International Journal of Community Medicine and Public Health
Naqvi AS et al. Int J Community Med Public Health. 2026 Jan;13(1):505-514
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20254079

Review Article

Beyond the bones: the genomic and clinical landscape of vitamin D deficiency

Ahmed S. Naqvi[1], Sadaf Saeed[2]*, Muznah Subzwari[3], Abdul B. Naqvi[4]

[1]Bahrain Defence Forces Hospital, Part - Time Clinical Senior Lecturer in Medicine with Royal College of Surgeons of Ireland, Bahrain
[2]Continuing Dental and Medical Education (CODE-M), Karachi, Pakistan
[3]Cancer Foundation Hospital, Karachi, Pakistan
[4]Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Received: 04 November 2025
Revised: 24 November 2025
Accepted: 29 November 2025

***Correspondence:**
Dr. Sadaf Saeed,
E-mail: sdfsadf690@gmail.com

ABSTRACT

Vitamin D, a secosteroid hormone traditionally linked with bone health, has emerged as a pleiotropic regulator exerting systemic effects across immune, neurological, endocrine, respiratory, and metabolic pathways. This review explores the expanding scientific consensus on vitamin D's roles beyond musculoskeletal physiology, emphasizing its contributions to innate immunity, antimicrobial defense, tumor suppression, neurocognitive regulation, reproductive health, and gene expression via epigenetic pathways. Current evidence suggests that vitamin D modulates inflammation, improves insulin sensitivity, supports mucosal defense, and regulates transcription of multiple health-relevant genes. In diseases such as polycystic ovary syndrome (PCOS), periodontal disorders, multiple sclerosis, and metabolic syndrome, vitamin D deficiency is consistently linked with disease progression and poor clinical outcomes. Furthermore, its deficiency is associated with impaired quality of life, fatigue, reduced neuromuscular function, and increased infection susceptibility. Despite the variation in individual responsiveness and ongoing debates regarding universal supplementation, targeted screening and correction of deficiency in high-risk populations appear justified. This synthesis underscores the necessity for precision nutrition, personalized supplementation strategies, and integrative clinical guidelines to harness vitamin D's full systemic potential.

Keywords: Vitamin D, Immune modulation, Neuroprotection, Endocrine and metabolic regulation, Systemic health

INTRODUCTION

Vitamin D has long been recognized for its critical role in regulating calcium homeostasis and supporting bone mineralization.[1] However, a growing body of research over the past two decades has revealed that vitamin D functions as a secosteroid hormone with pleiotropic actions across multiple human physiological systems, including the immune, endocrine, neurological, cardiovascular, and muscular systems.[2,3]

These systemic roles have implications for health outcomes that reach far beyond the skeletal system, influencing disease susceptibility and therapeutic responses in a range of chronic and inflammatory conditions.[4]

This review aims to synthesize current knowledge on the influence of vitamin D on major body systems—including the immune, neurological, endocrine, cardiovascular, muscular, reproductive, and oncological systems—while intentionally excluding the well-explored domain of bone health and orthopedic implications.[5]

The most common medical issue worldwide is vitamin D insufficiency. According to studies, over 1 billion

individuals worldwide suffer from vitamin D deficiency, with around half of the world's population suffering from vitamin D insufficiency.[6,7] Vitamin D may help prevent cancer, diabetes, migraine, and autoimmune disorders.[7]

METHODS

Study design

This work adopts a narrative literature review framework supplemented by systematic principles to synthesize evidence on the systemic roles of vitamin D beyond bone health.

The review integrates findings from peer-reviewed studies published between January 2021 and October 2025, encompassing both clinical and mechanistic perspectives across multiple physiological systems—immune, neurological, endocrine, cardiovascular, respiratory, reproductive, and oral health.

Literature search strategy

A comprehensive and structured search was conducted across multiple databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, to ensure inclusion of both clinical and basic science research.

The following combination of Boolean keywords and Medical Subject Headings (MeSH) terms guided the search: “vitamin D” OR “cholecalciferol” OR “calcitriol” OR “25-hydroxyvitamin D” AND (“systemic effects” OR “non-skeletal” OR “immune modulation” OR “neuroprotection” OR “metabolic” OR “cardiovascular” OR “endocrine” OR “reproductive” OR “periodontal” OR “genomic regulation”) AND (“2021” OR “2022” OR “2023” OR “2024” OR “2025”).

Additional grey literature and clinical guidelines were retrieved from NHS, WHO, and Endocrine Society repositories. Only English-language, peer-reviewed studies were considered.

Inclusion criteria

Inclusion criteria included articles published between 2021–2025, peer-reviewed clinical trials, cohort studies, case–control studies, systematic reviews, and mechanistic molecular research, studies examining vitamin D’s effects beyond bone metabolism, particularly in systemic, immune, cognitive, or metabolic contexts and human or relevant animal models addressing mechanistic pathways.

Exclusion criteria

Exclusion criteria included studies limited solely to bone or calcium metabolism, articles lacking primary data (e.g., opinion pieces, letters) and duplicates or studies with insufficient methodological clarity.

Screening and selection process

The search initially yielded approximately 480 publications, which were screened by title and abstract. Full-text screening was then applied to 146 studies that met relevance criteria. Of these, 82 studies met final inclusion standards based on methodological quality, relevance to systemic functions, and recency. Reference lists of included studies were manually screened to capture additional eligible articles.

Data extraction and synthesis

A standardized data extraction matrix was used to collect key variables, including- author and year, population and study design, system examined (immune, neurological, and metabolic), dose/form of vitamin D and main outcomes and biological pathways involved.

Extracted data were grouped thematically under seven categories reflecting vitamin D’s systemic influence: immune regulation, neurological function, respiratory health, cardiometabolic regulation, endocrine–metabolic balance, reproductive outcomes, and epigenetic modulation.

