



Possible Causes And Prevalent Consequences Of VitaminD Deficiency A Review.

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Abstract:

The three primary ways to obtain Vitamin D (VD) are through sunlight exposure, dietary intake, and supplements. Since food generally contains low levels of VD, the most effective methods for maintaining adequate VD levels are through skin synthesis and proper supplementation. VD₂ and VD₃, which are produced not only by certain invertebrates and plants but also within the human body. Alarming, VD deficiency is increasingly common across the global population and is now considered a widespread health issue. VD deficiency is particularly common in older adults and individuals with obesity. It is now linked to a higher risk of developing bone disorders, cardiovascular conditions, diabetes, cancer, autoimmune diseases, and allergies. Educating both the public and healthcare professionals about the benefits and sources of VD, along with promoting appropriate supplementation, can help reduce the prevalence of deficiency.

1. Introduction:

VD is unique among vitamins because it also functions as a hormone. It is classified as a fat-soluble vitamin. In humans, the two most significant forms are ergocalciferol (VD₂) and cholecalciferol (VD₃) [1]. VD₂ is produced by certain invertebrates and fungi, while VD₃ is generated in the bodies of vertebrates. Nearly 90% of the body's VD is produced in the skin through the activation of 7-dehydrocholesterol when exposed to ultraviolet B (UVB) sunlight. Therefore, limited sun exposure can contribute to VD deficiency. The remaining 10% comes from dietary sources, including codfish, mushrooms, milk, eggs, and fortified foods. While UVB exposure is crucial for VD production, several other factors—such as age, body weight, skin pigmentation, clothing habits, and sunscreen use—can also influence VD levels [2]. Risk factors for VD deficiency are premature birth, skin pigmentation, low sunshine exposure, obesity, malabsorption and advanced age. Risk groups are immigrants and the elderly [3].

2. VD metabolism:

There are two primary physiologically relevant forms of VD: cholecalciferol (VD₃), which is mainly produced in the skin from 7-dehydrocholesterol through exposure to UV-B radiation, and ergocalciferol (VD₂), which is obtained from dietary sources. On explaining briefly, once in the body, VD is first converted in the liver to 25-hydroxyVD [25(OH)D] by the enzyme VD 25-hydroxylase (25-OHase). This form then circulates to the kidneys, where it undergoes a second hydroxylation by the enzyme 25-hydroxyVD-1 α -hydroxylase (1 α OH ase), producing the biologically active form, 1, 25-dihydroxyVD

[1,25(OH)₂D], also known as calcitriol. This second hydroxylation at the 1 α position is the key regulatory step in the activation of VD and is tightly regulated by multiple factors including parathyroid hormone (PTH), calcium and phosphate levels, and a range of hormones such as oestrogens, androgens, growth hormone, prolactin, thyroxin, cortisol, and insulin [4].

The most reliable marker of VD status is serum 25(OH) D concentration due to its relatively long half-life (ranging from 1 to 3 months) and its ability to reflect VD obtained from both sunlight and dietary intake[5]. Although 1,25(OH)₂D is more biologically active and binds more strongly to the VD receptor (VDR), it is not a suitable marker for assessing VD status. This is because it circulates in much lower amounts, has a short half-life (less than 4 hours), and can remain normal or even rise in conditions like VD deficiency or secondary hyperparathyroidism [6]. The active form of VD binds to VDRs, which are found in a wide variety of cells and tissues. Research has shown that VD influences the expression of around 3% of the human genome, underscoring the broad and critical impact of VD on health and the potential consequences of its deficiency [7].

3. Physiological effects of VD :

VD is crucial for maintaining calcium and phosphorus balance in the body, which directly influences bone development. Under normal conditions, the body absorbs only about 10–15% of dietary calcium and around 60% of dietary phosphorus. However, when VD levels are adequate, calcium absorption can increase to 30–40%, and phosphorus absorption to approximately 80%. During life stages with heightened calcium demands—such as growth, pregnancy, and lactation—up to 60–80% of dietary calcium can be absorbed if VD levels are sufficient. This sufficiency is indicated by elevated levels of circulating 1,25-dihydroxyVD, which corresponds with improved mineral absorption. VD's importance in preventing bone-related diseases has been recognized across various age groups.

