**Journal of Academy of Biomedical Sciences (JABS)**
*An official Journal of* **Indian Academy of Biomedical Sciences (IABS)**

**Review Article**
PUBLISHED 15 SEPTEMBER 2024

# Vitamin D: A Comprehensive Review

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## Abstract

Consumption of Vitamin D supplements improves metabolic factors, reduces oxidative stress, cardiovascular benefits and plays an important role in the second trimester of pregnancy as it is needed for the growth and development of the foetus. The potential for innovative therapeutic approaches and preventive techniques emerges as studies on the potential role of vitamin D on health and sickness continue to disclose new dimensions, making this an intriguing subject for future exploration.

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**KEYWORDS:**
COVID-19, Vitamin D, VDR Gene

**HOW TO CITE:**
Tomar US, Singh M, Singh S, Chandra A, Puri S. Vitamin D: A Comprehensive Review. Journal of Academy of Biomedical Sciences. 2024;1(1):46-52

## INTRODUCTION

Vitamin D is a vital hormone crucial in various physiological functions, like metabolism, immune function, and bone health.[1,2] It contributes to the development of dopamine neurons and is implicated in neurodevelopmental disorders such as schizophrenia.[3] Many medical conditions, including type 2 diabetes, metabolic syndrome, cardiovascular disease, and obesity, have been associated with vitamin D insufficiency.[4,5] It has been demonstrated that consumption of Vitamin D supplements improves metabolic factors, reduces oxidative stress, cardiovascular benefits and plays an important role in the second trimester of pregnancy as it is needed for the growth and development of the foetus.[5]

In the early twentieth century, McCollum recognized the sunshine vitamin, now known as Hormone D, as the fourth member of the vitamin family after A, B, and C. Prohormone D is an essential component of bone mineralization, phosphate control, and calcium homeostasis. Sunlight exposure (UVB) causes the skin to synthesize, fat-soluble secosteroid and can be absorbed from a variety of food sources. The Nobel Prize in Chemistry was awarded in 1928 for the isolation and demonstration of its steroid structure. Vitamin D3, or Cholecalciferol, is the most metabolically active form, and its flexibility allows for the creation of analogues such as alphacalcidol and paricalcitol.

The field of vitamin D research has expanded recently, with studies exploring its role in conditions like COVID-19 and cancer. PubMed recorded an average four thousand articles annually over last 5 years, reflecting the widespread interest in its diverse metabolic activities. Various correlation studies involving animal models, cell systems, gene expression, epidemiology, and clinical therapeutics highlight associations with conditions such as osteomalacia, cardiovascular disorders, hypothyroidism, diabetes, and chronic liver disease.

## METABOLISM AND VITAMIN D ACTIVATION

Dietary or skin-synthesized vitamin D is initially metabolically inactive. The process of activation involves 25-hydroxylation, in which the liver converts 7-dehydrocholesterol to the prohormone calcifediol (25(OH)D). The release of calcifediol into the bloodstream, binding to Vitamin D-Binding Protein (VDBP), precedes its transport to the Proximal Convoluted

Tubule (PCT) of the kidney. The enzyme 25-hydroxyvitamin D3-1-alpha-hydroxylase rehydroxylates calcifediol at the 1-alpha site to produce the biologically active vitamin D i.e. Calcitriol. The regulation of this process involves parathyroid hormone stimulation and inhibition by calcium, phosphate, and EGF23.

The active form, Calcitriol is released into the bloodstream, binding with VDBP. It acts on various tissues, including the intestine, kidney, and bone, exhibiting genomic and non-genomic actions. Beyond the classic target organs, calcitriol is synthesized in other tissues like keratinocytes and lymphocytes when stimulated by cytokines, playing a role in innate immunity.

## VITAMIN D RECEPTOR (VDR): STRUCTURE AND FUNCTION

The VDR, sometimes called NR1I1, belongs to steroid hormone receptor family of ligand-dependent transcription factors. Discovered in the late 20th century, it regulates over 900 genes, impacting various physiological actions. Comprising N-terminal, C-terminal, and an extensive unstructured region, the VDR is organized for transcriptional changes upon binding with 1,25(OH)2D3.

Calcitriol binds to VDR, leading to homodimerization or heterodimerization with RXR (retinoid X receptor) which binds to Vitamin D Response Elements (VDRE) on DNA, influencing gene expression or trans-repression. VDR's role extends to anticancer activity, innate immunity activation, and physiological functions in the heart, skeleton muscles, pituitary, and breast.

