REVIEW | OPEN ACCESS

Medical Science

To Cite:
Glapiński F, Woźniak K, Stasiak M, Woźniak A, Żyro W, Żyro K. The Expanding Role of Vitamin D in Cancer: Mechanisms, Metabolism, and Therapeutic Potential. *Medical Science* 2025; 29: e92ms3575
doi: https://doi.org/10.54905/disssi.v29i160.e92ms3575

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Peer-Review History
Received: 7 March 2025
Reviewed & Revised: 16/March/2025 to 15/June/2025
Accepted: 18 June 2025
Published: 25 June 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

The Expanding Role of Vitamin D in Cancer: Mechanisms, Metabolism, and Therapeutic Potential

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ABSTRACT

Vitamin D is a fat-soluble prohormone. It plays a key role in maintaining calcium and phosphate balance. It also has many other functions beyond its role in the skeletal system. These include supporting the immune system, heart health, and cancer-related processes. This review explains the process of vitamin D synthesis, its mechanism of action, and its effects on the body. The review places special focus on its role in cancer. The review describes the process of vitamin D synthesis and its regulatory mechanisms. It also highlights the widespread presence of the vitamin D receptor (VDR) in many tissues. Research indicates that lower levels of serum vitamin D are associated with an increased risk of developing cancer - especially multiple myeloma, breast, prostate, and lung cancer. Observational studies often show positive results. However, randomized clinical trials have demonstrated mixed outcomes. This limits the role of vitamin D in cancer prevention. Still, it is essential to maintain adequate vitamin D levels, especially in cancer patients. More research is needed to find effective supplementation strategies in cancer care.

Keywords: Vitamin D, Calcium and phosphate metabolism, extraskeletal impact of vitamin D, colon cancer

1. INTRODUCTION

Vitamin D plays a vital role in human health. Scientists first recognized it as a key regulator of calcium and phosphate balance, which is essential for bone strength and structure. Over time, researchers discovered that vitamin D also influences many other biological processes. It now qualifies as a pleiotropic hormone with effects that extend far beyond the skeletal system. The body can produce vitamin D in the skin when exposed to sunlight, specifically ultraviolet B (UVB) radiation. People can also get it from food or supplements. Once in the body, vitamin D undergoes two metabolic steps—first in the liver and then in the kidneys. These steps convert it into its active form, calcitriol. Calcitriol binds to the vitamin D receptor (VDR), which is present in almost all human cells. This enables vitamin D to influence a broad range of genes and cellular functions.

Recent studies have shown that vitamin D supports immune responses, protects the cardiovascular system, and helps maintain muscle strength. It may also influence pregnancy outcomes, reduce the risk of chronic diseases, and even play a role in preventing some types of cancer. Low vitamin D levels are common worldwide and affect numerous groups, including newborns, older adults, individuals with limited sun exposure, and patients with chronic or oncologic diseases. Due to its wide-ranging effects, vitamin D has become a focus of research in numerous medical fields. Scientists continue to study how vitamin D works, how to measure its levels accurately, and how to utilize it in prevention and treatment. This review examines the metabolic pathways, mechanisms of action, and potential clinical applications of vitamin D, with a particular emphasis on its role in cancer biology (Muñoz & Grant, 2022; Zhao et al., 2024).

2. METHODOLOGY

For this review, we searched PubMed and Google Scholar for articles published between 2000 and 2024. We focused on studies about vitamin D and its role in the body, especially in cancer. We used keywords such as vitamin D, calcitriol, vitamin D receptor, cancer, and vitamin D metabolism. We first checked the titles and abstracts. Then, we read the full texts of the most relevant papers. We included studies that explained how vitamin D works and its effects on health. We specifically sought papers that linked vitamin D to cancer. We only used articles written in English and published in scientific journals.

We excluded studies that focused solely on animals or topics unrelated to cancer, unless they contributed to understanding how vitamin D functions in the body. We carefully chose the best articles to include in this review. Nine hundred forty-five records were identified through database searching; no duplicates were removed. Eight hundred seventy-six records were excluded based on titles and abstracts. Sixty-nine full-text articles were assessed for eligibility and finally included in the qualitative synthesis. Details are given in the PRISMA flowchart (Fig.1).

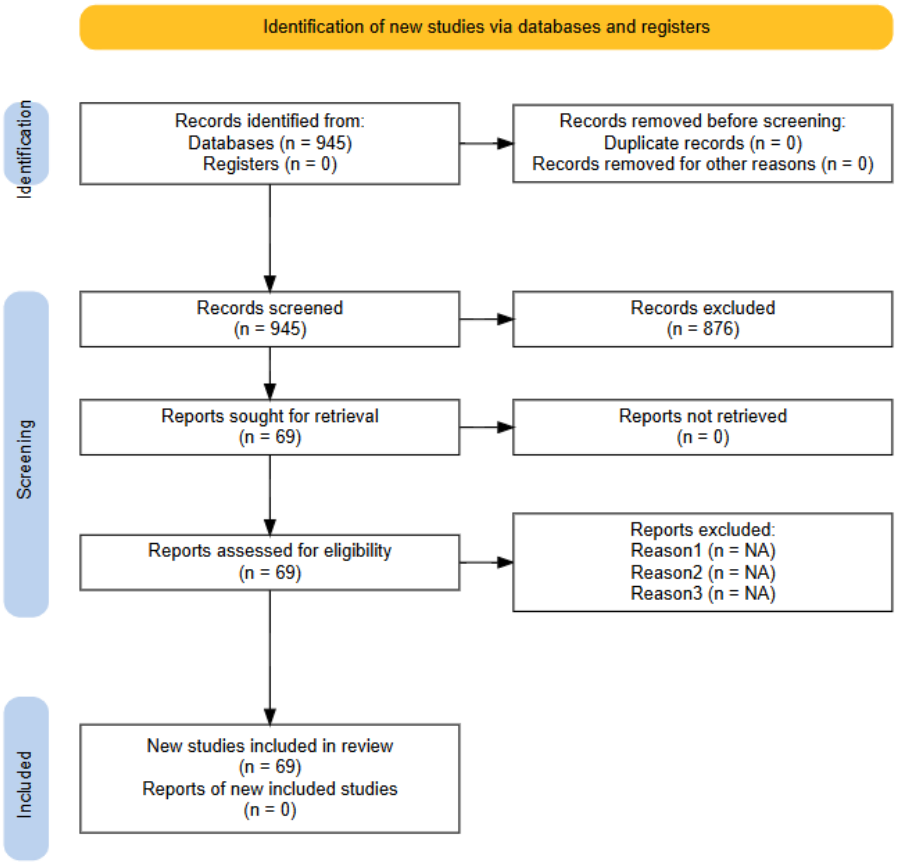

Figure 1: PRISMA flowchart.