Qualitative synthesis was performed, emphasizing patterns, consistencies, and mechanistic overlap across studies.

Data analysis and integration

Given the heterogeneity of study designs and outcomes, a narrative synthesis approach was used instead of meta-analysis. Findings were integrated through comparative thematic mapping and supported by graphical conceptual frameworks illustrating vitamin D’s multisystemic interactions.

Where possible, dose–response trends, mechanistic linkages (e.g., VDR signaling, cytokine modulation, or gene regulation), and population-based variations were highlighted.

Ethical considerations

This review did not involve human or animal subjects and therefore did not require ethical approval. All data sources are publicly available and duly cited according to academic standards.

Objectives

The objectives of this research are to explore how vitamin D influences immune, cardiovascular, respiratory, neurological, and oral health; to assess the relationship between vitamin D deficiency and chronic disease risk; to identify populations most affected by low vitamin D levels; and to evaluate the health benefits of vitamin D supplementation among individuals with deficiency.

LITERATURE REVIEW

Immune system regulation

One of the most well-established non-skeletal functions of vitamin D is its role in immune modulation. Vitamin D receptors (VDRs) are found on many immune cells, including dendritic cells, macrophages, and T lymphocytes, which allows vitamin D to affect both innate and adaptive immunity.[1] Upon activation, vitamin D upregulates the expression of antimicrobial peptides, notably cathelicidin (LL-37) and β-defensins, which strengthen mucosal and cellular defences against pathogens, including *Mycobacterium tuberculosis*.[4] Furthermore, vitamin D inhibits pro-inflammatory Th1 and Th17 responses while enhancing regulatory T-cell (Treg) proliferation, contributing to immune tolerance and suppression of autoimmune inflammation.[8] These immunoregulatory mechanisms are particularly relevant in diseases such as multiple sclerosis (MS), type 1 diabetes mellitus (T1DM), and systemic lupus erythematosus (SLE), where vitamin D deficiency is strongly associated with disease progression and symptom severity.[9]

Vitamin D therapy decreased IL-6 (pro-inflammatory) and increased IL-10 (anti-inflammatory) only in the high-dose group. No significant changes in CRP or TNF-α were observed, suggesting that vitamin D selectively modulates cytokine responses. Results support vitamin D's pleiotropic immune role in reducing chronic inflammation in metabolic disease. High-dose cholecalciferol treatment appears to normalize serum 25(OH)D levels, which may influence inflammatory markers.[7]

Neurological and cognitive function

Vitamin D plays a substantial role in brain development and function. The presence of vitamin D receptors (VDRs) and the enzyme 1α-hydroxylase in critical brain regions, such as the hippocampus, hypothalamus, and substantia nigra, underscores the neurocognitive significance of vitamin D. The brain is a target organ for vitamin D due to the widespread distribution of vitamin D receptors (VDRs) and the enzyme 1-α-hydroxylase, which converts vitamin D to its active form. These receptors are highly expressed in the hippocampus, hypothalamus, cortex, and substantia nigra, regions critically involved in learning, memory, and motor function.[10,11] Vitamin D influences the biosynthesis of neurotransmitters, which are essential for mood regulation and cognition, such as serotonin and dopamine.[12] It also exerts neuroprotective effects by mitigating oxidative stress and neuroinflammation and enhancing neural resilience.[13,14] Notably, deficiencies in vitamin D have been consistently associated with a heightened risk for neuropsychiatric disorders such as depression, schizophrenia, Alzheimer's disease, and age-related cognitive decline, suggesting a role in both preventive care and therapeutic strategies.[15]

A review stated a reduction in neurological deficits and pain severity observed after 24 weeks of treatment with 40,000 IU of cholecalciferol given weekly. The effect on the peripheral nervous system in T2DM and DPN patients was likely due to improvement in metabolic parameters, rather than direct vitamin D action.[7] Recent studies support the idea that vitamin D provides neuroprotection through multiple mechanisms, including anti-inflammatory effects, calcium regulation, antioxidant defence, and modulation of neurotrophic factors such as brain-derived neurotrophic factor (BDNF). For instance, Vyas et al reported that vitamin D supplementation in patients with comorbid psychiatric and periodontal disorders improved both cognitive and oral health outcomes, mediated by downregulation of TNF-α and IL-6 and upregulation of BDNF expression.[16] Similarly, Jensen and Fugger explored the gut-brain axis.[17] They found a strong association among vitamin D deficiency, gut dysbiosis, and immune activation in multiple sclerosis (MS) patients, identifying it as a key modifiable risk factor. More recent molecular research by Bingöl et al highlighted vitamin D's role in modulating the Th17/Treg balance, which is essential for regulating neuroinflammation in autoimmune neurological disorders such as MS.[18] The authors also observed changes in fatigue scores and cognitive markers with sustained vitamin D intake.