The VDR is a vital component of the mechanism that controls many biological activities, including calcium homeostasis, cell growth, differentiation and immune responses.[6] VDR mediates its functions by binding to its natural ligand, 1α,25-dihydroxyvitamin D3 (1,25D3), and regulating the transcription of target genes.[7] Studies on structure have shed light on VDR's ligand-binding manner and mechanism of action.[8] VDR gene polymorphisms have been associated with hereditary vitamin D-resistant rickets (HVDRR), a rare genetic disorder characterized by poor calcium absorption and bone mineralization.[9] Furthermore, this is currently demonstrated that upregulating VDR promotes muscle growth by improving translational efficiency, extracellular matrix remodeling, and protein synthesis.[10] It is essential to understand the structure and function of VDR to create therapies for autoimmune diseases, HVDRR, and disorders of the muscles.

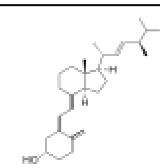
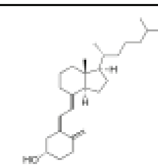
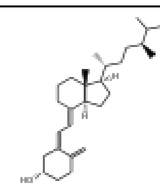
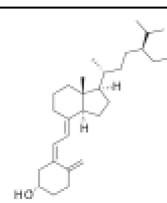
## ESTIMATION OF VITAMIN D

Vitamin D metabolism, 24,25-dihydroxyvitamin D (24,25(OH)2D), which can be used as a marker for kidney disease.[11] Assessing an individual's vitamin D status, recognizing problems with calcium homeostasis, and estimating vitamin D metabolites are crucial, especially 25-hydroxyvitamin D (25(OH)D).[12] While automated assays are commonly used for measuring 25(OH)D, they may not accurately measure 25(OH)D in all patient groups, including those using vitamin D2Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) is a more reliable method in such cases.[13] The measurement of additional vitamin D metabolites, such as 24,25(OH)2D, can provide insights into vitamin D status and metabolism. However, the evidence for the clinical value of measuring 24,25(OH)2D is inconclusive, and routine measurement of this metabolite may not be necessary for optimizing vitamin D supplementation.[14] LC-MS/MS is considered the method of choice for vitamin D analysis, as it provides greater specificity and can detect 25(OH)D2 and 25(OH)D3 separately.[15]

## VITAMIN D: TYPES & STRUCTURE

Vitamin D exists in various forms denoted by a number written as subscript (D1, D2, D3). Vitamin D1, initially identified, proved to be an error and is not used. The major forms are D2 (Ergocalciferol) & D3 (Cholecalciferol). The structure numbering of Vitamin D follows its parent compound cholesterol, with A, B, C, and D rings. The A ring is crucial for interaction with VDR, while the Seco B ring's flexibility enables the formation of different conformers.

**Table 1:** Chemical Composition and representation of Vitamin D Compounds.

| Name | Chemical composition | Structure |
|---|---|---|
| **Vitamin $D_1$** | Ergocalciferol and Lumisterol | |
| **Vitamin $D_2$** | Ergocalciferol (ergosterol derived) |  |
| **Vitamin $D_3$** | Cholecalciferol (A derivative of 7-dehydrocholesterol in the skin). |  |
| **Vitamin $D_4$** | 22-Dihydroergocalciferol |  |
| **Vitamin $D_5$** | Sitocalciferol (derivative of 7-dehydrositosterol) |  |

## PRODUCTION AND METABOLISM

Ingested or keratinocyte-synthesized Vitamin D3 is biologically inert, requiring key steps like 25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation for activation. An important part of these processes is performed by cytochrome P450 (CYP) enzymes, particularly located in the mitochondria and endoplasmic reticulum. Vitamin D metabolic journey: synthesis, activation and target organ effects. 7-dehydrocholestrol: Sunlight stimulates the synthesis of Vitamin D, this precursor molecule is converted to provitamin $D_3$. Previtamin $D_3$: Isomerized to vitamin D3 in the skin, prepared for bloodstream absorption. Vitamin D3: Obtained from both sun exposure and dietary sources, vitamin D3 is transported to the liver by vitamin D-binding protein (DBP).25-hydroxyvitamin D (25(OH)D): The major circulating form is produced in the hepatic cells by 25-hydroxylation of vitamin D3.1,25-dihydroxyvitamin D (1,25(OH)2D): The Vitamin D active form, synthesized in the kidneys from 25(OH)D by the enzyme 1α-hydroxylase (CYP27B1).DBP: Vitamin D-binding protein shuttles Vitamin D and its byproducts throughout the bloodstream. Target organs: Possessing receptors for 1,25(OH)2D, these organs include the intestines, bones, and kidneys, on which Vitamin D has a variety of physiological effects.

