# Unveiling the Power of Vitamin D: Key Insights into its Role in Health

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#### ABSTRACT

Vitamin D, often called the "sunshine vitamin," is essential for various physiological processes and overall health, produced in the skin through UVB exposure and obtainable from food and supplements. It regulates calcium and phosphorus, supports bone health, and prevents conditions like osteoporosis and rickets. Beyond skeletal benefits, evidence links vitamin D deficiency to chronic health issues such as metabolic syndrome, cancer, autoimmune diseases, inflammation, and mental health disorders. Research indicates that vitamin D could lessen the risk of these conditions by modulating immune function, reducing inflammation, and promoting cellular growth, while supplementation has shown promise in improving mood and alleviating depression and anxiety, particularly in deficient individuals. Additionally, vitamin D contributes to skin health, with potential benefits in treating psoriasis and preventing skin cancer. Its anti-inflammatory properties further suggest it may lower the risk of chronic diseases like cardiovascular and autoimmune disorders. Given its broad effects on health, maintaining adequate vitamin D levels is crucial for disease prevention and overall well-being, and additional research is required to gain a complete understanding of therapeutic potential in managing chronic conditions.

**Keywords:** Vitamin D, Metabolic syndrome, Cancer, Autoimmune diseases, Inflammation, Mental health disorders.

# **INTRODUCTION**

Vitamin D (VD), commonly known as the "sunshine vitamin," is a fat-soluble nutrient essential for numerous physiological functions, making it vital for overall human health. It is synthesized in the skin upon exposure to ultraviolet B radiation and can also be obtained from dietary sources and supplements (Borradale and Kimlin, 2009). Once synthesized, it undergoes conversion within the liver and kidneys to its active form, 1,25-dihydroxyvitamin D (calcitriol), which exerts a diverse array of biological effects on the body (Bikle, 2014). In addition to its well-established role in maintaining calcium and phosphorus balance, essential for bone mineralization, VD has been increasingly recognized for its involvement in various health conditions, such as metabolic syndrome, cancer, autoimmune diseases, mental health disorders, inflammation, and more (Bikle, 2014; Głąbska *et al.*, 2021).

Metabolic syndrome, a cluster of conditions including obesity, hypertension, hyperglycemia, and dyslipidemia, is a growing



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global health concern. Emerging evidence suggests that VD deficiency could worsen the risk of developing metabolic syndrome and its components (Mezza *et al.*, 2012; Prasad and Kochhar, 2016; Thomas-Valdés *et al.*, 2017; Mackawy and Badawi, 2014). Similarly, VD has been linked to a reduced risk of several cancers, including breast, prostate, and colorectal cancers, potentially through its effects on cellular growth, differentiation, and apoptosis (Garland *et al.*, 2006; Ingraham *et al.*, 2008). Furthermore, VD's effects extend to bone health, where it assists in controlling calcium and phosphate levels, helping bone formation and stopping circumstances such as osteoporosis and rickets (Turner *et al.*, 2012).

In addition to its musculoskeletal benefits, VD plays a role in skin health. Studies have shown that VD can influence the immune system of the skin, potentially reducing the risk of skin conditions like psoriasis and acne (Samanta, 2021; Wang *et al.*, 2021; Soleymani *et al.*, 2015). Inflammation, a critical factor in many chronic diseases, is another area where VD has shown potential benefits. VD's immunomodulatory effects may help reduce systemic inflammation and the risk of chronic inflammatory diseases (Wöbke *et al.*, 2014; Yin and Agrawal, 2014). Moreover, a growing body of evidence recommends that VD deficiency is associated with mood disorders such as anxiety and depression, possibly due to its effects on brain function and neurotransmitter regulation (Renteria *et al.*, 2024).

Given the broad range of biological processes influenced by VD, this review aims to explore its essential role in human health, focusing on its impact on metabolic syndrome, cancer, bone health, skin conditions, inflammation, and mental health. By synthesizing current knowledge, we aim to highlight the importance of maintaining optimal VD levels for overall well-being and disease prevention.