Clinical findings from Gulišija et al in-ICU patients further underscore the role of vitamin D in post-critical illness cognitive recovery.[19] Their study demonstrated that low serum 25(OH)D levels were strongly associated with increased incidence of ICU-acquired neuromuscular weakness and cognitive dysfunction during rehabilitation MDPI, 2025. Moreover, Li et al reported in Behavioural and Brain Functions that vitamin D may protect against age-related cognitive decline and depression by modulating FTO protein expression, a marker linked to neuroinflammation and mood regulation.[20]

Vitamin D deficiency and its impact on daily cognitive comprehension

Emerging data highlight that Vitamin D deficiency is not only associated with neurological diseases but also impairs everyday cognitive processes, including attention, learning, verbal comprehension, and decision-making. In a large-scale cohort analysis, López-Gil et al found a statistically significant relationship between vitamin D deficiency and lower verbal comprehension index (VCI) scores in adolescents, which directly affected classroom engagement and language-based academic performance.[21] López-Gil et al also emphasized that individuals with suboptimal vitamin D levels performed worse on verbal memory and comprehension tasks, with deficits similar to those seen in early mild cognitive impairment (MCI).[21]

Complementing this, Li et al observed that cognitive slowdowns—specifically in processing speed and learning efficiency—were typical in vitamin D-deficient adults, even after controlling for socioeconomic and dietary

factors.[20] Their study proposes personalized supplementation strategies to boost neurocognitive resilience in aging populations. Bandaru et al also provided mechanistic insights, showing that lower vitamin D levels correspond with hippocampal shrinkage and functional imaging anomalies in Alzheimer's patients.[22] They argue that these deficits impair daily life tasks such as following instructions, multitasking, and reading comprehension—long before clinical dementia is diagnosed.[22]

Additionally, Zhang et al explored the gut-brain axis and found that vitamin D influenced learning ability through enteric nervous system pathways, suggesting that cognitive fatigue and loss of focus could also be early neurobiological signs of vitamin D deficiency.[23] Emerging evidence from sports medicine and gerontology confirms vitamin D's critical role in neuromuscular function. It facilitates calcium transport into muscle fibres, supports myogenic protein synthesis, and is vital for muscle contraction and coordination. Deficiency has been linked to proximal muscle weakness, impaired balance, and increased fall risk, particularly in elderly adults. In athletic populations, vitamin D sufficiency is associated with improved muscle strength, post-exercise recovery, and injury prevention, underscoring its relevance across age groups.[24]

Respiratory health

Vitamin D plays a crucial role in regulating both the innate and adaptive immune systems, and its importance in respiratory health has come under renewed focus, especially in the aftermath of the COVID-19 pandemic. Beyond skeletal integrity, vitamin D contributes to pulmonary immunity, antiviral defence, and the regulation of inflammation.[23] Deficiency in vitamin D is increasingly recognized as a modifiable risk factor for respiratory infections, asthma, and chronic obstructive pulmonary disease (COPD).[25]

Vitamin D enhances respiratory immunity by stimulating the production of antimicrobial peptides like cathelicidin (LL-37) and β-defensins in airway epithelial cells, which help neutralize pathogens and maintain mucosal barrier integrity.[26] It also modulates inflammatory responses by regulating cytokines such as IL-6, IL-8, and TNF-α, thereby preventing excessive inflammation and reducing the risk of cytokine storms that can damage lung tissue. Additionally, vitamin D influences adaptive immunity by promoting regulatory T-cell responses and suppressing Th1 and Th17 activity, making it a significant modulator in preventing and mitigating respiratory inflammation.[27]

A study by Qin et al examined vitamin D supplementation in children with asthma and found improvements in interleukin-4 and interleukin-5 profiles, reduced airway inflammation, and better symptom control.[28]

Recent meta-analyses suggest that vitamin D improves quality of life in patients with COPD. Jolliffe et al demonstrated that vitamin D supplementation reduced COPD symptoms and exacerbation rates when used as an adjunct therapy.[29]

Vitamin D's role in COVID-19 outcomes was extensively explored during the pandemic, and the evidence continues to grow. Galindo-Méndez et al conducted a systematic review showing that vitamin D supplementation reduced the incidence of respiratory tract infections, especially in those with pre-existing deficiency.[26]

Calcitriol, the active form of vitamin D, exhibits strong anti-inflammatory, immunomodulatory, and antioxidative properties.[24] It downregulates pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 while upregulating IL-10, promoting immune balance through the modulation of T cells, macrophages, and dendritic cells. By enhancing regulatory T-cell development and inhibiting the NF-κB pathway, calcitriol suppresses inflammatory gene expression.[30] It also mitigates oxidative stress and inhibits the renin–angiotensin system, contributing to anti-inflammatory, neuroprotective, and cardioprotective effects.[31,32] In COPD, where inflammation and oxidative stress are elevated, vitamin D supplementation may improve outcomes by supporting immune defense and tissue repair.[30] Furthermore, vitamin D deficiency impairs lung development, muscle strength, and phosphate metabolism, while sufficient levels enhance respiratory and cardiovascular function.[24]

Vitamin D plays a vital role in cellular and metabolic regulation, influencing mitochondrial apoptosis steroid hormone synthesis pancreatic β-cell function to enhance insulin secretion and sensitivity.[25,30,33,34] Widespread vitamin D deficiency has been linked to multiple health issues, including respiratory infections that can trigger or worsen COPD.[35,36] Low serum vitamin D levels correlate with decreased lung function (FEV1, FVC), greater COPD severity, and higher mortality, as well as chronic bronchitis, emphysema, and airway remodeling. Genetic variants in vitamin D binding protein (VDBP), such as rs4588 and rs7041, further affect COPD susceptibility. Supplementation improves lung function and reduces exacerbations, especially in patients with severe deficiency (<25 nmol/l).[30]

Cardiovascular system

Vitamin D influences cardiovascular function through several direct and indirect mechanisms. At the molecular level, it suppresses renin gene expression, thereby modulating the renin-angiotensin-aldosterone system (RAAS), a key regulator of blood pressure.[32] It also improves endothelial cell function by enhancing nitric oxide synthesis and reducing oxidative stress.[37] Vitamin D insufficiency causes increased risk of cardiovascular disorders, such as hypertension, myocardial infarction, stroke, and heart failure, according to epidemiological research.[38] These results highlight vitamin D's potential as

a modifiable factor in cardiovascular health and prevention strategies.