3. RESULTS AND DISCUSSION

The modern definition of a vitamin differs from the original word's etymology. In 1910, Japanese scientist Umetaro Suzuki pulled a water-soluble nutrient mix from rice bran and named it aberic acid. Two years later in London, Polish biochemist Casimir Funk isolated the same mix, coined the word "vitamin," and called it the "anti-beri-beri factor." Today we know this nutrient as thiamine, or vitamin B1. Maximilian Nierenstein – a professor of biochemistry from the University of Bristol, reportedly suggested „vitamin" as an abbreviation for „vital amine" back then since scientists at the time believed all such compounds contained an amine group (Rosenfeld, 1997; Semba, 2012). Nowadays, vitamins are defined as chemicals that the organism needs in small amounts for maintaining homeostasis. Vitamins are obtained from plants and animal food products and dietary supplements. Vitamins are either fat-soluble or water-soluble (Wolf, 2004).

3.1. Vitamin D – vitamine or hormone?

Vitamin D is a fat-soluble vitamin acquired from diet and a seco-steroidal prohormone produced in the skin by ultraviolet B (UVB, 290-320nm) from sunlight. Hepatic 25-hydroxylase converts vitamin D to 25-hydroxyvitamin D, and renal 1α-hydroxylase produces the active hormone calcitriol, which signals through the vitamin D receptor (VDR). As Vitamin D is synthesized endogenously, it does not meet vitamin criteria. It is also a far more multipotent compound than other vitamins, typically serving as an enzyme cofactor. VDR is found in nearly all cells in the body. Many body cells widely express CYP27B1, the enzyme that produces the active metabolite of vitamin D and serves as the ligand for the VDR. This fact indicates that the role of vitamin D is not limited to its classical role in calcium and phosphate metabolism, but extends to a broad spectrum of metabolic pathways in the human body (Bikle, 2016).

3.2. Synthesis of vitamin D and primary food resources

The main source of Vitamin D3 is skin, where it is synthesized from 7-dehydrocholesterol (7-DHC). In contrast, both vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) can be present in the diet, especially in fish, dairy products, Shitake mushrooms, and liver, as vegetarians are particularly susceptible to vitamin D deficiency (Agnoli et al., 2017; Uusi-Rasi et al., 2015).

Once in circulation, vitamin D undergoes hydroxylation in the liver to form 25-hydroxyvitamin D [25(OH)D], followed by conversion to its active form, 1,25-dihydroxyvitamin D [1,25(OH)2D] – primarily in the kidneys, but also in activated macrophages, microglia, breast tissue, colon, parathyroid glands and keratinocytes (Adams et al., 2014). [25(OH)D] and [1,25(OH)2D] are subsequently metabolised to their inactive hydroxyforms – [24,25(OH)2D2/3], [1,24,25(OH)3D2/3], [23,25(OH)2D3], [1,23,25(OH)3D]. Vitamin D is highly lipophilic due to its steroid structure. It is usually bound to protein carriers that help maintain stable serum levels, with a half-life of 2-3 weeks for [1,25(OH)2D] and 5-8 hours for [25(OH)D] in non-obese patients (Lang et al., 2023).

Sunlight is the most well-known "substrate" for the synthesis of vitamin D. Still, the body needs chemical compounds it can convert into vitamin D. Although 7-DHC can be converted into vitamin D without enzymatic help, 7-DHC synthesis is impossible without enzymes. This subsequently leads to the conclusion that any disturbance in this process could result in vitamin D deficiency, even with adequate sunlight exposure. The 7-dehydrocholesterol reductase (DHCR7) enzyme converts 7-dehydrocholesterol (7-DHC) to cholesterol, so its activity dictates the amount of 7-DHC available for vitamin D synthesis (Fitzky et al., 1998). The regulation of DHCR7 is not fully known, although the fact is that cholesterol and vitamin D increase proteasomal degradation of DHCR7 and lead to increased vitamin D production (Prabhu et al., 2016).

After converting 7-DHC to cholecalciferol, the liver is the next station in the metabolic pathway, where 25-hydroxylases turn it into [25(OH)D], but noteworthy is the fact that numerous enzymes within mitochondria and microsomes have 25-hydroxylase activity. For instance, patients with inactivating mutations of CYP27A1, which was once suggested as the main 25-hydroxylase, used to develop cerebrotendinous xanthomatosis, but not rickets, which meant that other enzymes had 25-hydroxylase activity. Nowadays, data support CYP2R1 as a major 25-hydroxylase in the liver, but even after knocking out the CYP2R1 gene in mice models [25(OH)D], levels drop by 50%, but not more (Bikle, 2020). Interestingly, 25-hydroxylation of vitamin D is not primarily substrate dependent – a high-fat diet, rich in cholesterol, results in decreased serum level of [25(OH)D] and impaired expression of CYP2R1 in the liver. In contrast, vitamin D levels remain the same in mice models (Roizen et al., 2019).

