**Review Article**

**Vitamin D Metabolism in Health and Disease**

**Abstract**

Vitamin D, a secosteroid hormone synthesized in the skin via UVB exposure or obtained from dietary sources, is critical in numerous physiological processes. Its metabolism involves hepatic hydroxylation to 25-hydroxyvitamin D [25(OH)D], the main circulating form, followed by renal conversion to the biologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], which binds to the vitamin D receptor (VDR) to regulate gene expression. CYP2R1, GC, and VDR genetic polymorphisms influence vitamin D status and functional outcomes. Beyond its classical role in calcium-phosphate homeostasis and skeletal health, vitamin D modulates immune function, cardiovascular health, neuroprotection, and cellular proliferation. Deficiency, defined as serum 25(OH)D <20 ng/mL, is a global health concern linked to osteoporosis, autoimmune diseases, metabolic disorders, and increased infection susceptibility. Risk factors include limited sun exposure, obesity, malabsorption syndromes, and genetic predisposition. This review synthesizes current evidence on vitamin D metabolism, genetic determinants, pleiotropic physiological functions, and the clinical implications of deficiency, emphasizing the need for targeted screening and personalized supplementation strategies to optimize health outcomes.

**Keywords:** Vitamin D, 25-hydroxyvitamin D, VDR, calcium homeostasis, immune modulation, deficiency, genetics, supplementation.

**I. Introduction**

Vitamin D is a fat-soluble vitamin and a secosteroid that plays a crucial role in many physiological processes. In particular, it is essential for maintaining bone health and supporting the immune system. Unlike other vitamins, vitamin D shares characteristics with hormones, including syntheses in the body upon skin exposure to ultraviolet B (UVB) radiation from sunlight [1] and following a multistage conversion to its active form, which acts like a hormone [2]. The active form of vitamin D, calcitriol, binds to a nuclear receptor found in various tissues throughout the body, influencing gene expression by regulating the transcription of specific genes that mediate several functions [3]. These constitute the vitamin D endocrine system, comprising vitamin D, the metabolizing enzymes, and the vitamin D receptor (VDR).

These components play a vital role in skeletal metabolism, particularly in calcium absorption in the intestines and other metabolic pathways related to the immune response and cancer. For example, within the immune system, vitamin D promotes the differentiation of monocytes while restricting the proliferation of lymphocytes and the secretion of cytokines such as IL-2, interferon-γ, and IL-12 [4]. Additionally, vitamin D has shown antiproliferative effects in various cancer cell types [5]

Vitamin D deficiency is defined as having a serum 25(OH)D level of less than 20 ng/ml, while insufficiency is classified as a 25(OH)D level between 21 and 29 ng/ml. Many experts recommend maintaining a level above 30 ng/ml [6]. A study conducted between 2000 and 2022, focusing on individuals aged one year and older, revealed a high global prevalence of vitamin D deficiency. Specifically, 15.7% of people have serum 25(OH)D levels below 12 ng/ml, 47.9% have levels below 20 ng/ml, and 76.6% have levels below 30 ng/ml. The prevalence is particularly higher in the Eastern Mediterranean region, among lower to middle income countries, and females. It increases with latitude and during the winter-spring seasons [7]. Furthermore, vitamin D deficiency disproportionately impacts individuals with darker skin pigmentation, with studies indicating higher rates of deficiency in Black and Hispanic populations compared to Caucasian groups. This occurs because the melanin in darker skin serves as a natural sunscreen, limiting the skin's capacity to synthesize vitamin D upon exposure to sunlight [60].

**2. Vitamin D Metabolism: Sources, Synthesis, Mechanism of Action, and Regulation of Levels**

The metabolism of vitamin D involves several key processes, including synthesis in the skin, conversion in the liver, activation in the kidneys, and regulation through various feedback mechanisms.

Vitamin D is primarily synthesized in the skin, triggered by exposure to ultraviolet B (UVB) radiation from sunlight. This process converts 7-dehydrocholesterol, a cholesterol precursor found in the epidermis, into previtamin D3. Subsequently, previtamin D3 undergoes thermal isomerization to become vitamin D3 (also known as cholecalciferol), which is initially biologically inactive and requires further metabolic activation [1]. In addition to skin synthesis, vitamin D can be obtained from dietary sources. Animal-based foods such as fatty fish, fish liver oils, and egg yolks provide vitamin D3, while plant-based foods and fortified products contain vitamin D2 (ergocalciferol) [8].