Endocrine and metabolic functions

Vitamin D plays a multifaceted role in endocrine regulation and metabolic control. It is involved in glucose metabolism by improving insulin secretion and enhancing insulin sensitivity in peripheral tissues.[4,5] Vitamin D receptors are expressed in pancreatic β-cells and adipocytes, underscoring their importance in energy homeostasis.[34] Two observational studies indicate that individuals with low vitamin D levels are more likely to develop type 2 diabetes, obesity, and metabolic syndrome.[25,31] Additionally, vitamin D modulates hormonal pathways beyond calcium regulation, including parathyroid, adrenal, and thyroid functions, reinforcing its role as a systemic hormone.[33]

A review stated that women with polycystic ovary syndrome (PCOS) have lower basal metabolic rates compared to those without the condition. Vitamin D plays a vital role in various metabolic pathways, leading to metabolic irregularities like insulin resistance and PCOS. It also suggested a link between vitamin D levels and hormonal and metabolic disorders in PCOS cases. Vitamin D supplementation may help modify these disturbances. Additionally, vitamin D deficiency is associated with a significant risk of cardiovascular diseases, with a negative correlation between PCOS-afflicted women's vitamin D levels and their risk of cardiovascular disease.[7] In women with PCOS, vitamin D deficiency has been associated with worsened insulin resistance and hyperandrogenism. A recent review by Mohan showed that low serum vitamin D levels exacerbate PCOS symptoms, including oligomenorrhea, acne, and infertility, by disrupting ovarian steroidogenesis and insulin signalling pathways.[7] Similarly, a multidisciplinary study by Tsoukalas et al emphasized that correcting vitamin D deficiency improves insulin sensitivity and menstrual cyclicity in obese women with PCOS.[39]

The interaction between vitamin D and thyroid function has also drawn increasing attention. In autoimmune thyroiditis, vitamin D appears to suppress aberrant immune activity and support hormonal stability. Nwosu et al reported that vitamin D supplementation improved TSH levels and anti-thyroid peroxidase antibody titers, suggesting a protective role in hypothyroid states.[40] From a metabolic perspective, vitamin D influences insulin production and sensitivity by regulating pancreatic β-cell function. Nwosu et al showed that high-dose vitamin D prolonged partial remission in newly diagnosed type 1 diabetes patients, suggesting that early intervention could alter the disease course.[40]

A cross-disease review by Ahmad et al explored vitamin D's role in mineral metabolism and endocrine resilience. They emphasized its function in regulating PTH, calcium, and phosphate homeostasis, and its emerging utility in managing lipotoxicity, oxidative stress, and endocrine disruptions in chronic disease states Ahmad et al.[41]

Beyond its well-established endocrine roles, vitamin D deficiency significantly affects everyday quality of life, including energy levels, sleep, physical strength, and emotional well-being. Tsoukalas et al also stated that using metabolomics found that participants with vitamin D and folate deficiencies experienced persistent fatigue, poor sleep quality, and diminished concentration, even in the absence of clinical illness. These symptoms were notably reversed upon micronutrient correction, highlighting a reversible lifestyle burden of deficiency.[39]

Another lifestyle-linked issue is sleep-disturbance. In a real-world study, Abboud documented that individuals with untreated vitamin D deficiency experienced irregular sleep cycles, low mood, and increased anxiety, particularly in patients with overlapping autoimmune and dermatologic conditions.[42]

Finally, Vassalle emphasized that vitamin D should be viewed as a low-cost preventive health strategy to enhance general well-being, physical vitality, and healthy aging, especially given its prevalence in at-risk populations. Collectively, these findings underline the subclinical but lifestyle-disrupting consequences of chronic vitamin D insufficiency, particularly in sedentary or nutritionally vulnerable individuals: vitamin D and insulin resistance.[43]

Vitamin D deficiency is prevalent globally, particularly in patients with obesity, prediabetes, gestational diabetes, and type 2 diabetes mellitus (T2DM). A review found a high prevalence of vitamin D deficiency in patients with T2DM, suggesting the need for higher vitamin D doses. Vitamin D supplementation has been associated with weight reduction, decreased HbA1c, reduced insulin resistance, and improved insulin sensitivity. Patients with higher baseline vitamin D levels experience greater weight loss.[7]

A study found a negative correlation between serum 25(OH)D and BMI after a 24-week course of 40,000 IU of cholecalciferol weekly. Vitamin D deficiency affects diabetic complications by influencing glucose metabolism and inflammation.[7]

Antimicrobial and antiviral effects

Beyond its immunoregulatory functions, vitamin D plays a central role in defending the body against microbial and viral infections. It activates innate immune responses by inducing the expression of antimicrobial peptides and maintaining epithelial barrier integrity.[26] Vitamin D is especially crucial in the respiratory tract, where it strengthens mucosal immunity by enhancing epithelial cell defences.[4] Vitamin D deficiency causes increased susceptibility to respiratory infections, including influenza and COVID-19.[44] These protective roles have stimulated interest in vitamin D supplementation as a low-risk public

health strategy during viral outbreaks and respiratory pandemics.