The widespread non-skeletal effects of VD are largely due to the presence of VD receptors (VDR) in the majority of tissues and organs throughout the body[10]. Different studies such as case control and prospective and retrospective trials have affirmed the connection between VD and 15 different types of cancer where the anticancer mechanism of VD by VDR is associated with the regulation of proliferation, differentiation, apoptosis and angiogenesis in normal and cancerous cells [11, 12]. VD impacted to cardiovascular disease prevention due to the availability of VDR on the endothelium and vascular smooth muscle and cardiac muscle cells. The anti-atherosclerotic effects of VD included the inhibition of the foam cell formation and smooth cell proliferation, the expression of adhesion molecules on endothelial cells and the release of inflammatory mediators [13].

VD also plays a role in managing hypertension, one of the most prevalent non-communicable diseases. Its blood pressure-lowering effects are primarily linked to the suppression of the renin-angiotensin system within the kidney's juxtaglomerular apparatus. Specifically, the active form of VD, 1,25(OH)₂D (calcitriol), reduces renin gene expression by interfering with the transcription factor cAMP-CRE-binding protein, thereby inhibiting renin production in the kidneys. Additionally, VD helps prevent primary hyperparathyroidism and supports calcium metabolism—both of which contribute to its overall antihypertensive effect[14,15].

Research investigating the role of VD in the development and modulation of autoimmune diseases has shown encouraging results. These studies highlight VD's importance in regulating cytokine production, reducing inflammation, and influencing immune cell activity. Specifically, VD has been found to boost the number of Th2 lymphocytes and to have immunoregulatory and anti-inflammatory properties, partly by promoting the proliferation of dendritic cells [16, 17]. The impact of VD on autoimmune mechanisms has primarily been studied in conditions like diabetes, multiple sclerosis, rheumatoid arthritis, and Crohn's disease. Several factors support the potential role of VD in preventing diabetes, including the presence of VD receptors (VDR) on pancreatic beta cells, calcitriol's ability to enhance insulin secretion, its role in lowering insulin resistance in muscle tissue, and its anti-inflammatory effects associated with insulin resistance [18].

The key elements supporting VD's role in brain development and normal brain function are the presence of 1α -hydroxylase and VD receptors (VDR) in the human brain. Researchers have explored the link between VD and the underlying mechanisms of conditions such as cognitive decline, Alzheimer's disease, anxiety, and depression [19].

4. Risk factors for VD deficiency:

Several factors can contribute to low VD levels. Individuals with darker skin tones, those with chronic kidney disease, or those who are bedridden for extended periods are at higher risk. Certain medical conditions, such as malabsorption disorders like Crohn's disease, cystic fibrosis, and severe liver diseases, can also impair VD absorption. Additionally, the use of specific medications—including rifampicin, anticonvulsants, thiazide diuretics, and corticosteroids—can negatively affect VD levels. Substances that interfere with absorption, such as mineral oils, cholestyramine, and some laxatives, can further reduce VD availability [20].

Excess body weight is another contributing factor, as VD tends to become sequestered in adipose tissue, lowering its levels in the bloodstream [21]. Overall, VD deficiency commonly results from inadequate dietary intake or insufficient exposure to sunlight [22]. VD deficiency is particularly common in individuals undergoing corticosteroid treatment. These medications promote calcium loss through the kidneys and decrease its absorption in the intestines. Additionally, corticosteroids accelerate bone resorption and impair bone regeneration, leading to decreased bone density and a higher risk of pathological fractures (23). Studies have also found that corticosteroids enhance hydroxylase activity, further reducing VD levels in the body (24).

