and ameliorates symptoms of IBD in an experimental mouse model. As a result of vitamin D deficiency, local production of 1,25-(OH)2D3 by mucosal epithelial cells as well as by macrophage [88,89] within inflammatory lesions falls below a level that is critical for

suppression of enhanced Th1-cell responses, which are typically associated with chronic enterocolitis[90].

The involvement of vitamin D has been suggested in the etiology of both Type-1 and Type-2 Diabetes mellitus.Vitamin D plays an important role in the pathogenesis of diabetes and in glucose control through several mechanisms, such as inhibiting the inflammatory response and modulating self-immune response, promoting insulin synthesis and secretion,increasing insulin sensitivity and the polymophisms of vitamin D-related genes[91].Type 1 DM is recognized as a T-cell-mediated autoimmunedisease[92]. Vitamin D is known to suppress T-cell activation by binding to the VDR[93-95]andthus, VDR gene polymorphisms are likely to be related to Type-1 Diabetes mellitus. Furthermore, β-cells possess VDR and insulinsecretion is impaired in vitamin D deficiency and restored by1-25(OH) vitamin D[96].

## 8. Conclusion

Vitamin D is essential for strong bones, muscles and overall health. Vitamin D insufficiency is a global problem. Many studies have shown associations between low 25(OH)D concentration and wide range of acute and chronic health disorders. In the past, vitamin D deficiency is limited only with rickets in the children and bone related disorders in adults but recently vitamin D deficiency has also been linked with the pathogenesis and/or progression of several other diseases like cancer, hypertension, multiple sclerosis, diabetes mellitus etc. Despite the close link of vitamin D with human health, vitamin D insufficiency is not widely recognized as a problem by physicians and patients. At this time, further studies are needed to evaluate the role of vitamin D in pathogenesis of various diseases and thereby modify the therapeutic approach to treat such disorders.

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