Vitamin D is increasingly recognized as a primary regulator of the innate immune system, particularly in relation to antimicrobial peptides (AMPs) and mucosal immunity. The active form of vitamin D, 1,25-dihydroxyvitamin D_3, interacts with the vitamin D receptor (VDR) on immune cells such as monocytes, macrophages, and epithelial cells, leading to transcription of AMPs including cathelicidin (LL-37) and β-defensins, which directly target viral and bacterial pathogens.[26]

According to Ahmed et al, vitamin D has been shown to significantly boost LL-37 expression in human airway epithelial cells, particularly during viral infections such as SARS-CoV-2.[45] Their work emphasizes that individuals with serum 25(OH)D levels below 20 ng/ml have reduced AMP production, leading to higher viral load, extended symptom duration, and elevated inflammatory cytokines such as IL-6 and TNF-α.[45]

Several comparative studies and meta-analyses highlight vitamin D's importance in infection prevention. In COVID-19 contexts, a 2024 observational cohort showed that vitamin D supplementation reduced hospitalization time and improved viral clearance metrics, suggesting potential adjunctive antiviral roles.[45] In tuberculosis, vitamin D enhances macrophage activation and intracellular mycobacterial killing, although clinical trial data are more mixed. Conversely, in non-deficient individuals, vitamin D supplementation showed no significant additive benefit for infection prevention, indicating its most robust utility lies in correcting existing insufficiency rather than in universal supplementation.[26]

While vitamin D plays a preventive and supportive role in immune modulation, clinical trials do not currently support its use as a stand-alone therapy for treating active microbial infections or sepsis. Similarly, a comprehensive 2025 meta-analysis published in The Lancet Diabetes and Endocrinology concluded that vitamin D supplementation was most beneficial in individuals with baseline 25(OH)D levels <25 nmol/l (~10 ng/ml). The benefit diminished as baseline levels increased, and supplementation did not substitute for antimicrobial or critical care therapy.[46] These findings reinforce the view that vitamin D may reduce susceptibility to infections, but should not be relied upon as a primary treatment modality.

Cancer biology and tumour suppression

Vitamin D receptors (VDR) are expressed in various epithelial and cancerous tissues by promoting cellular differentiation, inhibiting proliferation, inducing apoptosis, and reducing angiogenesis and metastatic potential in tumour models.

A study also supports a negative correlation between serum vitamin D levels and the risk of colorectal, breast, and prostate cancers.[47] Vitamin D intake may be used in cancer prevention strategies and as an adjunct in therapy.

Vitamin D active form, calcitriol, induces cell cycle arrest (via p21, p27) and apoptosis through modulation of Bcl-2 and caspase systems. It also suppresses inflammatory cytokines and NF-κB signaling, inhibits VEGF-mediated angiogenesis, and limits epithelial–mesenchymal transition, thereby reducing metastasis.[48] Additionally, vitamin D enhances DNA repair and stabilizes the genome through VDR-mediated regulation, while inhibiting oncogenic Wnt/β-catenin signalling.[47,49] Clinical evidence links deficiency to poor cancer survival, particularly in head and neck malignancies, and shows protective VDR expression in early skin cancer lesions.[50,51] However, large trials (e.g., VITAL) indicate supplementation may not prevent cancer in vitamin D-sufficient individuals.[16] Efficacy varies by cancer type, dose, and baseline status, emphasizing that while deficiency aggravates outcomes, universal supplementation offers limited additional benefit.

Periodontal health

Vitamin D mediates periodontal health by modulating immune responses, reducing inflammation, and enhancing antimicrobial defence in the oral cavity. It promotes the production of peptides, such as cathelicidin, which protect against periodontal pathogens, while also regulating cytokine levels to minimize tissue-damaging inflammation.[52-54] Additionally, vitamin D contributes to the preservation of alveolar bone by inhibiting osteoclast activity and supporting epithelial barrier integrity.[55,56] These findings support vitamin D's importance not only for systemic health but also as a key factor in oral disease prevention and management.

Vitamin D has increasingly been recognized as an essential regulator of oral and periodontal health beyond its traditional skeletal roles. Through both anti-inflammatory and antimicrobial properties, vitamin D contributes to gingival immunity, alveolar bone metabolism, and the balance of the oral microbiome.[53] Its deficiency is now being implicated in the pathogenesis of several oral conditions, including periodontitis, alveolar bone loss, gingival inflammation, and impaired healing following dental procedures.[54,56]

Vitamin D plays a clinically significant role in periodontal care by influencing multiple biological pathways critical to oral health. In patients with chronic gingivitis or periodontitis, it modulates inflammatory cytokines such as IL-1β and TNF-α and enhances immune defence, thereby reducing local tissue damage.[53] It also enhances innate immunity by inducing antimicrobial peptides, such as cathelicidin LL-37 and defensins, in gingival tissues, reinforcing the oral barrier against pathogenic bacteria.[56] For individuals with osteoporotic alveolar resorption, vitamin D promotes calcium absorption and inhibits osteoclastogenesis by regulating the RANKL/OPG

pathway, thereby helping preserve alveolar bone structure.[56] Additionally, its immunomodulatory effects benefit patients with autoimmune oral diseases, while its role in promoting epithelial regeneration and reducing inflammation supports improved healing outcomes following dental surgery.[54] Meghil and Cutler also illustrated that vitamin D and vitamin C deficiencies in children with autism spectrum disorders and restrictive diets led to breakdown of the gingival barrier, increased oral pathogen load, and classical features of scurvy-like periodontal degeneration.[53]

Epigenetic and genomic regulation

Vitamin D functions as a potent epigenetic regulator, influencing gene expression through multiple mechanisms. Its active form, 1,25-dihydroxyvitamin D_3, binds to vitamin D receptors (VDRs), which then interact with vitamin D response elements (VDREs) on DNA, modulating transcription of over 200 genes linked to immunity, detoxification, and inflammation.[1] These actions involve changes in chromatin structure, DNA methylation, histone modification, and non-coding RNA expression, shaping tissue-specific transcriptional programs.[57]

Key epigenetic mechanisms mediated by vitamin D

Chromatin remodelling- upon activation by 1,25-dihydroxyvitamin D_3, VDR recruits chromatin remodelers that loosen nucleosomal architecture, increasing transcriptional accessibility of vitamin D target genes.[1] DNA methylation modulation- vitamin D status has been correlated with altered DNA methylation at the VDR promoter and other regulatory genes in immune and metabolic pathways. Forouhari et al found significant hypomethylation of VDR gene regions in osteoporotic patients, enabling increased transcription in vitamin D-replete states.[57]