5. Manifestations Of VD Deficiency:

5.1 The effect of VD on gastrointestinal and endocrine systems; VD plays a significant role in the gastrointestinal and endocrine systems. In the cells of the gastrointestinal tract, calcitriol enhances the absorption of calcium and phosphorus. Along with calcitriol, parathyroid hormone (PTH) also regulates the metabolism of these minerals. PTH stimulates the enzyme responsible for converting 25(OH)D into calcitriol, leading to increased levels of active VD. In turn, calcitriol inhibits PTH activity, limits the growth of parathyroid cells, and reduces their hormone secretion [25].

5.2 Effect on bone tissue; Calcitriol, in conjunction with parathyroid hormone (PTH), plays a key role in regulating bone metabolism. VD receptors (VDRs) found on osteoblasts enable calcitriol to enter bone cells, where it promotes the expression of specific genes, particularly those involved in the activation of the receptor activator of nuclear factor κ B ligand (RANKL). RANKL then interacts with receptors on cells of the monocyte lineage, promoting their clustering, differentiation, and maturation into osteoclasts. These mature osteoclasts secrete various enzymes, such as collagenases and hydrochloric acid, which break down collagen and facilitate the release of calcium and phosphorus into the bloodstream [26].

5.3 Effect on immune system; VD is recognized for its role in stimulating the innate immune system and modulating the adaptive immune response [27]. It enhances the production of specific peptides, such as cathelicidin, in respiratory tract cells, which possess antimicrobial properties. Cathelicidin helps disrupt bacterial membranes [28]. A deficiency in VD is linked to a greater susceptibility to respiratory infections [29, 30, 31]. Insufficient VD levels are also associated with an elevated risk of infection by the SARS-CoV-2 virus [32]. Furthermore, low VD status has been correlated with an abnormal cytokine response, which can lead to severe complications in COVID-19 patients [29, 33–35]. Blood levels of VD are therefore considered a potential biological marker for predicting the severity and outcome of COVID-19 infection [36].

5.4 Effect on the occurrence of malignant diseases; VD deficiency has been linked to certain types of cancer [37, 38]. Studies have shown that many individuals with melanoma exhibit either insufficient or deficient levels of VD [39]. Similarly, low VD levels have been observed in patients with thyroid cancer [40]. Among women with breast cancer, those with VD deficiency tend to experience more rapid disease

progression and lower survival rates compared to those with adequate VD levels [41]. Additionally, a long-term study in Japan found that over a 15-year period, women with low VD concentrations had a higher incidence of both breast and liver cancer [42].

5.5 Effect on the cardiovascular system; previous studies have emphasized the importance of maintaining sufficient VD levels for optimal cardiovascular health. Elevated parathyroid hormone (PTH) levels are closely linked to increased blood pressure, whereas calcitriol, the active form of VD, may help lower blood pressure by reducing PTH concentrations [43]. Additionally, research has shown that calcitriol can suppress the production of renin [44]. Experiments on mice further revealed that calcitriol directly affects sarcomeres by regulating their contractions, reinforcing the connection between VD and cardiovascular conditions [45].

Effect on insulin secretion and blood glucose regulation; VD positively influences pancreatic beta cells by enhancing their ability to secrete insulin. In peripheral tissues, it improves cellular sensitivity to insulin, promoting glucose uptake into the cells. This effect also indirectly lowers the risk of cardiovascular diseases associated with elevated blood glucose levels [43]. A study by Maestro and colleagues demonstrated that calcitriol can activate the transcription of the insulin receptor gene in promonocyte cells [46].

Conclusion:

VD plays a crucial role in supporting various functions within the human body. It is important to highlight that a deficiency in VD can be harmful, as it is associated with the development of numerous health conditions discussed in this paper. The severity of deficiency directly impacts the intensity of symptoms and the likelihood of disease onset. Given its widespread implications, VD deficiency represents a serious public health concern. Therefore, maintaining adequate VD levels is essential, and supplementation should be guided by healthcare professionals who are familiar with the patient's medical history and specific deficiency status.

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