Notably, mit ochondrial CYP11A1 initiates the process by cleaving the carbon-20, initiating the synthesis of pre-vitamin D3. The liver synthesizes 25-hydroxyvitamin D3 (calcifediol) by CYP2R1 and CYP27A1, and the renal synthesis of 1,25-dihydroxyvitamin D3 (calcitriol) by CYP27B1, plays vital role.

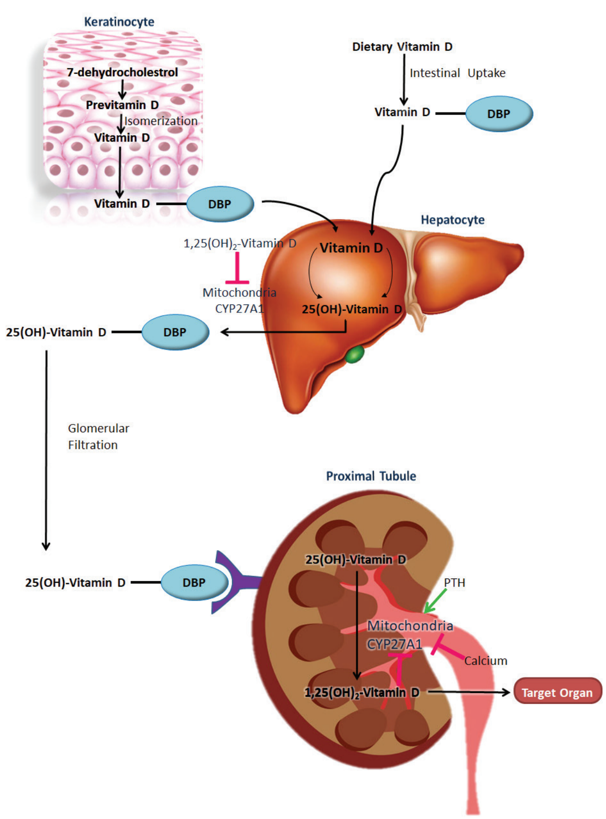



**Figure 1:** Vitamin D Metabolism Pathway

## VITAMIN D ACTIONS

### *Classical Actions*

Vitamin D has classical actions in maintaining musculoskeletal health, regulating calcium & phosphate levels, and promoting bone health.[16-18] It regulates the balance of Calcium & phosphate, and deficiencies can result in diseases including osteomalacia and rickets.[19] Vitamin D plays a role in immune modulation and has been implicated in autoimmune illnesses such as multiple sclerosis and Type 1 Diabetes Mellitus (T1DM).[20] In addition to its classical functions, vitamin D has non-classical effects on a variety of tissues, such as the lung and colon. Numerous tissues, including the colon, have VDR expression, which controls colonic epithelial transport function. Overall, vitamin D has both classical and alternative actions in the body, impacting musculoskeletal health, immune modulation, and various other physiological functions.

### *Vitamin D: Non-Classical Actions and Immune System*

Vitamin D has non-classical actions on the immune system, acting as an immune modulator and influencing immune cell responses. It promotes tolerogenic immunological action and immune modulation, while also regulating the expression and release of antimicrobial peptides and anti-inflammatory cytokines. Vitamin D deficiency negatively affects autoimmune diseases and increases the risk and severity of viral respiratory diseases, including COVID-19. Conversely, enough vitamin D inhibits the production of proinflammatory cytokines and offers protection against COVID-19. The VDR gene expression is found in various immune cell types, and Vitamin D shows metabolic activity in immune cells. In addition to having an anti-inflammatory effect and suppressing autoimmunity, vitamin D and its receptor also support the development of regulatory T cells and lower the release of inflammatory cytokines. Numerous researchers have discovered connections between immune-related diseases and vitamin D deficiency; nonetheless, additional carefully planned clinical trials are required to completely comprehend its role in infections and immunological disorders.[21-25]