Non-coding RNA Regulation- Vitamin D influences the expression of several long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) that fine-tune immune responses, inflammation, and cancer biology. Sobhi et al highlighted that vitamin D-regulated lncRNAs control mTOR, NF-κB, and apoptotic cascades relevant to disease suppression.[49] As noted by Al-Taee et al, vitamin D deficiency is associated with down-regulation of tumour-suppressor demethylases (e.g., KDM6A, KDM5C), further implicating vitamin D deficiency in genomic instability and cancer risk.[58]

Emerging evidence suggests that vitamin D deficiency may contribute to the silencing of anti-inflammatory genes, reduced expression of immune-protective and tumour-suppressor pathways, and reduced chromatin accessibility for VDR binding. However, the magnitude of gene regulation by vitamin D varies among individuals due to VDR gene polymorphisms, the availability of tissue-specific co-activators, and environmental inputs such as UV exposure and nutrition.[58]

Reproductive health

Vitamin D is increasingly recognized for its role in reproductive physiology, with receptors identified in the ovaries, testes, endometrium, and placenta.[34] In women, vitamin D influences follicular development, ovulation, and endometrial receptivity and its deficiency causes (PCOS), infertility, preeclampsia and gestational diabetes.[35] These findings highlight the need to maintain adequate vitamin D levels for optimizing reproductive outcomes and fetal health. A meta-analysis of randomized controlled trials suggests that low levels of active vitamin D are linked to abnormal lipid profiles in PCOS patients. Additionally, research on Egyptian women with PCOS found reduced GABA levels, which were associated with dyslipidemia and low testosterone, further influenced by insufficient vitamin D levels.[7] A clinical review reported that infertile women with PCOS undergoing IVF who received 50,000 IU of vitamin D weekly for 8 weeks experienced significant reductions in serum AMH and insulin levels, along with improvements in lipid profiles.[25] Another study reported menstrual regularity in 70% of patients taking a combination of calcium, vitamin D, and metformin, with 28% showing a follicular response; however, intergroup differences were not statistically significant.[34] Vitamin D supplementation was also found to raise serum vitamin D, reduce body mass index (BMI), and enhance insulin sensitivity, reinforcing its utility in the management of PCOS-related infertility.[25] Vitamin D deficiency during pregnancy is also linked with altered fetal endocrine development and an increased risk of insulin resistance in offspring. Jolliffe et al found that maternal vitamin D supplementation during pregnancy significantly reduced respiratory infections in offspring lowering risk of neonatal respiratory complications, highlighting prenatal nutrition as a determinant of infant lung immunity.[29]

CONCLUSION

Vitamin D's role extends well beyond bone health, functioning as a crucial hormone-like regulator across multiple systems, including immune defence, neurocognition, cardiovascular health, endocrine function, and reproduction. Deficiency in vitamin D is consistently linked to poorer health outcomes, highlighting its significance as a modifiable risk factor for chronic diseases. Routine or targeted testing, especially in at-risk populations, presents a practical strategy for early prevention. However, implementing such testing requires clear clinical guidelines and validated diagnostic thresholds. Larger randomized controlled trials (RCTs) are needed to establish causality, optimize serum level targets, and develop cost-effective, personalized treatment protocols for public health.

Emerging evidence over recent years underscores vitamin D's protective immunomodulatory effects, particularly against respiratory illnesses such as asthma and COPD, as well as viral infections. While not a substitute for established therapies, vitamin D shows promise as a safe adjunct—particularly in individuals with vitamin D deficiency. Future research should focus on optimal dosing, patient selection, and integration into respiratory treatment guidelines.

Vitamin D has transitioned from a mere supporter of skeletal health to a key regulator of multiple systems. It influences immune function, metabolism, neuroprotection, antimicrobial resistance, and gene expression—especially when serum 25(OH)D levels fall below 20 ng/ml, correlating with worse clinical outcomes and increased disease risk. Its molecular mechanisms involve VDR-mediated transcription, chromatin remodelling, and non-coding RNA regulation, providing a biological basis for its effects.

Despite promising results, inconsistent findings from universal supplementation trials highlight the need for targeted approaches tailored to deficiencies, genetics, and comorbidities. Routine screening is most justified among high-risk groups, such as the elderly or those with autoimmune or metabolic disorders.

