Essential Roles, Established Benefits and Emerging Evidence of Vitamin D

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Abstract

Vitamin D is an essential fat-soluble vitamin vital for the proper absorption of calcium and phosphorus. Beyond its direct role in mineral metabolism, it significantly influences crucial physiological processes including muscle function, nerve transmission, and immune defense. Despite its multifaceted importance, vitamin D deficiency presents a substantial global health concern, affecting an estimated one billion people worldwide. This review confirms the well-established role of vitamin D in bone health, where it is crucial for preventing rickets and osteomalacia and reducing fracture risk. However, its impact on non-skeletal conditions, such as autoimmune diseases, cancers, and cardiometabolic disorders, remains less conclusive, with observational studies showing associations but randomized trials often yielding mixed results, suggesting that low vitamin D might indicate poor health rather than being a direct cause. Similarly, its involvement in neurodegenerative and psychiatric disorders is still uncertain, and it's important to note that factors like obesity can impair absorption, while high-dose supplementation carries risks. Vitamin D is undeniably crucial for maintaining optimal bone health, effectively preventing conditions like rickets and osteomalacia, and reducing the risk of fractures. Polymeric nanospheres protect the fat-soluble vitamin D from degradation caused by light, heat, and moisture. This encapsulation improves the vitamin's stability and bioavailability in food and pharmaceuticals. These nanospheres also enhance the delivery of vitamin D, allowing for more effective topical applications and targeted drug delivery systems. However, its broader therapeutic claims regarding non-skeletal conditions, including autoimmune diseases, cancers, cardiometabolic disorders, and neurodegenerative/ psychiatric conditions, require more rigorous and conclusive evidence from well-designed randomized controlled trials. The current evidence for these non-skeletal benefits is often based on observational associations, which may not imply causality. Therefore, while supplementation is vital for addressing deficiency and supporting bone health, any broader therapeutic claims necessitate cautious, individualized supplementation strategies guided by comprehensive medical assessment.

Keywords: Vitamin D, bone health, deficiency, calcium absorption, non-skeletal conditions, supplementation

1. Introduction

Vitamin-D is also known as calciferol, which is a mixture of ergosterol and 7-dehydrocholesterol. It is a fat-soluble vitamin and helps to absorb calcium and phosphorus, which play a key role in muscle movement, in the nervous system and in the immune system. Vitamin-D deficiency is a significant concern worldwide. Approximately half of the population is vitamin-D deficient, while approximately 1 billion individuals globally have inadequate vitamin-D levels [1]. Implementing a global public health initiative incorporating vitamin-D supplementation at-risk populations is crucial to prevent and control vitamin-D insufficiency. Vitamin-D is a mixture of cholecalciferol (Vitamin-D3) and ergosterol (Vitamin-D2) [2]. Cholecalciferol is a steroid hormone, but not ergosterol. Our skin is a vitamin D factory. When the skin is exposed to UVB rays, the 7-dehydrocholesterol in the epidermis converts into vitamin D3 (cholecalciferol). Vitamin D2 is not synthesized by the body and has to be taken form food supplements like oily fish (like salmon and tuna), egg yolks and fortified foods (like milk and cereals). A portion of the vitamin D3 can also be procured from these food supplements. These vitamins D2 and D3 convert into their active forms in the body through the enzymatic reactions. The enzyme, 25-Hydroxylase in the liver, initiates the first step of vitamin D activation. It adds a hydroxyl group (oxygen and hydrogen atom) to vitamin D, turning D2 and D3 into 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 (calcidiol), respectively. Calcidiol is a prehormone. Calcidiol is the major circulating form of vitamin D in the body. It's not super active yet, but it acts as a reservoir that the body can draw upon when needed. The enzyme, 1-α-Hydroxylase (CYP27B1), found primarily in the kidneys, is the gatekeeper of active vitamin D production. It adds another hydroxyl group to calcidiol, to get 1,25-dihydroxyvitamin D2 and 1,25-dihydroxyvitamin D3 (calcitriol) (Fig. 1) [3]. Calcitriol is a hormone. The production of calcitriol is carefully regulated by the body. Factors like parathyroid hormone (PTH), calcium levels and phosphate levels influence the concentration of 1-α-hydroxylase. This ensures that the body has the right amount of active vitamin D at any given time.