Unlike the 25-hydroxylases, there is only one 25(OH)-1α-hydroxylase – CYP27B1, which primarily concentrates in the kidneys, but is also expressed in the epidermis, bones, placenta, and immune system cells. Paracrine and autocrine agents strictly regulate CYP27B1. It is upregulated by parathyroid hormone (PTH) and insulin-like growth factor-1 in the kidneys. In other tissues, primarily immune cells, interferon-gamma (IFN-γ), tumor growth factor alpha (TNFα), and transforming growth factor beta1 (TGFβ1) upregulate its

expression). Also, interleukins could impact CYP27B1 activity – IL-1, IL-2, and IL-15 are inducers, whereas IL-4 is a suppressor. Thus, hypercalcemia often occurs in granulomatous diseases, such as sarcoidosis and lymphomas (Bartonkova et al., 2018; Noyola-Martínez et al., 2014).

The active form of vitamin D is not permanent. Every chemical compound in the human body undergoes catabolic processes, turning it into inactive forms and evicted from the system. CYP24A1 and CYP3A4 are both main enzymes, which catylyst 24(23)-hydroxylation of [1,25(OH)2D]. CYP24A1 is the dominant 24-hydroxylase in most tissues, but CYP3A4, a highly expressed protein in liver and intestinal tissues, plays a big role. Both enzymes have 24-hydroxylase and 23-hydroxylase activity, but the proportions of these two are specific for each species (Ketha et al., 2018; Tuckey et al., 2019). Nevertheless, we shouldn't label CYP3A4 as a pure catabolic enzyme, as [1,24,25(OH)3D2/3] maintains some affinity to VDR – about 10% of [1,25(OH)2D].

Furthermore, [24,25(OH)2D2/3], which is also commonly treated as an inactive form, can bind to specific G-protein-coupled membrane receptors, usually expressed in bones and skin, and can play a crucial role in fracture repair (Martineau et al., 2018). CYP24A1 is upregulated by [1,25(OH)2D], fibroblast growth factor 23 (FGF23), calcium, and also by 5α-dihydrotestosterone via progesterone receptor, which explains the higher frequency of osteoporosis in the post-menopausal population of women (Lee et al., 2018).

3.3. Mechanism of action

Vitamine D acts mainly via VDR, with [1,25(OH)2D] as the primary ligand. VDR is a transcription factor found in nearly all cells, which results in vitamin D participation in many cellular processes, especially the regulation of intestinal calcium absorption. Researchers have recently identified 11,031 genes influenced by VDR activity, including 43% involved in metabolism, 19% in cell and tissue morphology, 10% in cell junction and adhesion, 10% in differentiation and development, 9% in angiogenesis, and 5% in the epithelial-to-mesenchymal transition. Despite VDR acting mainly as a transcription factor, it has also been shown to have nongenomic actions via its location in the plasma membrane and mitochondria (Bouillon et al., 2019; Saccone et al., 2015).

Every cell in the body has a different regulation of VDR expression. The most critical factor that regulates VDR expression is [1,25(OH)2D] – for example, it influences VDR presence in bone cells but not in the intestine. Many other factors, such as growth factors, insulin, PTH, glucocorticoids, estrogen, and retinoic acid, act through various transcription factors and regulate VDR expression. Calcium upregulates VDR expression in the parathyroid gland through its calcium-sensing receptor. On the other hand, SNAIL 1 and 2 (SLUG) downregulate VDR expression in several cell lines (Carlberg, 2017).

3.4. Vitamin D influence to body tissues

The effect of vitamin D on individual body systems was shortly summarized in Table 1. Each point has been developed in detail below in the following paragraphs.

Table 1: summary of most important vitamin D influence to body parts

Body system	Effects of Vitamin D
Skeletal System	Regulates calcium and phosphate metabolism; essential for bone mineralization and preventing rickets/osteomalacia (Bouillon et al., 2019).
Immune System	Modulates innate and adaptive immunity; suppresses proinflammatory cytokines (Hewison, 2010).
Cardiovascular System	Regulates expression of renin and other cardiovascular genes; deficiency linked to hypertension and cardiac hypertrophy (Latic & Erben, 2020).
Muscular System	Promotes muscle cell differentiation and function; deficiency causes muscle weakness, especially in infants and elderly (Bollen et al., 2022).

Skin	Topical and systemic effects in conditions like psoriasis and potentially protective against UV-induced DNA damage (Kechichian & Ezzedine, 2018).
Reproductive System (Pregnancy)	Reduces risk of pre-eclampsia (Fogacci et al., 2020).
Gastrointestinal System	Reduces inflammation and supports mucosal immunity in Crohn's disease (Wu et al., 2010).
Oncology	Antiproliferative effects was shown in lab studies (Muñoz & Grant, 2022).

3.5. Calcium and phosphate metabolism

Vitamin D is best known for its role in regulating calcium and phosphate metabolism. [1,25(OH)2D], PTH and FGF23, forms a triumvirate that tightly regulates serum-ionized calcium concentrations and phosphate homeostasis. Maintaining serum levels of ionized calcium is crucial for a range of physiological functions, including enzyme activity, hormone production, intestinal calcium absorption, DNA repair, mitochondrial energy production, and the mineralization and structural integrity of the skeleton (Kägi et al., 2018; Kroll et al., 2015). Blood calcium balance relies on three coordinated actions which is increased intestinal absorption of calcium, osteoclast-mediated release of calcium from bone, and reduced renal excretion. Together with osteoblast activity, these processes support bone mineralization and remodeling, keeping serum calcium and phosphate within physiological range. Calcitriol regulates intestinal fractional calcium absorption in local cells, thereby affecting the concentrations of calcium-binding proteins, such as calbindin. Furthermore, circulating parathyroid hormone (PTH) and calcitriol regulate serum ionized calcium levels by influencing the expression of genes such as CYP2R1, which encodes 25-hydroxylase, and CYP24A1, which encodes 24-hydroxylase. In turn, ionized calcium levels affect both the synthesis and release of PTH as well as the activity of 24-hydroxylase. Consequently, vitamin D deficiency disrupts calcium homeostasis and phosphate metabolism at many independent stages – chronic hypovitaminosis D can delay skeletal maturation and calcification, leading to the accumulation of unmineralized bone tissue known as osteoid, which presents clinically as rickets in children and osteomalacia in adults (Dahlquist et al., 2015; Mark et al., 2016; Wacker & Holick, 2013).