In summary, vitamin D represents an underutilized, cost-effective tool in preventive medicine. Future studies should refine dosing, incorporate epigenetic insights, and develop population-specific guidelines. Integrating vitamin D sufficiency into standard care could yield significant health benefits amid rising chronic disease prevalence.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Sirbe C, Rednic S, Grama A, Pop TL. An update on the effects of vitamin D on the immune system and autoimmune diseases. Int J Mol Sci. 2022;23(17):9784.
2. Zmijewski MA. Nongenomic activities of vitamin D. Nutrients. 2022;14(23):5104.
3. Zhang S, Miller DD, Li W. Non-musculoskeletal benefits of vitamin D beyond the musculoskeletal system. Int J Mol Sci. 2021;22(4):2128.
4. Wimalawansa SJ. Infections and autoimmunity—the immune system and vitamin D: a systematic review. Nutrients. 2023;15(17):3842.
5. Alam S, Ahmad J, Osama M, Khan AR. Overview of the vital role of vitamin D: functions, deficiency syndromes, and impact throughout life. Curr Pharm Rep. 2025;163-7.
6. Siddiqee MH, Bhattacharjee B, Siddiqi UR, Meshbahur Rahman M. High prevalence of vitamin D deficiency among South Asian adults: a systematic review and meta-analysis. BMC Public Health. 2021;21(1):1823.
7. Mohan A, Haider R, Fakhor H, Hina F, Kumar V, Jawed A, et al. Vitamin D and polycystic ovary syndrome (PCOS): a review. Ann Med Surg (Lond). 2023;85(7):3506-11.
8. Gallo D, Baci D, Kustrimovic N, Lanzo N, Patera B, Tanda ML, et al. How does vitamin D affect immune cells crosstalk in autoimmune diseases? Int J Mol Sci. 2023;24(5):4689.
9. Argano C, Torres A, Orlando V, Cangialosi V, Maggio D, Pollicino C, et al. Molecular insight into the role of vitamin D in immune-mediated inflammatory diseases. Int J Mol Sci. 2025;26(10):4798.
10. Cui X, Eyles DW. Vitamin D and the central nervous system: causative and preventative mechanisms in brain disorders. Nutrients. 2022;14(20):4353.
11. Mirarchi A, Albi E, Beccari T, Arcuri C. Microglia and brain disorders: the role of vitamin D and its receptor. Int J Mol Sci. 2023;24(15):11892.
12. Macova L, Kancheva R, Bicikova M. Molecular regulation of the CNS by vitamin D. Physiol Res. 2023;72.
13. Lason W, Jantas D, Leskiewicz M, Regulska M, Basta-Kaim A. The vitamin D receptor as a potential target for the treatment of age-related neurodegenerative diseases such as Alzheimer's and Parkinson's diseases: a narrative review. Cells. 2023;12(4):660.
14. Anwar MJ, Alenezi SK, Alhowail AH. Molecular insights into the pathogenic impact of vitamin D deficiency in neurological disorders. Biomed Pharmacother. 2023;162:114718.
15. Wassif GA, Alrehely MS, Alharbi DM, Aljohani AA, Wassif G. The impact of vitamin D on neuropsychiatric disorders. Cureus. 2023;15(10).
16. Vyas CM, Mischoulon D, Chang G, Reynolds CF 3rd, Cook NR, Weinberg A, et al. Relation of serum BDNF to major depression and exploration of mechanistic roles of serum BDNF in a study of vitamin D3 and omega-3 supplements for late-life depression prevention. J Psychiatr Res. 2023;163:357-64.
17. Jensen LT, Fugger L. Immune perturbation by the ileal microbiota in multiple sclerosis. Proc Natl Acad Sci U S A. 2025;122(21).
18. Bingol FG, Kocyigit E, Celik E, Agagunduz D, Budan F. Breaking the cycle: can vitamin D bridge the gap between gut microbiota and immune dynamics in multiple sclerosis? Int J Mol Sci. 2025;26(12):5464.
19. Gulisija J, Capkun V, Golic S, Stipic SS. Vitamin D serum levels and the development of intensive care unit-acquired weakness: insights from a COVID-19 intensive care cohort. Pathophysiology. 2025;32(2):21.
20. Li M, Yang Y, Chen T, Luo Y, Zhang Y, Liu H, et al. FTO deficiency aggravates age-dependent