Vitamin D3 is transported to the liver, where it undergoes hydroxylation by the enzyme 25-hydroxylase (CYP2R1) to produce 25-hydroxyvitamin D [25(OH)D], also known as calcidiol. This is the primary circulating form of vitamin D and is the most reliable measure of vitamin D status in the body [9]. After that, 25(OH)D is hydroxylated by the enzyme 1α-hydroxylase (CYP27B1) in the kidneys to produce 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as calcitriol. Calcitriol is the biologically active form of vitamin D, which exerts various physiological effects [10]. The production of calcitriol is tightly regulated by factors such as parathyroid hormone (PTH), calcium, and phosphate levels.



Figure 1. Illustrates the synthesis and metabolism of vitamin D. In the skin, 7-dehydrocholesterol (a precursor of vitamin D3) absorbs UVB radiation and converts to previtamin D3, which then undergoes thermal isomerization to form vitamin D3. Prolonged UVB exposure can break down previtamin D3 and vitamin D3 into inactive photo products. Dietary vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are absorbed in the gastrointestinal tract and enter the systemic circulation. The vitamin D obtained from the diet and the skin binds to the vitamin D-binding protein when it enters the circulation. In the liver, circulating vitamin D is metabolized to 25-hydroxyvitamin D [25(OH)D] by the enzyme vitamin D-25-hydroxylase, with its activity being inhibited by 25(OH)D through negative feedback. 25(OH)D re-enters circulation and is further metabolized in the kidney and other tissues to the active metabolite 1,25-dihydroxyvitamin D [1,25(OH)2D] by 25(OH)D-1α-hydroxylase. Renal production of 1,25(OH)2D is inhibited by elevated serum levels of phosphorus, calcium, and fibroblast growth factor 23 (FGF-23), but stimulated by parathyroid hormone. The cytochrome P-450 enzymes CYP24 and CYP3A4 primarily mediate the catabolism of 25(OH)D and 1,25(OH)2D into biologically active molecules.

Calcitriol exerts its effects by binding to the vitamin D receptor (VDR), a nuclear receptor found in various tissues, including the intestines, bones, kidneys, and immune cells. Upon binding to calcitriol, the VDR undergoes a conformational change that allows it to form a heterodimer with the retinoid X receptor (RXR) [11]. The VDR-RXR complex binds to specific DNA sequences known as vitamin D response elements (VDREs) in the promoter regions of target genes. This binding regulates the transcription of genes involved in calcium and phosphate absorption, bone mineralization, and immune response. For example, in the intestines, vitamin D enhances the expression of the calcium-binding protein calbindin, which facilitates calcium absorption from the diet [12], figure 2.



Figure 2. Vitamin D receptor (VDR) action at target cells. Intracellular calcitriol [1,25(OH)2D] binds to the VDR, thus causing its dimerization with the retinoid X receptor (RXR). The ligand-bound VDR–RXR complex binds to structurally distinct vitamin D response elements (VDREs) in multiple, widely spaced vitamin D-responsive regions, and this causes a modification in the recruitment of co-activators or co-repressors, which leads to positive or negative transcriptional regulation of gene expression.

In addition to its genomic actions, vitamin D also exerts other rapid actions via non-genomic pathways. These include activating second messenger systems, such as the phospholipase C pathway, leading to the mobilization of intracellular calcium and modulation of cellular functions. These non-genomic actions are critical in immune cells, where vitamin D modulates cytokine production and inflammatory responses [13]. While the genomic pathway modulates gene expression over hours to days, the non-genomic effects trigger cellular responses within minutes. The genomic aspect is strictly linked to the VDR [14].

The parathyroid hormone (PTH) is crucial for regulating vitamin D metabolism. When blood calcium levels are low, the parathyroid glands release PTH, which enhances the conversion of 25(OH)D to calcitriol in the kidneys by increasing the activity of 1α-hydroxylase. Calcitriol then enhances calcium absorption in the intestines, reabsorption in the kidneys, and mobilization from bones, ultimately increasing blood calcium levels [15]. On the other hand, fibroblast growth factor 23 (FGF23), primarily secreted by osteocytes, works to lower calcitriol levels by inhibiting 1α-hydroxylase activity and increasing the expression of 24-hydroxylase (CYP24A1). This enzyme breaks down 1,25(OH)2D into inactive metabolites, helping to prevent hypercalcemia and maintain phosphate balance. Additionally, calcitriol exerts negative feedback on its production by inhibiting the expression of CYP27B1 in the kidneys and promoting the breakdown of 25(OH)D and 1,25(OH)2D into inactive forms through the induction of CYP24A1 expression. These feedback mechanisms are essential for maintaining optimal levels of active vitamin D and preventing toxicity [15].