3.6. Vitamin D effects beyond the skeletal system

3.6.1. Pregnancy

Although best known for its role in calcium and phosphate metabolism, vitamin D is a multipotent hormone involved in numerous molecular pathways essential for maintaining homeostasis. Sufficient vitamin D serum level lowers pre-eclampsia risk, whereas impaired vitamin D metabolism in trophoblasts and placental endothelial cells increases that risk (Ma et al., 2012).

3.6.2. Skin

Despite the plethora of preclinical data and randomized clinical trials regarding vitamin D and skin cell interaction, it remains speculative whether vitamin D deficiency contributes to the development of cutaneous diseases in humans or is merely a marker of illness or inflammatory status. Three primary study directions involve psoriasis, skin cancer, and balding (Autier et al., 2014).

Studies are still investigating the relationship between vitamin D and psoriasis. Psoriasis pathogenesis consists of increased proliferation and decreased final differentiation of keratinocytes, and inflammation contributes to clinical expression. Although long-term studies showed no association between vitamin D intake and psoriasis, some data suggest improving the clinical course of psoriasis during oral calcitriol therapy (Merola et al., 2014). Moreover, topical application of [1,25(OH)2D] or analogs to psoriasis plaques could have beneficial effects – with safety and efficacy compared to topical corticosteroid therapy without side effects of corticosteroids (Soleymani et al., 2015).

Vitamin D influence on skin cancer is still ambiguous. UVB light, responsible for vitamin D synthesis in skin cells, is carcinogenic. On the other hand, vitamin D metabolites display anticarcinogenic activities, serving as key factors in DNA damage repair (De Haes et al., 2005; Tongkao-On et al., 2013). Numerous studies have investigated the link between vitamin D intake and nonmelanoma skin cancer (NMSC) and found an inverse association between [1,25(OH)2D] serum levels and NMSC incidence (Tang et al., 2010).

However, another study showed that keeping [1,25(OH)2D] serum levels above a certain threshold is associated with an increased risk of NMSC (Asgari et al., 2010).

Regarding the relationship between vitamin D and melanoma, there is evidence of a protective effect of [1,25(OH)2D], but UV radiation—the main source of vitamin D—is mutagenic. In recent studies, low-dose vitamin D and calcium supplementation have shown no difference in melanoma incidence compared to a placebo during a 7-year follow-up (Tang et al., 2011).

Balding, despite being non-lethal, is also a concerning condition, affecting especially mental health. A cross-sectional study of 296 healthy men showed no association between the severity and extent of baldness and serum[1,25(OH)2D] levels. Furthermore, calcipotriol failed to improve alopecia in patients with scalp psoriasis (Bolland et al., 2008).

3.6.3. Muscles

The expression of VDR in muscles is still ambiguous topic (Girgis et al., 2013; Wang & DeLuca, 2011). [1,25(OH)2D] has apparent antiproliferative effects on cultured muscle cells and regulates muscle cell maturation, which prevents hypertrophy and fibrosis, especially in heart muscle. However, vitamin D deficiency is associated with muscle weakness and cardiomyopathy in infants – particularly in patients with congenital absence of CYP27B1 or severe renal osteodystrophy, followed by rapid improvement after administering vitamin D in such patients (Bouillon et al., 2019). Different studies have shown that treatment with 800 IU of vitamin D daily in elderly, D-deficient individuals reduces body sway and falling incidents (Cangussu et al., 2016; Lips et al., 2010). Nevertheless, overdosing on vitamin D supplementation may increase the risk of falling and fracture (Bischoff-Ferrari et al., 2016; Sanders et al., 2010).

3.6.4. Immunity

The immune system comprises two primary yet interacting forms of immunity: adaptive and innate. At the same time, cells specialized in antigen presentation initiate adaptive immunity. Almost every cell of the immune system, including epithelial cells, expresses VDR and CYP27B1. However, the regulation of CYP27B1 differs from that in the kidney, as it's insensitive to PTH and FGF23, [1,25(OH)2D] and calcium. Thus, it undergoes regulation by TNFα and IFN γ (Gyetko et al., 1993). Moreover, several of these cells express CYP2R1 and at least theoretically can produce [1,25(OH)2D] from circulating vitamin D (Bikle, 2009; Liu et al., 2007). [1,25(OH)2D] slows the maturation of dendritic cells (DC) and decreases their ability to present antigens. By suppressing IL-12, IL-23, and IL-6 production, vitamin D reduces Th1 and Th17 cells. Consequently, the recruitment and proliferation of T cells is impaired (Daniel et al., 2008).

Most studies have found inverse correlations between [1,25(OH)2D] serum level and autoimmune diseases such as multiple sclerosis, type 1 diabetes, Crohn's disease, rheumatoid arthritis, lupus, and Graves-Basedow thyroiditis (Knip et al., 2010; Lee & Bae, 2016). Vitamin D and the relation to immunity influence infections. Vitamin D deficiency increases the risk of infectious diseases, particularly those of the upper respiratory tract, a phenomenon recognized since the 19th century, as sunlight exposure was a common form of tuberculosis treatment (White, 2008). Besides tuberculosis, vitamin D supplementation has been shown to prevent infections, such as seasonal influenza and ear infections (Camargo et al., 2012).

Vitamin D regulates immunity by helping to prevent infectious diseases and mitigate autoimmune diseases, especially in patients with inflammatory bowel disease (IBD), particularly those with Crohn's. Vitamin D deficiency is common among patients with CD, which results in a combination of chronic inflammation, intestinal malabsorption of vitamin D, and lifestyle. Although the correlation between vitamin D and IBD has been known for a long time, the mechanism by which it works at the cellular level remains unclear.