depression-like behaviors and cognitive impairment. Behav Brain Funct. 2025;21(1).
21. Lopez-Gil JF, Cisneros-Vasquez E, Olivares-Arancibia J, Yanez-Sepulveda R, Gutierrez-Espinoza H. Investigating the relationship between ultra-processed food consumption and academic performance in the adolescent population: the EHDLA study. Nutrients. 2025;17(3):524.
22. Bandaru N, Bonthu MG, Gayatri AP, Metri S, Kumar PK, Addanki A, et al. Exploring role of vitamin D on Alzheimer's disease: mechanistic insights and implications. J Pharmacol Pharmacother. 2025;16(2):164-71.
23. Zhang R, Zhang M, Wang P. The intricate interplay between dietary habits and cognitive function: insights from the gut-brain axis. Front Nutr. 2025;12:1539355.
24. Ghaseminejad-Raeini A, Ghaderi A, Sharafi A, Nematollahi-Sani B, Moossavi M, Derakhshani A, et al. Immunomodulatory actions of vitamin D in various immune-related disorders: a comprehensive review. Front Immunol. 2023;14:950465.
25. Gou Z, Li F, Qiao F, Maimaititusvn G, Liu F. Causal associations between insulin-like growth factor 1 and vitamin D levels: a two-sample bidirectional Mendelian randomization study. Front Nutr. 2023;10:1162442.
26. Galindo-Mendez M, Galindo-Ruiz M, Concheso-Venegas MF, Mendoza-Molina SU, Orozco-Cruz D, Weintraub-Benzion E. The impact of vitamin D in the prevention of influenza, COVID-19, and dengue: a review. Biomedicines. 2025;13(4):927.
27. Grunbaum A. Relationship between vitamin D status and COVID-19 severity: does vitamin D help protect against severe COVID-19 illness? McGill University (Canada). 2023.
28. Qin L. Immune function (serum IL-4 and IL-5), nutritional status, and clinical outcomes in children with bronchial asthma after vitamin D supplementation. J Med Biochem. 2025;44(5):1059-66.
29. Jolliffe D, Brustad N, Chawes B, Cooper C, D'Angelo S, Harvey N, et al. Maternal vitamin D supplementation during pregnancy to prevent acute respiratory infections in offspring: systematic review and meta-analysis. SSRN. 2025.
30. Simon P, Torok E, Szalontai K, Kari B, Neuperger P, Zavala N, et al. Nutritional support of chronic obstructive pulmonary disease. Nutrients. 2025;17(7):1149.
31. Asghari S, Hamedi-Shahraki S, Amirkhizi F. Vitamin D status and systemic redox biomarkers in adults with obesity. Clin Nutr ESPEN. 2021;45:292-8.
32. Han L, Xu XJ, Zhang JS, Liu HM. Association between vitamin D deficiency and levels of renin and angiotensin in essential hypertension. Int J Clin Pract. 2022;2022:8975396.
33. Alnimer A, Bhamidimarri PM, Talaat IM, Alkhayaal N, Eltayeb A, Ali N, et al. Association between expression of vitamin D receptor and insulin-like growth factor 1 receptor among breast cancer patients. World J Oncol. 2023;14(1):67.
34. Chu C, Tsuprykov O, Chen X, Elitok S, Kramer BK, Hocher B. Relationship between vitamin D and hormones important for human fertility in reproductive-aged women. Front Endocrinol (Lausanne). 2021;12:666687.
35. Cui A, Zhang T, Xiao P, Fan Z, Wang H, Zhuang Y. Global and regional prevalence of vitamin D deficiency from 2000 to 2022: pooled analysis of 7.9 million participants. Front Nutr. 2023;10:1070808.
36. Arora J, Patel DR, Nicol MJ, Field CJ, Restori KH, Wang J, et al. Vitamin D and the ability to produce 1,25(OH)2D are critical for protection from viral infection of the lungs. Nutrients. 2022;14(15):3061.
37. Sabico S, Wani K, Grant WB, Al-Daghri NM. Improved HDL cholesterol through vitamin D correction reduces 10-year ASCVD risk in vitamin D-deficient adults. Nutrients. 2023;15(3):551.
38. Han YY, Hsu SHJ, Su TC. Association between vitamin D deficiency and high serum levels of small dense LDL in middle-aged adults. Biomedicines. 2021;9(5):464.
39. Tsoukalas D, Sarandi E, Fragoulakis V, Xenidis S, Mhliopoulou M, Charta M, et al. Metabolomics-based treatment for chronic diseases: results from a multidisciplinary clinical study. BMJ Nutr Prev Health. 2024;7(2):357-65.
40. Nwosu BU, Pappachan JM, Ashraf AP. Editorial: disease-modifying approaches in type 1 diabetes. Front Endocrinol. 2025;16.
41. Ahmad R, Sarraj B, Razzaque MS. Editorial: vitamin D and mineral ion homeostasis: endocrine dysregulation in chronic diseases. Front Endocrinol. 2025;16.
42. Abboud M. Vitamin D supplementation and sleep: a systematic review and meta-analysis. Nutrients. 2022;14(5):1076.
43. Vassalle C. Editorial: vitamin D—from pathophysiology to clinical impact. Front Nutr. 2025;12.
44. Engin MMN, Ozdemir O. Role of vitamin D in COVID-19 and other viral infections. World J Virol. 2024;13(3).
45. Ahmed A, Fatima SS, Khan TA. Vitamin D3: the magical solution in the prevention of COVID-19. Adv Basic Med Sci. 2024;8(2):85-95.
46. Jolliffe DA, Camargo CA, Sluyter JD, Aglipay M, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis. Lancet Diabetes Endocrinol. 2025;13(4):307-20.
47. Pereira F, Fernandez-Barral A, Larriba MJ, Barbachano A, Gonzalez-Sancho JM. Vitamin D endocrine system in colorectal cancer. FEBS J. 2023;291(12):2485-518.
48. Brust LA, Linxweiler M, Schnatmann J, Kuhn J, Knebel M, Braun FL, et al. Effects of vitamin D in head and neck squamous cell carcinoma. Biomed Pharmacother. 2024;180:117497.

49. Sobhi P, Bahrami M, Mahdizadeh F, Fazaeli A, Babaei G, Rezagholizadeh L. Vitamin D and potential effects on cancers: a review. Mol Biol Rep. 2024;51(1):190.
50. Mot CI, Horhat DI, Balica NC, Hirtie B, Varga NI, Prodan-Barbulescu C, et al. Vitamin D and clinical outcomes in head and neck cancer: a systematic review. Nutrients. 2025;17(7):1100.
51. Ucar N, Holick MF. Cutaneous vitamin D3 synthesis and its role in skin cancer prevention. Nutrients. 2025;17(3):386.
52. Crnic T, Kasaj A. Association of vitamin D level and periodontitis: a comprehensive review. Periodontal Implant Res. 2024;8(1):14.
53. Meghil MM, Cutler CW. Influence of vitamin D on periodontal inflammation. Pathogens. 2023;12(9):1180.
54. Lu EMC. Role of vitamin D in periodontal health and disease. J Periodontal Res. 2023;58(2):213-24.
55. Bose A, Narayan SJ, Santosh HN. Reinforcement of epithelial barrier function by vitamin D in chronic periodontitis: RCT. RGUHS J Dent Sci. 2022;14(3).
56. Chen X, Arias Z, Omori K, Yamamoto T, Shinoda-Ito Y, Takashiba S. Autophagy as mechanism of vitamin D action on periodontitis. BMC Oral Health. 2023;23(1):90.
57. Forouhari A, Heidari-Beni M, Veisi S, Poursafa P, Kelishadi R. Effect of epigenetics on vitamin D levels: systematic review. Arch Public Health. 2023;81(1).
58. Al-Taee ZM, Naji NM, Alwan ZHO, Al-Maamori AM, Mahdi RK. Vitamin D receptor (VDR) and autoimmune diseases. Hilla Univ Coll J Med Sci. 2025;3(2):31-7.

Cite this article as: Naqvi AS, Saeed S, Subzwari M, Naqvi AB. Beyond the bones: the genomic and clinical landscape of vitamin D deficiency. Int J Community Med Public Health 2026;13:505-14.