**3.0 Genetics of Vitamin D Metabolism: Implications for Health and Disease**

Vitamin D-metabolizing enzymes play a crucial role in converting vitamin D into its active form and regulating its inactivation to maintain the optimal level of calcitriol required for effective VDR signaling. The signaling entails the binding and activation of nuclear transcription factors in various vitamin D-sensitive tissues, ultimately mediating the genomic actions of vitamin D. The genes encoding these enzymes namely, *CYP2R1, CYP27B1, CYP24A1, VDR, and GC (Group-Specific Component),* are expressed in a regulated way to ensure the optimal availability of calcitriol [12]. Therefore, genetic variations in these genes affect key enzymes, receptors, and binding proteins and contribute to differences in how individuals metabolize and maintain vitamin D levels, leading to a wide range of phenotypes in many bodily systems.

The *CYP2R1, CYP27B1*, and *CYP24A1* genes encode three members of the cytochrome P450(CYP) superfamily of enzymes*. These* are membrane-bound, heme-containing isozymes present in most tissues, with the highest concentration in the liver [16]. These monooxygenases catalyze numerous reactions involved in drug metabolism and the synthesis of cholesterol, steroids, and other lipids [17].

The *CYP2R1* gene encodes 25-hydroxylase, a protein consisting of 501 amino acids expressed in the endoplasmic reticulum of hepatocytes. This enzyme converts vitamin D3 into 25-hydroxyvitamin D (25(OH)D), the primary circulating form of vitamin D [18]. Variants of the *CYP2R1* gene, such as the rs10741657 polymorphism, are linked to lower 25(OH)D levels, which may increase the risk of vitamin D deficiency [19]. Furthermore, other cytochrome enzymes, particularly CYP27A1 located in mitochondria, also exhibit vitamin D 25-hydroxylase activity [13].

The *CYP27B1* gene encodes 25-hydroxyvitamin D 1-alpha-hydroxylase, also known as calcidiol 1-monooxygenase or cytochrome P450 27B1 (CYP27B1). It is sometimes referred to simply as 1-alpha-hydroxylase. 1α-hydroxylase is found in the proximal tubule of the kidney and a various other sites, including keratinocytes (skin), immune cells [20], and osteoblasts (bone) [21, where it catalyzes the conversion of 25(OH)D to 1,25-dihydroxy vitamin D. Mutations in *CYP27B1* are known to cause rare disorders such as vitamin D-dependent rickets type 1, characterized by severe rickets and hypocalcemia due to impaired conversion of vitamin D into its active form [22](Huang et al., 2010).

The CYP24A1 gene encodes the enzyme known as 24-hydroxylase (CYP24A1), which is responsible for breaking down 1,25-dihydroxyvitamin D (calcitriol). This enzyme hydrolyzes the side chain of calcitriol, resulting in the production of calcitroic acid and other metabolites that are excreted in the bile. Mutations in the CYP24A1 gene can lead to a condition called idiopathic infantile hypercalcemia, characterized by elevated levels of calcium in the blood due to decreased degradation of active vitamin D [23].

Recently, there has been an increasing number of adult patients being diagnosed with hypercalcemia associated with mutations in this gene [24]. In addition to elevated serum calcium levels, these patients often exhibit elevated serum 1,25-(OH)2D, suppressed parathyroid hormone (PTH) concentrations, nephrocalcinosis (calcium deposits in the kidney), nephrolithiasis (kidney stones), hypercalciuria (high calcium levels in urine), and, in some cases, reduced bone density.