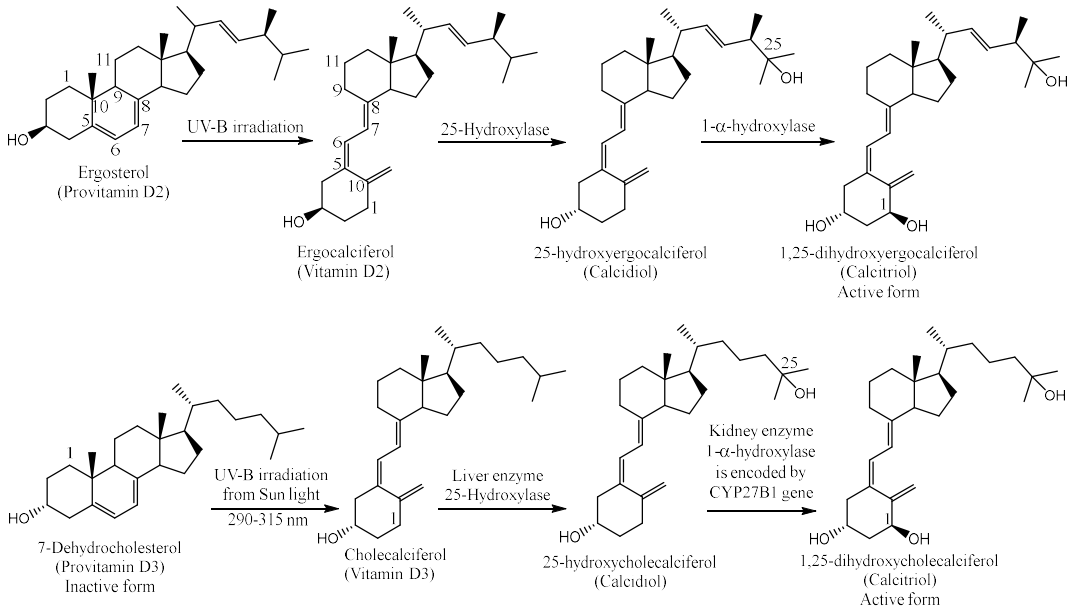

Fig. 1. Synthesis of calcitriol from ergosterol and 7-dehydrocholesterol

The assessment of an individual's vitamin D status is primarily based on serum 25-hydroxyvitamin-D levels. Vitamin-D sufficiency is generally defined as a serum total 25-hydroxyvitamin-D level greater than 30 ng/mL (50 nmol/L). Levels of 50 nmol/L (20 ng/mL) or more are generally considered adequate for bone and overall health in most healthy individuals. Vitamin-D insufficiency is typically defined as a level between 12 and 30 ng/mL (30 to 77 nmol/L), while vitamin-D deficiency is characterized by levels below 12 ng/mL (30 nmol/L). It is important to note that concentrations greater than 125 nmol/L (50 ng/mL) can be associated with adverse effects, particularly above 150 nmol/L (60 ng/mL) [4][5]. Lower calcium levels are associated with reduced bone and skeletal density, decrease in the uptake of calcium in the intestine and disruption of immunological functions.

Studies have shown that polymorphisms in the Vitamin D receptor (VDR) gene play an essential role in the molecular pathophysiology of various neurological disorders, including cognitive dysfunction [6]. Distinct expression profiles of VDR polymorphisms have been observed in neurological illnesses, such as Alzheimer’s disease, Parkinson’s disease and, muscular dystrophy. Vitamin D acts as a transcription factor and regulates various genes in the central nervous system (CNS) through synergy with the VDR. The role of vitamin D in the pathophysiology of various neurological diseases and their mechanisms should be studied in order to develop therapeutic interventions. Fig. 2 displays the organization of the human

vitamin D receptor (VDR) gene located on chromosome 12, specifically within the 12q12-12q14.1 region. The upper part of the image shows a simplified representation of chromosome 12 with its various bands and sub-bands. The lower part details the VDR gene structure, indicating multiple exons (numbered 1F, 1E, 1A, 1B, 1C, 2, 3, 4, 5, 6, 7, 8, 9) and their orientation from 5' to 3'. Importantly, the image highlights several common single-nucleotide polymorphisms (SNPs) within or near the VDR gene, including Taq-I (C/T), Apa-I (A/C and G/T), Bsm-I (A/G), Fok-I (C/T) and Cdx-2 (G/T), all of which are indicated with their respective allelic variations (Fig. 2) [7]. These SNPs are frequently studied for their potential influence on VDR function and susceptibility to various diseases.