Recent studies have shown that the gene encoding the pattern recognition receptor NOD2 targets [1,25(OH)2D]. NOD2 signalling pathway mutations contribute strongly to CD development (White, 2018). Moreover, downstream signalling of NOD2 activates transcription of gene DEB4/HBD2, which is responsible for the antimicrobial peptide strongly correlated with CD susceptibility, which is the direct target of the VDR (Stefanic et al., 2013). In a large prospective cohort, women whose predicted serum 25OHD reached 75 nmol/L had a multivariate-adjusted HR of 0.38 (95% CI, 0.15 to 0.97) for developing CD compared with those whose levels were below 50nmol/L. (Ulitsky et al., 2011).

3.6.5. Cardiovascular system

Vitamin D signaling regulates key cardiovascular genes, including renin, plasminogen activator inhibitor (PAI), and thrombomodulin. Preclinical studies have shown that [1,25(OH)2D] benefits endothelial, smooth muscle, and cardiac muscle cells. Hence, Vdr-null and Cyp27b1-null mice develop high-renin hypertension and cardiac hypertrophy, probably due to the downregulation of renin by

[1,25(OH)2D]. Observational studies documented an inverse relationship between vitamin D status and cardiovascular risk, adjusting for other risk factors such as BMI, chronic kidney disease, hypertension, diabetes, and smoking. Prevalence of heart failure and peripheral arterial diseases appears among patients with lower [1,25(OH)2D] values (Wang et al., 2012). Despite the promising results of observational studies, intervention studies are less convincing. A meta-analysis did not show a significant effect of oral vitamin D supplementation on cardiovascular risk factors such as lipids, hyperglycemia, and high blood pressure. Subsequently, only patients with hypovitaminosis may likely benefit from vitamin D supplementation. It is also noteworthy that excess vitamin D could have severe adverse effects on the cardiovascular system, such as vascular calcification, organ failure, and even death (Jorde et al., 2010; Pittas et al., 2010).

Moreover, various glands, including pancreatic islets and parathyroid cells, express CYP2B1, suggesting that [1,25(OH)2D] plays a vital role in autocrine or paracrine signalling in peripheral target cells (Rondini et al., 2015).

3.6.6. Oncology

Researchers first linked vitamin D to cancer in 1979, when they discovered the VDR receptor in a breast cancer cell line. Later, researchers confirmed that many cancer cell lines and tissues contain VDR receptors, leading them to conclude that VDR is not only a marker of malignancy but may also play a crucial role in carcinogenesis. Moreover, CYP27B1 is also expressed in many cancer cell lines in higher concentrations than in neighbouring tissues (Eisman et al., 1979). [1,25(OH)2D] has been proven to have an antiproliferative impact on cancer and normal cells by inhibiting the cell cycle at the G1 stage. Inspired by this fact, numerous trials were conducted to determine the optimal ratio between antiproliferative effects and calcemic effects. Unfortunately, most of them were disappointing because cancer cells lost VDR expression before the antiproliferative effect had a chance to take effect. As adjuvant treatments, active vitamin D metabolites, and analogs have been tested in clinical trials. Hence, hypercalcemia limits the efficacy of those trials (Bikle, 2011).

In addition to the well-documented link between sun exposure and skin cancers (melanoma, NMSC), researchers also investigated a similar association with other types of cancer. In 1980, studies showed that populations with lower solar radiation had higher rates of mortality from colon cancer. Later, more similar discoveries were made. However, the results were often controversial. Nevertheless, the association between colon cancer and low vitamin D status is relatively consistent (Mondul et al., 2017). A systematic review carried out in 2013 concluded that chronic sun exposure was responsible for reduced colorectal, breast, and prostate cancers, as well as non-Hodgkin's lymphoma. Interestingly, prostate cancer risk and serum [1,25(OH)2D] level have shown a U-shaped curve with increased risk for lower and higher concentrations (van der Rhee et al., 2013). Despite promising results from some preclinical and observational studies, RCTs did not bring such positive outputs. Nine out of ten ~RCTs did not show a beneficial influence of vitamin D supplementation in reducing cancer incidence. Therefore, vitamin D supplementation cannot be recommended for primary prevention of cancer (Bouillon et al., 2019).

3.7. Summary

Vitamin D is now seen as a hormone with many functions. It controls several biological processes through its active form, $1,25(OH)_2D$. This form exerts its effects by binding to the vitamin D receptor (VDR), present in numerous body tissues. The paper explains how vitamin D is synthesized and metabolized in the body. It highlights essential enzymes like CYP27B1 and CYP24A1. It also shows how cytokines and hormones affect vitamin D activity. Vitamin D does more than support bone health. It helps regulate the immune system, protects the heart, and supports muscle function. These roles may have medical benefits. The review primarily focuses on the relationship between vitamin D and cancer. It looks at breast, prostate, lung cancer, and multiple myeloma. Lab studies and observational research suggest that vitamin D might help prevent cancer. However, clinical trials have had mixed results. Because of this, vitamin D is not recommended to avoid cancer for everyone. Still, it may help people who are at high risk or have low vitamin D levels. The review encourages a more personalized approach. The use of vitamin D in cancer care should be based on solid evidence and patient needs. Safety and possible benefits should always be considered.

4. CONCLUSIONS

Researchers now view vitamin D as more than a regulator of calcium and phosphate; it acts as a pleiotropic hormone. The skin, liver, and kidneys synthesize and metabolize vitamin D, then calcitriol activates vitamin D receptors in target cells. Calcitriol modulates numerous cellular pathways, including immune responses, cardiovascular function, and skeletal muscle maintenance. Recent studies

link vitamin D signaling to carcinogenesis. Preclinical data show that calcitriol inhibits cell proliferation, promotes differentiation, and shapes antitumor immunity in breast, prostate, and colon cancers. Observational cohorts support these anticancer effects. Randomized clinical trials, however, report mixed results, which prevent the development of firm clinical guidelines. Future investigators will likely design personalized supplementation protocols that consider baseline 25-hydroxyvitamin D levels, individual risk factors, and tumor biology.