# **CLINICAL BENEFITS OF VITAMIN D**

VD is a lipophilic vitamin that is crucial for several vital bodily functions. It is most commonly known for its function in regulating calcium and phosphorus, which are essential for bone formation and mineralization. Beyond bone health, VD also contributes to immune system function, cell growth, and the reduction of inflammation. Insufficient levels of VD have been linked with a range of health issues, comprising osteoporosis, cardiovascular disease, and autoimmune disorders. As evidence of its broader health benefits continues to emerge, VD's clinical applications have become increasingly important in the fields of preventive medicine and disease management. Table 1 summarizes the clinical benefits of VD supplementation across various health conditions.

## **Bone health**

Recent research underscores the key function of VD in supporting bone health. Adequate levels of VD, as measured by serum 25-hydroxyvitamin D, help prevent osteoporosis by boosting bone mineral density and lowering risk of bone breakage. VD also plays a crucial part in regulating calcium and phosphate balance in the bloodstream, helping to prevent osteomalacia. Furthermore, studies show that 25-hydroxyvitamin D is altered into 1,25-dihydroxyvitamin D in bone cells, which promotes mineralization and reduces bone resorption. Additionally, dietary calcium works with VD to impact bone health, either stimulating bone formation or increasing bone breakdown, depending on the situation (Turner et al., 2012). Recent meta-analyses of randomized controlled trials emphasize the beneficial impact of VD in reducing fracture risk by preventing falls and enhancing bone density. VD was found to lower hip fractures by 18%, and non-vertebral fractures by 20%. These effects were dosedependent, with fall prevention occurring at doses of at least 700 IU per day and fracture prevention requiring more than 400 IU per day. Anti-fall benefits were observed with 25-hydroxyvitamin D levels of 60 nmol/L or higher, while prevention of fracture was effective at levels above 75 nmol/L. Both outcomes improved with higher VD levels. Based on these results, daily VD supplementation of 700 to 1000 IU is recommended for preventing falls and fractures, with an optimal blood level of 75 nmol/L for fracture prevention. Additional studies are desired

to decide the best doses to achieve these levels in the wider population (Bischoff-Ferrari *et al.*, 2005).

Research indicates that the requirement for VD to prevent rickets may have played a role in the selection of lighter skin among populations in temperate regions. As societies adopted more sedentary lifestyles, bone health suffered, resulting in a greater risk of fractures. While natural selection did not evolve to prevent osteoporosis, the condition can be largely managed through physical activity and ensuring adequate VD intake from environmental and dietary sources. A meta-analysis of four randomized controlled trials demonstrated that daily supplementation with 800 IU (20 µg) of vitamin D3 lowered the risk of hip and non-vertebral fractures by approximately 30% in people aged 65 and older, with lower doses proving ineffective. The least serum 25-hydroxyvitamin D level linked to a decrease in fracture risk was 74 nmol/L, suggesting that older adults should aim to maintain levels above this threshold. VD supplementation supports bone health by improving balance, muscle strength, and reducing fracture risk (Vieth, 2005).

#### Cancer

Research has shown that elevated levels of 25-hydroxyvitamin D (25(OH)D) in the blood are strongly linked to a lower risk of various forms of cancers, like colon, breast, ovarian, renal, pancreatic, and aggressive prostate cancers. The DINOMIT model outlines how VD and calcium metabolites contribute to cancer prevention by affecting different stages of cancer progression. Raising serum 25(OH)D levels to 40-60 ng/mL (100-150 nmol/L) a distinctive approach could help avert around 58,000 new breast cancer cases and 49,000 new colorectal cancer cases annually, potentially reducing cancer mortality by up to 75% in the US and Canada. Case-fatality rates could also be cut by 50% for individuals diagnosed with breast, colorectal, and prostate cancers by this approach. A daily consumption of 2000 IU of vitamin D3 is considered safe, and a national effort to increase VD and calcium intake is recommended to maximize these benefits (Garland et al., 2009).