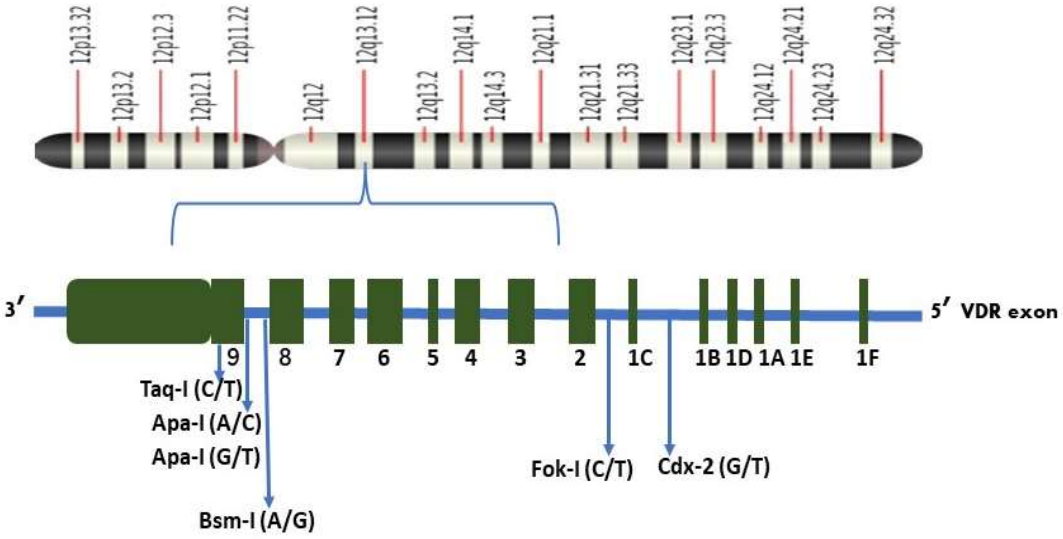

Fig. 2. Vitamin D receptor polymorphisms in cognitive disorder and neurology associated diseases.

The discovery of widespread vitamin-D receptors (VDRs) across nearly all body tissues, including the brain and, the presence of the activating enzyme (1α-hydroxylase) in immune cells and other target organs, revealed that vitamin-D operates more akin to a steroid prohormone. This means it influences genetic expression and modulates a vast array of cellular processes, including cell growth, differentiation, apoptosis, immune function and, even neurotransmitter regulation [8]. The role of Vitamin-D in various diseases and their mechanisms should be studied for the development of therapeutic interventions. Since there is a high danger of developing hypercalcemia from calcitriol, it needs to be used under extremely close observation. The absorption of dietary calcium by the intestine is controlled by calcitriol

[9]. Calcitriol also plays a role in bone remodelling. It can stimulate the breakdown of bone tissue (resorption) to release calcium into the bloodstream when needed. This is a tightly regulated process that helps to maintain calcium balance. Calcitriol is normally made in the kidney, and it binds and activates the vitamin-D receptor in the nucleus of the cell, which increases the expression of many cells and helps to reabsorb from the blood and increases the uptake of calcium and phosphorus from the intestine, preventing them from being lost in the urine. This helps to maintain the body's mineral stores. Vitamin-D plays a role in cell growth, development and differentiation. It may influence processes like immune function and cancer prevention. Vitamin-D involved in causing several other diseases like diabetes, hypertension, infectious diseases, metabolic syndrome, autoimmune disorders and cancer [10]. It is a pandemic disease in all age groups irrespective of the exposure tosunlight [11].