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Acknowledgments

No acknowledgments.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Adams JS, Rafison B, Witzel S, Reyes RE, Shieh A, Chun R, Zavala K, Hewison M, Liu PT. Regulation of the extrarenal CYP27B1-hydroxylase. J Steroid Biochem Mol Biol 2014;144 Pt A:22–7. doi: 10.1016/j.jsbmb.2013.12.009.
2. Agnoli C, Baroni L, Bertini I, Ciappellano S, Fabbri A, Papa M, Pellegrini N, Sbarbati R, Scarino ML, Siani V, Sieri S. Position paper on vegetarian diets from the working group of the Italian Society of Human Nutrition. Nutr Metab Cardiovasc Dis 2017;27:1037–52. doi: 10.1016/j.numecd.2017.10.020.
3. Asgari MM, Tang J, Warton ME, Chren M-M, Quesenberry CP Jr, Bikle D, Horst RL, Orentreich N, Vogelman JH, Friedman GD. Association of prediagnostic serum vitamin D levels with the development of basal cell carcinoma. J Invest Dermatol 2010;130:1438–43. doi:10.1038/jid.2009.402.
4. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol 2014;2:76–89. doi:10.1016/S2213-8587(13)70165-7.
5. Bartonkova I, Kallay E, Dvorak Z. Effects of human interleukins in the transgenic gene reporter cell lines IZ-VDRE and IZ-CYP24 designed to assess the transcriptional activity of vitamin D receptor. PLoS One 2018;13:e0193655. doi:10.1371/journal.pone.0193655.
6. Bikle DD. Extraskeletal actions of vitamin D. Ann N Y Acad Sci 2016;1376:29–52. doi:10.1111/nyas.13219.

7. Bikle DD. The vitamin D receptor: a tumor suppressor in skin. Discov Med 2011;11:7–17.
8. Bikle DD. Vitamin D and immune function: understanding common pathways. Curr Osteoporos Rep 2009;7:58–63. doi:10.1007/s11914-009-0011-6.
9. Bikle DD. Vitamin D: Newer concepts of its metabolism and function at the basic and clinical level. J Endocr Soc 2020;4:bvz038. doi:10.1210/jendso/bvz038.
10. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, Staehelin HB, Meyer OW, Theiler R, Dick W, Willett WC, Egli A. Monthly high-dose vitamin D treatment for the prevention of functional decline: A randomized clinical trial. JAMA Intern Med 2016;176:175–83. doi:10.1001/jamainternmed.2015.7148.
11. Bolland MJ, Ames RW, Grey AB, Horne AM, Mason BH, Gamble GD, Reid IR. Does degree of baldness influence vitamin D status? Med J Aust 2008;189:674–5. doi:10.5694/j.1326-5377.2008.tb02241.x.
12. Bollen SE, Bass JJ, Fujita S, Wilkinson D, Hewison M, Atherton PJ. The Vitamin D/Vitamin D receptor (VDR) axis in muscle atrophy and sarcopenia. Cell Signal 2022;96:110355. doi:10.1016/j.cellsig.2022.110355.
13. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, Lips P, Munns CF, Lazaretti-Castro M, Giustina A, Bilezikian J. Skeletal and extraskeletal actions of vitamin D: Current evidence and outstanding questions. Endocr Rev 2019;40:1109–51. doi:10.1210/er.2018-00126.
14. Camargo CA Jr, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, Sumberzul N, Rich-Edwards JW. Randomized trial of vitamin D supplementation and risk of acute respiratory infection in Mongolia. Pediatrics 2012;130:e561-7. doi:10.1542/peds.2011-3029.
15. Cangussu LM, Nahas-Neto J, Orsatti CL, Poloni PF, Schmitt EB, Almeida-Filho B, Nahas EAP. Effect of isolated vitamin D supplementation on the rate of falls and postural balance in postmenopausal women fallers: a randomized, double-blind, placebo-controlled trial. Menopause 2016;23:267–74. doi:10.1097/GME.0000000000000525.
16. Carlberg C. Molecular endocrinology of vitamin D on the epigenome level. Mol Cell Endocrinol 2017;453:14–21. doi:10.1016/j.mce.2017.03.016.
17. Dahlquist DT, Dieter BP, Koehle MS. Plausible ergogenic effects of vitamin D on athletic performance and recovery. J Int Soc Sports Nutr 2015;12:33. doi:10.1186/s12970-015-0093-8.
18. Daniel C, Sartory NA, Zahn N, Radeke HH, Stein JM. Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. J Pharmacol Exp Ther 2008;324:23–33. doi:10.1124/jpet.107.127209.
19. De Haes P, Garmyn M, Verstuyf A, De Clercq P, Vandewalle M, Degreef H, Vantieghem K, Bouillon R, Segaert S. 1,25-Dihydroxyvitamin D3 and analogues protect primary human keratinocytes against UVB-induced DNA damage. J Photochem Photobiol B 2005;78:141–8. doi:10.1016/j.jphotobiol.2004.09.010.
20. Eisman JA, Martin TJ, MacIntyre I, Moseley JM. 1,25-dihydroxyvitamin-D-receptor in breast cancer cells. Lancet 1979;2:1335–6. doi:10.1016/s0140-6736(79)92816-2.
21. Fitzky BU, Witsch-Baumgartner M, Erdel M, Lee JN, Paik YK, Glossmann H, Utermann G, Moebius FF. Mutations in the Delta7-sterol reductase gene in patients with the Smith-Lemli-Opitz syndrome. Proc Natl Acad Sci U S A 1998;95:8181–6. doi:10.1073/pnas.95.14.8181.
22. Fogacci S, Fogacci F, Banach M, Michos ED, Hernandez AV, Lip GYH, Blaha MJ, Toth PP, Borghi C, Cicero AFG, Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. Clin Nutr 2020;39:1742–52. doi:10.1016/j.clnu.2019.08.015.
23. Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev 2013;34:33–83. doi:10.1210/er.2012-1012.
24. Gyetko MR, Hsu CH, Wilkinson CC, Patel S, Young E. Monocyte 1 alpha-hydroxylase regulation: induction by inflammatory cytokines and suppression by dexamethasone and uremia toxin. J Leukoc Biol 1993;54:17–22. doi:10.1002/jlb.54.1.17.
25. Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010;39:365–79, table of contents. doi:10.1016/j.ecl.2010.02.010.
26. Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. J Intern Med 2010;267:462–72. doi:10.1111/j.1365-2796.2009.02181.x.
27. Kägi L, Bettoni C, Pastor-Arroyo EM, Schnitzbauer U, Hernando N, Wagner CA. Regulation of vitamin D metabolizing enzymes in murine renal and extrarenal tissues by dietary phosphate, FGF23, and 1,25(OH)2D3. PLoS One 2018;13:e0195427. doi:10.1371/journal.pone.0195427.
28. Kechichian E, Ezzedine K. Vitamin D and the skin: An update for dermatologists. Am J Clin Dermatol 2018;19:223–35. doi:10.1007/s40257-017-0323-8.
29. Ketha H, Thacher TD, Oberhelman SS, Fischer PR, Singh RJ, Kumar R. Comparison of the effect of daily versus bolus dose