An important component of the vitamin D metabolic pathway is the vitamin D-binding protein (DBP), which is encoded by the *GC* gene. The DBP is primarily known for its role in transporting vitamin D and its metabolites in the bloodstream, but it also serves various other functions, such as scavenging actin after tissue injury, mediating C5a-induced chemotaxis, and facilitating T-cell responses and macrophage activation[25]. Variants of the *GC* gene, such as rs4588 and rs7041, influence the different isoforms of DBP. These isoforms, in turn, affect both total and free circulating concentrations of 25(OH)D, leading to individual variations in vitamin D status and the associated risk of deficiency [26].

The *VDR* gene encodes the vitamin D receptor (VDR), an essential component of the nuclear receptor superfamily involved in regulating calcitriol signaling. Upon activation through its binding with calcitriol, VDR forms a complex with the retinoid X receptor (RXR), enabling it to translocate into the nucleus and regulate the transcription of genes that mediate the effects of vitamin D. *VDR* is mapped at 12q13.11 and is known to have over 900 reported alleles. Various polymorphisms of the *VDR* —such as *Apal (rs7975232), BsmI (rs1544410), Taql (rs731236)*, and *Fokl (rs10735810)*—have been extensively researched concerning their impacts on bone density, immune response, and susceptibility to chronic diseases, including osteoporosis, cancer, and autoimmune disorders [27]. Table 1 summarizes the common mutations in vitamin D metabolizing enzymes, and their plausible effects are shown in table

**Table 1: Summary of common genetic variations in vitamin D metabolizing enzymes**

|  |  |  |  |
| --- | --- | --- | --- |
| **Genes involved in Vitamin metabolism**  | **Mutation/molecular genetics** | **Plausible effects on vitamin D metabolism** | **References** |
| *CYP2R1* | * *rs10741657*
 | Low serum calcitriol level, compromised calcium absorption, and bone mineralization |  [19] |
| *CYP27B1* | * *rs10877012*

(A-1260C);* rs4646536
 | Altered vitamin D absorption, poor calcium absorption |  [22] [28] |
| *CYP24A1* | Loss of function mutations:* c.1186C>T (p. Arg396Trp),
* c.1226G>A (p. Arg409His),
* c.428C>T (p.Pro143Leu)
 | Reduced inactivation of 1,25(OH)₂D, elevated levels of active vitamin D, and increased intestinal calcium absorption. |  [23] [29] |
| *VDR* | * *rs2228570*

(*FokI* Polymorphism, c.2T>C, p. Met1Thr)* *rs1544410*

(*BsmI* Polymorphism, c.352T>C)* *rs7975232*

(*Apa*I Polymorphism, c.1024A>C)* *rs731236*

(*TaqI* Polymorphism, c.1056T>C) | * A shorter, more transcriptionally active version of the VDR protein with enhanced vitamin D signaling
* Influence VDR mRNA stability or splicing, potentially affecting the overall expression of the VDR protein
 |  [27][30][31][59] |
| *GC*  | * *rs7041*

(Asp416Glu)* *rs4588*

(Thr420Lys) | * Variable isoforms affect DBP's affinity for vitamin D metabolites.
 |  [26] |

**4.0 The Critical Role of Vitamin D in Health and Disease**

The vitamin D receptor is expressed in nearly every tissue throughout the body, explaining why vitamin D functions as a pleiotropic hormone. While it has traditionally been acknowledged for its role in calcium homeostasis and bone health, recent research underscores its broader impact on immune regulation, cardiovascular health, metabolic function, and neuroprotection. This pleiotropic nature indicates that a deficiency in vitamin D can contribute to a range of chronic diseases. Vitamin D deficiency is a significant global health issue, affecting approximately 1 billion people worldwide and linked to various chronic conditions. The physiological roles of vitamin D, the mechanism by which it mediates these actions, and the evidence supporting its clinical impact are summarized in Tables 2 and 3.