Studies using animal models and cell cultures provide compelling evidence that 1.25(OH)2D and its analogs may help prevent cancer or slow its progression and spread once it develops (Bikle, 2004). The mechanisms through which 1,25(OH)<sub>2</sub>D exerts its anti-cancer effects are diverse and often depend on the specific type of cell. These mechanisms include inhibiting cell proliferation by targeting key elements of the cell cycle, disrupting growth factor signaling, triggering apoptosis, enhancing DNA repair, preventing angiogenesis (the growth of blood vessels that supply tumors), and limiting metastasis. While preclinical research is promising, the majority of clinical evidence comes from observational studies, which suggest that VD supplementation may have potential benefits, particularly for colon and breast cancer. However, there is a need for large-scale, long-term randomized clinical trials with adequate doses of VD to establish definitive evidence (Chung et al., 2011; Manson et al., 2011). Moreover, developing VD analogs that specifically target certain tissues without affecting calcium metabolism or bone resorption could greatly improve the effectiveness of cancer treatments. Increasing evidence from preclinical and certain clinical studies suggests that VD deficiency could increase the likelihood of developing cancer. While epidemiological data and early clinical trials have yielded mixed results, ensuring adequate VD levels through supplementation could be a safe and affordable way to lower cancer risk and improve outcomes (Feldman et al., 2014). VD has shown potential in fighting cancer, especially breast cancer, by being activated within breast cells. Research from preclinical and ecological studies suggests that VD may play a role in preventing breast cancer, with reduced levels of serum 25-hydroxyvitamin D are linked to an increased risk, recurrence, and mortality. However, clinical trials on VD supplementation have produced inconsistent results. Still, VD deficiency is common in the U.S. and negatively affects bone health, particularly in breast cancer survivors, underscoring the need to address this deficiency (Shao et al., 2012).

This meta-analysis explored the relationship between VD intake and breast cancer risk. Of the 1731 studies reviewed, only 6 provided relevant data. The analysis found no significant link between VD intake and breast cancer risk overall (RR=0.98, 95% CI: 0.93-1.03). However, when focusing on VD intakes of  $\geq$ 400 IU/day, a trend toward a reduced breast cancer risk was observed (RR=0.92, 95% CI: 0.87-0.97). These findings suggest that higher VD intake may lower breast cancer risk, but additional research, particularly randomized-controlled trials, is needed for confirmation (Gissel *et al.*, 2008).

#### Skin diseases

Previous research has focused on the usage of 1.25(OH),D analogs, such as calcipotriol and maxacalcitol, in the treatment of psoriasis, a skin disorder characterized by excessive cell growth. This demonstrates an application of VD beyond its traditional role in bone health. Psoriasis is marked by an overproduction of skin cells and impaired differentiation, often driven by immune system dysfunction. The therapeutic benefits of 1.25(OH)<sub>2</sub>D and its analogs in managing psoriasis are thought to stem from their ability to reduce cell proliferation, support proper differentiation, and modulate immune responses associated with the disease (Bikle, 2012). Similarly, nonmelanoma skin cancer, which also involves abnormal growth and differentiation of keratinocytes, shares some underlying mechanisms with psoriasis. Studies in mice have shown that the absence of the vitamin D receptor (VDR) in keratinocytes increases susceptibility to UVB-induced or chemically-induced skin cancer. Local application of 1.25(OH),D has demonstrated protective effects against UV damage, suggesting its potential in skin cancer prevention (Teichert et al., 2011; Mason and Reichrath, 2013). However,

despite these promising findings in animal models, the clinical use of VD analogs for preventing skin cancer has not been widely explored in human clinical trials.

Previous studies have shown that the active metabolites of vitamin D3 and lumisterol provide anti-aging and photo protective effects for the skin. These effects are achieved through immune modulation, reducing inflammation, regulating keratinocyte growth, and reinforcing the epidermal barrier. They also boost antioxidant activity, shield against DNA damage, and facilitate DNA repair, helping to prevent skin aging and reduce the risk of skin cancer. These metabolites hold promise for both preventing and treating skin aging through oral and topical use, but further clinical trials are needed to verify their efficacy (Bocheva et al., 2021). This meta-analysis explored the relationship between VD levels and Atopic Dermatitis (AD), as well as the impact of VD supplementation on AD severity. It reviewed observational studies and randomized controlled trials from MEDLINE, EMBASE, and Cochrane databases up until May 2015. The findings showed that AD patients had significantly lower serum 25-hydroxyvitamin D (25(OH)D) levels compared to healthy individuals, with a more pronounced deficiency in children. Additionally, VD supplementation resulted in a notable reduction in AD severity, as reflected by improved SCORAD and EASI scores. These results suggest that VD supplementation could be an effective treatment for AD (Kim et al., 2016).