maternal vitamin D3 supplementation on the 24,25-dihydroxyvitamin D3 to 25-hydroxyvitamin D3 ratio. Bone 2018;110:321–5. doi:10.1016/j.bone.2018.02.024.
30. Knip M, Virtanen SM, Akerblom HK. Infant feeding and the risk of type 1 diabetes. Am J Clin Nutr 2010;91:1506S-1513S. doi:10.3945/ajcn.2010.28701C.
31. Kroll MH, Bi C, Garber CC, Kaufman HW, Liu D, Caston-Balderrama A, Zhang K, Clarke N, Xie M, Reitz RE, Suffin SC, Holick MF. Temporal relationship between vitamin D status and parathyroid hormone in the United States. PLoS One 2015;10:e0118108. doi:10.1371/journal.pone.0118108.
32. Lang JE, Ramirez RG, Balevic S, Bickel S, Hornik CP, Majure JM, Venkatachalam S, Snowden J, O'Sullivan B, James L. Pharmacokinetics of oral vitamin D in children with obesity and asthma. Clin Pharmacokinet 2023;62:1567–79. doi:10.1007/s40262-023-01285-9.
33. Latic N, Erben RG. Vitamin D and cardiovascular disease, with emphasis on hypertension, atherosclerosis, and heart failure. Int J Mol Sci 2020;21:6483. doi:10.3390/ijms21186483.
34. Lee SR, Park M-Y, Yang H, Lee G-S, An B-S, Park B-K, Jeung E-B, Hong E-J. 5α-dihydrotestosterone reduces renal Cyp24a1 expression via suppression of progesterone receptor. J Mol Endocrinol 2018;60:159–70. doi:10.1530/JME-17-0187.
35. Lee YH, Bae S-C. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: a meta-analysis. Clin Exp Rheumatol 2016;34:827–33.
36. Lips P, Binkley N, Pfeifer M, Recker R, Samanta S, Cohn DA, Chandler J, Rosenberg E, Papanicolaou DA. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am J Clin Nutr 2010;91:985–91. doi:10.3945/ajcn.2009.28113.
37. Liu PT, Krutzik SR, Modlin RL. Therapeutic implications of the TLR and VDR partnership. Trends Mol Med 2007;13:117–24. doi:10.1016/j.molmed.2007.01.006.
38. Ma R, Gu Y, Zhao S, Sun J, Groome LJ, Wang Y. Expressions of vitamin D metabolic components VDBP, CYP2R1, CYP27B1, CYP24A1, and VDR in placentas from normal and preeclamptic pregnancies. Am J Physiol Endocrinol Metab 2012;303:E928-35. doi:10.1152/ajpendo.00279.2012.
39. Mark KA, Dumas KJ, Bhaumik D, Schilling B, Davis S, Oron TR, Sorensen DJ, Lucanic M, Brem RB, Melov S, Ramanathan A, Gibson BW, Lithgow GJ. Vitamin D promotes protein homeostasis and longevity via the stress response pathway genes skn-1, ire-1, and xbp-1. Cell Rep 2016;17:1227–37. doi:10.1016/j.celrep.2016.09.086.
40. Martineau C, Naja RP, Husseini A, Hamade B, Kaufmann M, Akhouayri O, Arabian A, Jones G, St-Arnaud R. Optimal bone fracture repair requires 24R,25-dihydroxyvitamin D3 and its effector molecule FAM57B2. J Clin Invest 2018;128:3546–57. doi:10.1172/JCI98093.
41. Merola JF, Han J, Li T, Qureshi AA. No association between vitamin D intake and incident psoriasis among US women. Arch Derm Res 2014;306:305–7. doi:10.1007/s00403-013-1426-6.
42. Mondul AM, Weinstein SJ, Layne TM, Albanes D. Vitamin D and cancer risk and mortality: State of the science, gaps, and challenges. Epidemiol Rev 2017;39:28–48. doi:10.1093/epirev/mxx005.
43. Muñoz A, Grant WB. Vitamin D and cancer: An historical overview of the epidemiology and mechanisms. Nutrients 2022;14:1448. doi:10.3390/nu14071448.
44. Noyola-Martínez N, Díaz L, Zaga-Clavellina V, Avila E, Halhali A, Larrea F, Barrera D. Regulation of CYP27B1 and CYP24A1 gene expression by recombinant pro-inflammatory cytokines in cultured human trophoblasts. J Steroid Biochem Mol Biol 2014;144 Pt A:106–9. doi:10.1016/j.jsbmb.2013.12.007.
45. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, Patel K, Lichtenstein AH, Lau J, Balk EM. Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307–14. doi:10.7326/0003-4819-152-5-201003020-00009
46. Prabhu AV, Luu W, Sharpe LJ, Brown AJ. Cholesterol-mediated degradation of 7-dehydrocholesterol reductase switches the balance from cholesterol to vitamin D synthesis. J Biol Chem 2016;291:8363–73. doi:10.1074/jbc.M115.699546.
47. Roizen JD, Long C, Casella A, O'Lear L, Caplan I, Lai M, Sasson I, Singh R, Makowski AJ, Simmons R, Levine MA. Obesity decreases hepatic 25-hydroxylase activity causing low serum 25-hydroxyvitamin D: Effects of mechanical loading on long bone defect repair. J Bone Miner Res 2019;34:1068–73. doi:10.1002/jbmr.3686.
48. Rondini EA, Pant A, Kocarek TA. Transcriptional regulation of cytosolic sulfotransferase 1C2 by intermediates of the cholesterol biosynthetic pathway in primary cultured rat hepatocytes. J Pharmacol Exp Ther 2015;355:429–41. doi:10.1124/jpet.115.226365.
49. Rosenfeld L. Vitamine--vitamin. The early years of discovery. Clin Chem 1997;43:680–5. doi:10.1093/clinchem/43.4.680.
50. Saccone D, Asani F, Bornman L. Regulation of the vitamin D receptor gene by environment, genetics and epigenetics. Gene 2015;561:171–80. doi:10.1016/j.gene.2015.02.024.
51. Sanders KM, Stuart AL, Williamson EJ, Simpson JA, Kotowicz MA, Young D, Nicholson GC. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial: A randomized controlled trial. JAMA 2010;303:1815–22. doi:10.1001/jama.2010.594.