**Table 2: Physiological functions, mechanism, and clinical impact of deficiency of vitamin D**

|  |  |  |  |
| --- | --- | --- | --- |
| **Physiological function** | **Mechanisms**  | **Clinical impact**  | **References** |
| Calcium and Bone Metabolism | Enhances **intestinal calcium absorption** by upregulating **calbindin-D9k**, a calcium-binding protein in enterocytes. It also regulates **bone mineralization** by maintaining serum calcium and phosphate levels through:* **Parathyroid hormone (PTH) suppression** (prevents excessive bone resorption).
* **Renal calcium reabsorption** (via TRPV5 channels in the kidneys).
* **Osteoblast-osteoclast balance** (modulates RANKL/OPG signaling).
 | Rickets in children, osteomalacia in adults, and osteoporosis. | [12][13] |
| Immune System Modulation | Acts as an **immunomodulator**, influencing both innate and adaptive immunity:* **Enhances antimicrobial peptide (cathelicidin, defensins) production** in macrophages.
* **Regulates T-cell differentiation** (promotes T-regulatory cells and suppresses Th17-mediated autoimmunity).
* **Reduces pro-inflammatory cytokines** (TNF-α, IL-6, IL-17).
 | Autoimmune diseases (MS, RA, T1D), increased infection susceptibility (TB, COVID-19) | [32][33][55] |
| Cardiovascular Health | Vitamin D influences:* **Endothelial function** (reduces oxidative stress, improves NO bioavailability).
* **RAAS regulation** (lowers angiotensin II, reducing hypertension risk).
* **Anti-fibrotic effects** (inhibits cardiac fibroblast proliferation).
 | Hypertension, atherosclerosis, heart failure | [34][35][58] |
| Metabolic and Endocrine Effects | * **Insulin sensitivity**: Enhances β-cell function and GLUT4 translocation.
* **Adipocyte regulation**: Inhibits adipogenesis and inflammation (reduces leptin resistance).
* **Thyroid function**: Modulates TSH secretion and thyroid hormone conversion.
 | Type 2 diabetes, metabolic syndrome, obesity | [36][37[38] |
| Neuroprotection and Mental Health | * **Neuronal calcium homeostasis** (protects against excitotoxicity).
* **Neurotrophic factor regulation** (BDNF, NGF).
* **Anti-neuroinflammatory effects** (reduces microglial activation).
 | Depression, Alzheimer’s disease, Parkinson’s disease | [39][56] |

**Table 3: Evidence for the clinical impact of Vitamin D deficiency**

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| --- | --- | --- |
| **Disorder**  | **Evidence from various studies** | **References**  |
| **Musculoskeletal Disorders** | Low vitamin D increases fracture risk by **30-50% and linked to muscle weakness** (myopathy due to impaired calcium-dependent muscle contraction). |  [40] |
| **Autoimmune Diseases** | Lower vitamin D predicts higher relapse rates in **multiple sclerosis (MS)**Deficiency exacerbates joint inflammation in **rheumatoid arthritis (RA)**Low prenatal vitamin D increases **Type 1 Diabetes (T1D**) risk in offspring Low vitamin in early life increases the risk of TID |  [41][42][43] [44][45] |
| Cardiovascular diseases | Vitamin D suppresses renin, reducing BP (10)Deficiency increases myocardial infarction risk (11). |  [35] [46][47] |
| Metabolic Disorders | Supplementation improves **HbA1c in prediabetes** (lowers insulin resistance**Obesity worsens vitamin D deficiency** because adipose tissue sequesters vitamin D. | [36] [48][49][57] |
| Neurological and Psychiatric Conditions | **In depressive patients, meta-analyses show improved mood with Vitamin D supplementation.****Low vitamin D substantially increases dementia risk**  | [43] [50] [51] |
| Cancer Risk Modulation | Vitamin D regulates cell proliferation via VDR-mediated gene transcription, and **higher vitamin D levels lower the incidence of colorectal, breast, and prostate cancer**. | [52] |
| Gynecological disorders | **Fibroadenoma** with deficient vitamin D were significantly more (70%) as compared to the controlWorsening symptoms in **PCOS** is associated with low vitamin level | [53][54] |

**5.0 Conclusion**

Vitamin D is a multifunctional hormone that regulates numerous essential physiological processes, making optimal levels vital for overall health. The clinical consequences of a deficiency can be far-reaching. Deficiencies may occur due to inadequate sun exposure (as UVB radiation is necessary for synthesis), malabsorption syndromes (such as Crohn’s and celiac disease), obesity (where vitamin D is sequestered in adipose tissue), chronic kidney disease (which impairs 1α-hydroxylation), and genetic polymorphisms that affect key genes in the vitamin metabolic pathway. Screening for deficiencies should account for these varied causes, and supplementation should adopt tailored strategies to address individual needs. Given the diverse effects of deficiency on health, there is a growing interest in assessing vitamin D status among routine patients, which could serve as a cost-effective approach to enhancing the overall health of many populations worldwide.

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