#### Metabolic syndrome

The study emphasized the essential role of VD in metabolic regulation and its influence on conditions such as non-insulin dependent diabetes, impaired insulin sensitivity, excessive body fat, and syndrome X. VD helps reduce insulin resistance, inflammation, and the severity of these conditions through autocrine and paracrine effects on tissues like muscle and pancreatic β-cells. Observational studies indicate a negative correlation between VD levels and hyperglycemia, diabetes severity, and obesity. However, the results remain unclear due to factors such as small sample sizes, inconsistent VD dosages, and insufficient focus on glycemic outcomes. Further clinical trials are necessary to better understand the impact of VD supplementation on these conditions (Wimalawansa, 2018). The study revealed that 78.3% of Chinese adolescents and young adults at risk for metabolic syndrome had VD deficiency. After accounting for age, gender, and season, lower levels of 25(OH)D were linked to larger neck circumference, higher body fat percentage, elevated LDL cholesterol, and increased glucose levels. Individuals with obesity, high triglycerides, type 2 diabetes, or syndrome X had notably reduced 25(OH)D levels in comparison to individuals without these conditions. Those in the lowermost tertile of 25(OH)D were 2.5 times more likely to develop metabolic syndrome than those in the uppermost tertile. The findings highlight the widespread VD deficiency in this population and suggest the need for further

Health condition	Findings
Bone health	Prevent osteoporosis, increase BMD, and reduce fractures; regulates calcium and phosphate balance, preventing osteomalacia.
Cancer	Inhibiting cell proliferation, triggering apoptosis, enhancing DNA repair, preventing angiogenesis, limiting metastasis; $\downarrow$ risk for several cancers (colon, breast, ovarian, etc.); $\downarrow$ cancer mortality.
Skin diseases	Used in psoriasis treatment; promotes skin cell differentiation, $\downarrow$ proliferation, and modulates immune response; $\downarrow$ skin aging and cancer risk.
Metabolic syndrome	$\downarrow$ Insulin resistance, inflammation, and conditions like obesity and diabetes; Improves blood sugar regulation in T2D; $\downarrow$ metabolic syndrome risk.
Cardiovascular disease	Reduction in blood pressure, atherosclerosis, and vascular inflammation; Prevent musculoskeletal complications in HTN; reduce markers of cardiac hypertrophy; VD deficiency linked to cardiomyopathy.
Inflammatory diseases	Regulates immune responses; ↓ Inflammatory markers, improves conditions (asthma, CKD, IBD etc.); Supports autoimmune disorders.
Mood disorders	Improves mood, esp. in MDD; $\downarrow$ depression & anxiety symptoms, particularly in VD-def. individuals.

Table 1: Clinical benefits associated with VD supplementation.

studies on the potential benefits of VD supplementation for youth at risk of metabolic syndrome (Fu *et al.*, 2019).

VD deficiency can impair insulin production and release, potentially leading to glucose intolerance and the progress of type 2 diabetes. Supplementing with VD has been found to improve blood sugar regulation and insulin release in individuals with type 2 diabetes and low VD levels, suggesting it contributes to the development of diabetes. The presence of VD receptors and binding proteins in pancreatic tissue, along with genetic variations that affect insulin function, supports this hypothesis. VD's impact on type 2 diabetes is thought to stem from its regulation of calcium levels, which influence insulin secretion, as well as its direct effect on pancreatic  $\beta$ -cells (Palomer *et al.*, 2008). People with obesity often have lower levels of 25OHD and face a higher risk of developing conditions such as diabetes mellitus and metabolic syndrome. Adipocytes (fat cells) have VDR, and the active form of VD, 1,25(OH),D, is crucial in promoting fat storage (lipogenesis) and inhibiting fat breakdown (lipolysis) (Shi et al., 2001). The pancreas also expresses VDRs, and 1,25(OH),D contribute to insulin secretion (Norman et al., 1980). Additionally, VD deficiency is linked to insulin resistance (Kayaniyil et al., 2010). Research involving individuals with diabetes or those at risk (pre-diabetic) suggests that VD supplementation could help manage or prevent the development of full-blown diabetes (Mitri et al., 2011; Pittas et al., 2007). However, larger and longer randomized clinical trials are needed to confirm these results.