52. Semba RD. The discovery of the vitamins. Int J Vitam Nutr Res 2012;82:310–5. doi:10.1024/0300-9831/a000124.
53. Soleymani T, Hung T, Soung J. The role of vitamin D in psoriasis: a review. Int J Dermatol 2015;54:383–92. doi:10.1111/ijd.12790.
54. Stefanic M, Rucevic I, Barisic-Drusko V. Meta-analysis of vitamin D receptor polymorphisms and psoriasis risk. Int J Dermatol 2013;52:705–10. doi:10.1111/j.1365-4632.2012.5813.x.
55. Tang JY, Fu T, Leblanc E, Manson JE, Feldman D, Linos E, Vitolins MZ, Zeitouni NC, Larson J, Stefanick ML. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. J Clin Oncol 2011;29:3078–84. doi:10.1200/JCO.2011.34.5967.
56. Tang JY, Parimi N, Wu A, Boscardin WJ, Shikany JM, Chren M-M, Cummings SR, Epstein EH Jr, Bauer DC, Osteoporotic Fractures in Men (MrOS) Study Group. Inverse association between serum 25(OH) vitamin D levels and non-melanoma skin cancer in elderly men. Cancer Causes Control 2010;21:387–91. doi:10.1007/s10552-009-9470-4.
57. Tongkao-On W, Gordon-Thomson C, Dixon KM, Song EJ, Luu T, Carter SE, Sequeira VB, Reeve VE, Mason RS. Novel vitamin D compounds and skin cancer prevention. Dermatoendocrinol 2013;5:20–33. doi:10.4161/derm.23939.
58. Tuckey RC, Cheng CYS, Slominski AT. The serum vitamin D metabolome: What we know and what is still to discover. J Steroid Biochem Mol Biol 2019;186:4–21. doi:10.1016/j.jsbmb.2018.09.003.
59. Ulitsky A, Ananthakrishnan AN, Naik A, Skaros S, Zadvornova Y, Binion DG, Issa M. Vitamin D deficiency in patients with inflammatory bowel disease: association with disease activity and quality of life: Association with disease activity and quality of life. JPEN J Parenter Enteral Nutr 2011;35:308–16. doi:10.1177/0148607110381267.
60. Uusi-Rasi K, Patil R, Karinkanta S, Kannus P, Tokola K, Lamberg-Allardt C, Sievänen H. Exercise and vitamin D in fall prevention among older women: a randomized clinical trial: A randomized clinical trial. JAMA Intern Med 2015;175:703–11. doi:10.1001/jamainternmed.2015.0225.
61. van der Rhee H, Coebergh JW, de Vries E. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. Eur J Cancer 2013;49:1422–36. doi:10.1016/j.ejca.2012.11.001.
62. Wacker M, Holick MF. Sunlight and Vitamin D: A global perspective for health: A global perspective for health. Dermatoendocrinol 2013;5:51–108. doi:10.4161/derm.24494.
63. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies: A meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 2012;5:819–29. doi:10.1161/CIRCOUTCOMES.112.967604.
64. Wang Y, DeLuca HF. Is the vitamin d receptor found in muscle? Endocrinology 2011;152:354–63. doi:10.1210/en.2010-1109.
65. White JH. Vitamin D deficiency and the pathogenesis of Crohn's disease. J Steroid Biochem Mol Biol 2018;175:23–8. doi:10.1016/j.jsbmb.2016.12.015.
66. White JH. Vitamin D signaling, infectious diseases, and regulation of innate immunity. Infect Immun 2008;76:3837–43. doi:10.1128/IAI.00353-08.
67. Wolf G. The discovery of vitamin D: the contribution of Adolf Windaus. J Nutr 2004;134:1299–302. doi:10.1093/jn/134.6.1299.
68. Wu S, Liao AP, Xia Y, Li YC, Li J-D, Sartor RB, Sun J. Vitamin D receptor negatively regulates bacterial-stimulated NF-kappaB activity in intestine. Am J Pathol 2010;177:686–97. doi:10.2353/ajpath.2010.090998.
69. Zhao S, Qian F, Wan Z, Chen X, Pan A, Liu G. Vitamin D and major chronic diseases. Trends Endocrinol Metab 2024;35:1050–61. doi:10.1016/j.tem.2024.04.018.