### *VDR Gene Polymorphism and Disease Associations*

VDR gene polymorphisms have been studied in relation to various diseases. The VDR gene polymorphism of ApaI does not appear to be linked with postmenopausal osteoporosis in Asians and Caucasians.[26] Other VDR gene polymorphisms, such as FokI, BsmI, and TaqI, have been associated with chronic liver disease, resulting in higher liver stiffness and reduced VDR expression levels.[27] These VDR gene variants have also been connected to autoimmune illnesses, with specific alleles and genotypes raising or decreasing the probability of developing these conditions.[28] The FokI variant of the VDR gene is attributed to Inflammatory Bowel Disease (IBD), with a higher frequency seen among Iraqi patients.[29] Additionally, The ApaI polymorphism of the VDR gene has been correlated with hypertensive disorders of pregnancy (HDP) susceptibility, notably among Asians.[30]

## REGULATION OF VDR ACTIVITY

VDR activity is regulated through various mechanisms. VDR expression is lost in colon tumour cells, which correlates with β-catenin nuclear localization and is associated with elevated levels of repressing class I histone deacetylases (HDAC) and downregulated VDR-activating retinoid X receptors (RXR).[31] Muscle undergoing atrophy upregulated VDR and contributed to the regulation of simulated microgravity-induced atrophy by controlling the expression of atrophy-related genes.[32] A novel synthetic VDR agonist encourages the intestinal defence system by increasing the expression of drug-metabolizing enzyme CYP3A4, detoxification enzyme UGT1A, and excretion transporter MRP2.[33] Vitamin D3 shows high-affinity nuclear target for VDR, and VDR knockout leads to total loss of 1,25(OH)2D3-induced gene regulation, indicating that there are no VDR-independent non-genomic actions of 1,25(OH)2D3.[34] Notably, VDR can simultaneously activate and repress gene expression. Its modes of action are more diverse than previously believed, entailing interactions with auxiliary factors and other transcription factors.[35]

## VDR GENE AND ASSOCIATED DISEASE MUTATIONS

Numerous research have reported five mutations in the VDR gene. Agliardi *et al*. examined the literature and discovered that autoimmune diseases have been linked to specific single nucleotide polymorphisms (SNPs) located in the VDR gene, including ApaI, BsmI, TaqI, and FokI[36] Jafarpoor *et al*. conducted a case-control study and identified a significant association for the rs2228570 SNP of the VDR gene and susceptibility to COVID-19.[37] Kashyap *et al*. studied HVDRR, a rare genetic disorder caused by VDR gene polymorphisms, and found that these variations impair the receptor's functioning and may contribute to disease development.[38] Aziz *et al*. investigated the association between VDR gene polymorphism (ApaI) and preeclampsia and reported no significant association among preeclampsia patients.[39] A study on SARS-CoV-2 variants in Cyprus found significant differences in genotype frequencies of VDR gene polymorphisms (FokI and TaqI) between COVID-19 patients and controls, suggesting a potential impact on infection susceptibility.[40]

## VITAMIN D CONJUGATED AS AN ANTICANCER DRUG

Vitamin D conjugated nanoparticles have shown potential as anticancer drugs. Calcium carbonate nanoparticles loaded with vitamin D were found to effectively supply vitamin D to breast cancer cells and inhibit cancer cell proliferation.[41] Folic acid-conjugated 5-fluorouracil (5-FU) increased the bioavailability of 5-FU and showed enhanced anticancer activity in breast, colorectal, stomach, and skin cancer tissues.[42] Vitamin D analogs, modified in the cyclohexane ring and aliphatic sidechain, potentiated the efficiency of cytostatic and cooperated efficiently with polyphenol in leukaemia cells and animal models of leukaemia and solid tumours.[43] Versatile nanoparticles were engineered from biocompatible vitamin D3 and conjugated with cytotoxic drugs and PI3 kinase inhibitor, showing potential in cancer therapeutics.[44] Vitamin D compounds, such as 1,24(OH)2D3 and 1,25(OH)2D3, possess antineoplastic activity and can enhance the cytotoxic effects of tyrosine kinase inhibitors and cytostatic in lung cancer cells.[45]

## VITAMIN D AND COVID-19

Numerous studies have demonstrated the protective effects of vitamin D intake against COVID-19. Numerous studies indicate that vitamin D supplementation may have positive effects on COVID-19, such as decreased rates of ICU admission, mortality events, and RT-PCR positivity.[46] Oxidative stress has been linked to vitamin D insufficiency; supplementation may lessen oxidative stress and inhibit viral entry, thereby preventing COVID-19 infection or lessening the severity of the disease.[47] Vitamin D can also stimulate the production of anti-microbial peptides and reduce pro-inflammatory cytokines, which are responsible for causing cytokine storms and fatal pneumonia.[48] However, the evidence for vitamin D supplementation in preventing or treating COVID-19 is inconclusive, with small observational studies and a high risk of bias.[49] While laboratory studies and some observational studies show protective associations between higher vitamin D levels and reduced risk and severity of COVID-19, Mendelian randomization studies have yielded null results.[49] Therefore, current evidence does not support the routine use of vitamin D supplements for COVID-19 prevention or treatment.