The systematic review and meta-analysis explored the relationship between serum VD concentrations and the risk of metabolic syndrome. It analyzed 23 observational studies, including 19 cross-sectional and 4 cohort studies, which were identified through searches of MEDLINE, PubMed, and Embase up until February 2020. The findings showed that a 25-nmol/L increase in serum VD was linked to a 20% reduced risk of metabolic syndrome in cross-sectional studies (OR=0.80) and a 15% reduced risk in cohort studies (RR=0.85). The association was consistent across different subgroups, with no significant publication bias detected. These results suggest that higher VD levels may lower the risk of metabolic syndrome, but further research is required to confirm a causal relationship (Lee and Kim, 2021).

## **Cardiovascular Disease**

Experimental studies suggest that VD may provide antihypertensive and vascular protection, such as inhibiting the renin-angiotensin-aldosterone system, regulating cardiovascular risk factors, and offering anti-atherosclerotic effects. It also appears to have neuroprotective properties. Epidemiological research links VD deficiency to an increased risk of hypertension and stroke. However, randomized controlled trials have shown mixed findings, with some indicating a slight reduction in blood pressure with VD supplementation, but not consistently. As a result, VD is not currently recommended for preventing or treating hypertension and stroke. Nevertheless, addressing VD deficiency in individuals with hypertension and cerebrovascular diseases may help prevent related musculoskeletal complications (Kienreich et al., 2013). VD deficiency is common and may contribute to the development of arterial hypertension. Its potential antihypertensive effects include lowering renin and parathyroid hormone levels, as well as providing kidney protection, reducing inflammation, and supporting vascular health. Low levels of 25-hydroxyvitamin D are recognized as a risk factor for hypertension. Meta-analyses of randomized controlled trials indicate that VD supplementation can reduce systolic blood pressure by 2-6 mmHg. Although more research is needed, the widespread deficiency, along with the safety, affordability, and encouraging evidence of its benefits, suggests that VD

supplementation should be considered in the management of hypertension and other chronic diseases (Pilz and Tomaschitz, 2010).

Both heart myocytes and fibroblasts contain the VDR and CYP27B1 (Chen et al., 2008). Research has demonstrated that 1,25(OH),D and its analogs can reduce markers of cardiac hypertrophy (Chen et al., 2011; Gardner et al., 2013). However, the lack of VDR in the heart results in hypertrophy. Mice lacking both VDR and CYP27B1 develop hypertension, with an increase in renin production in the heart and kidneys, which leads to elevated angiotensin II levels (Zhou et al., 2008). This heightened renin-angiotensin system may accelerate atherosclerosis in these animals. Severe VD deficiency in humans is associated with cardiomyopathy, and several large epidemiological reports have found a link between low 25OHD levels and an elevated risk of cardiovascular disease (Uysal et al., 1999; Brøndum-Jacobsen et al., 2012). However, no extensive randomized clinical trials have specifically scrutinised the role of VD or its analogs in preventing or treating cardiovascular disease, and the results from fracture studies, with cardiovascular disease as a secondary outcome, have been inconclusive.

#### Inflammatory diseases

VD is crucial for regulating the immune system, aiding in the control of inflammatory cytokine production and limiting the proliferation of pro-inflammatory cells, both of which play a significant role in inflammatory diseases. Studies have shown that low VD levels are linked to a higher risk and worse outcomes in acute infections, while supplementation has been shown to enhance clinical responses to these infections. Moreover, chronic inflammatory conditions, such as cardiovascular disease related to atherosclerosis, asthma, inflammatory bowel disease, chronic renal disease, and non-alcoholic fatty liver disease, often exhibit low VD levels, suggesting that VD may affect the development of these conditions (Yin and Agrawal, 2014). The study demonstrated that VD helps reduce inflammation in adipose tissue by lowering inflammatory markers and inhibiting leukocyte infiltration. VD was found to suppress the expression of three miRs (miR-146a, miR-150, and miR-155) induced by TNFa in human adipocytes, with similar effects observed in 3T3-L1 adipocytes. In overweight mice caused by a high-fat diet, VD supplementation lowered the increased levels of these miRs in adipose tissue. The study also showed that VD inhibits NF-kB signaling by preventing p65 and IKB phosphorylation, which may underlie its ability to regulate inflammation through miR expression (Karkeni et al., 2018).

VD plays a vital role in regulating immune responses and is essential for managing autoimmune conditions like Inflammatory Bowel Diseases (IBD), comprising Crohn's disease and Ulcerative Colitis (UC). Animal studies show that VD helps control gastrointestinal inflammation, and epidemiological data advocate that higher VD levels are associated with a reduced risk of Crohn's disease and colorectal cancer. Consequently, VD supplementation is considered a promising, affordable option for treating IBD (Ghaly and Lawrance, 2014). In VD -deficient patients with active UC, VD supplementation reduced intestinal inflammation, as shown by lower faecal calprotectin levels, decreased platelet counts, and increased albumin levels. These changes were not seen in patients with inactive UC or non-IBD controls. Although there were no significant alterations in overall fecal microbial diversity, a marked rise in the abundance of *Enterobacteriaceae* was observed in UC patients (Garg *et al.*, 2018).

#### **Mood disorders**

Recent studies suggest that insufficient VD levels are associated with more intense symptoms of depression and anxiety. Due to its antioxidant properties and its role in brain function, VD is essential for preventing or managing mood disorders. As a result, incorporating VD screening into prevention and treatment plans for these conditions is recommended (Akpınar, and Karadağ, 2022). The majority of clinical studies suggest that VD supplementation can reduce symptoms of depression and anxiety, especially in individuals with Major Depressive Disorder (MDD). Of the 13 studies conducted on MDD patients, 12 showed positive results with VD supplementation. However, some inconsistencies were observed, likely due to factors such as genetic differences, varying supplementation methods, baseline VD levels, and factors like age, sex, and symptom severity. While VD shows promise for improving mental health, further studies are required to fully comprehend its effects on mood regulation (Casseb et al., 2019). VD supplementation significantly reduced anxiety and depression symptoms in diabetic women with VD deficiency. The treatment group showed a decrease in hs-CRP levels and an increase in IL-10 concentrations. These changes were associated with improved mood and reduced inflammation, suggesting that VD supplementation can enhance mood and decrease inflammation in this population (Fazelian et al., 2019).

## CONCLUSION

VD is essential for a wide range of biological functions, making it crucial for overall health and the prevention of various chronic diseases. Its well-known impact on bone health and calcium metabolism, combined with its emerging roles in immune function, inflammation reduction, and mental health, underscores the importance of maintaining optimal VD levels. As research continues to expand, particularly in the fields of metabolic syndrome, cancer prevention, and cardiovascular health, the significance of adequate VD intake for disease prevention becomes increasingly clear. While supplementation is often necessary for those with deficiencies, further research is needed to refine optimal dosages and treatment strategies across diverse populations. Ultimately, VD should be recognized not only for its vital role in bone health but also for its significant contribution to the prevention and management of many chronic diseases, offering promising potential for improving global public health.

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# **CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

#### **ABBREVIATIONS**

AD: Atopic dermatitis; BMD: Bone mineral density; CKD: Chronic kidney disease; HTN: Hypertension; IBD: Inflammatory bowel diseases; LDL: Low-density lipoprotein; MDD: Major depressive disorder; TNF-a: Tumor Necrosis Factor Alpha; UC: Ulcerative colitis; VD: Vitamin D.

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