## VITAMIN D AND DIABETES

Research on Vitamin D suggests that it has an impact on diabetes mellitus and its aftereffects, including diabetic foot, nephropathy, neuropathy, and diabetic retinopathy.[46] Due to its impact on an individual's immunity and beta cells, it contributes to both the pathophysiology and prevention of T1DM.[47] Additionally, vitamin D therapy may aid in immune system regulation and the prevention of T1DM.[48] Insulin sensitivity and secretion in people with T2DM may be impacted by vitamin D insufficiency, which has been associated with a decreased incidence or prevalence of the condition.[49] Despite this, there is still inconsistent data from clinical trials regarding the benefit of vitamin D therapy for treating T2DM and autoimmune illnesses.[50] Additional research, particularly well-designed randomized clinical trials, is needed to completely comprehend that vitamin D can help in the prevention and treatment of diabetes.

## VITAMIN D DEFICIENCY WORLDWIDE & INDIA

Vitamin D deficiency is quite prevalent and poses a serious threat to public health worldwide. Studies have connected calcium insufficiency to several types of illnesses, including autoimmune diseases, cardiovascular issues, neoplastic diseases, and abnormalities of the bones. There are differences in the prevalence of vitamin D insufficiency in different demographic groups and geographical areas. Worldwide, 15.7% of people have blood 25-hydroxyvitamin D values below 30 nmol/L, 47.9% have levels less than 50 nmol/L, and 76.6% have levels less than 75 nmol/L.[46] It was established that 59.39% of patients who came to the tertiary care centre, outpatient department of medicine were vitamin D deficient.[47] Vitamin D research is primarily conducted in Northern America and Western European nations, while Africa, South America, and Asian countries have a minor role in global research production.[48] In the United States, patients with cardiovascular illnesses and cerebrovascular diseases are among the clinical subpopulations with a greater prevalence of vitamin D insufficiency.[49]

Vitamin D deficiency is a prevalent issue in India.[50] Studies suggest that our country has significant prevalence rates of vitamin D insufficiency in all age categories.[51] Factors contributing to this deficiency include lack of sunlight exposure, vegetarian eating habits, and low consumption of vitamin D-enriched foods.[52] Vitamin D insufficiency is particularly common in some populations, such as pregnant women.[53] In a study conducted in Rajasthan, 68.875% of antenatal women had vitamin D deficiency, with a mean level of 13.8 ± 3.9 ng/mL.[54] A different study carried out in north India discovered that vitamin D deficiency affected 76% of patients with metabolic syndrome. In a healthcare facility in Western India, 45.97% of the faculty members were vitamin D deficient. The results of this study emphasize the necessity of raising awareness and implementing treatments to address vitamin D insufficiency in India.

Vitamin D insufficiency is widely widespread in Uttar Pradesh, India. A Gorakhpur study revealed that vitamin D deficiency affected 31.25% of non-pre-eclamptic pregnant women and 82.8% of pre-eclamptic pregnant patients.[55] Another study carried out in a rural North Indian community found that adult females between the ages of 20 and 60 had a prevalence of vitamin D insufficiency of 90.8%.[56] Additionally, a study investigating haemoglobin variants in unrelated individuals residing in Lucknow found a prevalence of 1.5% for haemoglobin 'D' trait.[57] Furthermore, a study in North India observed a high prevalence of vitamin D deficiency (91.1%) in newly detected youth-onset diabetes patients.[58] Lastly, 85% of participants in a study conducted among medical professionals in Northern India had a baseline blood 25-hydroxyvitamin D level below 10 ng/mL, implicating vitamin D inadequacy.[59]

## CONCLUSION

In conclusion, this thorough analysis dives into the complex domain of vitamin D, examining its synthesis, structure, and potential applications. This review offers a thorough summary of this important mineral, including everything from its historical discovery to the most recent developments in our knowledge of vitamin D's non-classical activities and the wide range of functions of the vitamin D receptor. The potential for innovative therapeutic approaches and preventive techniques emerges as studies on the potential role of vitamin D on health and sickness continue to disclose new dimensions, making this an intriguing subject for future exploration. Understanding the complexities of vitamin D biology helps in addressing deficiencies and harnessing its therapeutic potential in various medical conditions.

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