Given that a prohormone with such diverse systemic actions is deficient in a large segment of the global population, it logically follows that its deficiency could theoretically contribute to, or be associated with, a wide array of disparate, seemingly unrelated pathologies across multiple organ systems. The pleiotropic effects of vitamin-D, coupled with its intricate interactions with numerous other biological pathways, genetic predispositions and environmental factors, make isolating the specific impact of vitamin-D supplementation in clinical trials exceptionally difficult. This inherent complexity contributes directly to the mixed and often inconclusive findings observed in randomized controlled trials for non-skeletal outcomes, which stand in stark contrast to the clearer, more definitive evidence for its role in bone health. This highlights the necessity for a cautious, evidence-based approach, consistently distinguishing between observed associations from epidemiological data and proven causality from robust interventional studies.

2. Bone Health and Musculoskeletal Conditions

The role of vitamin-D in maintaining bone health and preventing musculoskeletal disorders is unequivocally established and represents the foundational understanding of its biological importance [12]. Multiple independent sources consistently and unequivocally affirm that vitamin-D is essential for calcium absorption and bone metabolism.

2.1. Rickets and Osteomalacia

Deficiency of vitamin-D in children causes a rare but severe condition, rickets disease, where bones soften and become prone to fractures. Similarly, in adults, it can increase the risk of osteomalacia (bone softening) resulting from extreme vitamin-D deficiency. The association is a direct causal link, where a lack of vitamin-D impairs proper bone mineralization. Supplementation with vitamin-D is a proven and effective method and standard treatment to both prevent and treat this condition [13]. Historically, the fortification of milk with vitamin-D in North America during the 1930s was a highly successful public health intervention specifically aimed at eradicating dietary rickets in children [14].

2.2. Osteoporosis and Fracture Risk

Osteoporosis or weakened porous bones is a widespread bone-thinning condition, particularly prevalent in older adults, which significantly increases the risk of bone fractures due to reduced bone mineral density. A deficiency in vitamin-D is directly linked to the development and progression of osteoporosis [15]. Studies consistently indicate that individuals who achieve sufficient vitamin-D and calcium intake in their diets can effectively slow bone mineral loss, thereby helping to prevent the onset of osteoporosis and reduce the incidence of bone fractures associated with the condition. Furthermore, clinical evidence supports the use of vitamin-D supplementation, with doses ranging from 700 to 1000 IU/day, demonstrating an improvement in musculoskeletal health, specifically by reducing the rate of fractures and falls in older adults aged 65 years and above [16].

2.3. Inherited Bone Conditions

Certain genetic conditions, such as familial hypophosphatemia, are characterized by the body's inherent inability to properly absorb or utilize vitamin-D. For individuals suffering from these inherited bone conditions, vitamin-D supplements are a recognized and essential therapeutic approach to help in the management and treatment of the underlying metabolic abnormalities [17].

2.4. Muscle Weakness and Falls

Beyond its direct effects on bone structure, vitamin-D plays a crucial role in neural and muscle functions. Nerves require adequate vitamin-D to effectively transmit messages and, muscles depend on it for proper movement. Consequently, vitamin-D deficiency is associated with muscle weakness and an increased risk of falls, particularly in older adult populations [18]. It is important to note a paradoxical effect, while deficiency can cause muscle weakness and taking very high doses of vitamin-D might also induce muscle weakness as an adverse effect, highlighting the importance of appropriate dosing [19].

3. Immune system

Vitamin-D plays a multifaceted role in the immune system, influencing both innate and adaptive immune responses. Its active form, 1,25-dihydroxy vitamin D3 ($1,25(OH)_2D3$ or calcitriol), affects immune cells like T and B lymphocytes, their antibody production and generally helps to reduce pro-inflammatory reactions during an autoimmune response [20]. The presence of vitamin-D receptors in immune cells and their ability to metabolize calcitriol underscore their importance in immunity.

3.1. General Mechanisms of Immune System Modulation by Vitamin-D

Vitamin-D is crucial for normal thymic development, where T cells (a type of white blood cell) mature and learn to distinguish between the body's own healthy tissues and foreign or unhealthy cells. A deficiency in vitamin-D can disrupt this process, leading to the development of autoreactive T cells that attack the body's own tissues, resulting in an autoimmune response [21].

3.2. Specific Autoimmune Conditions and Vitamin-D's Role

Observational data consistently link vitamin-D deficiency to an elevated risk of developing various autoimmune diseases. Vitamin D plays a promising preventive role in a range of conditions, with the VITAL study providing strong evidence for its efficacy in reducing the incidence of rheumatoid arthritis, psoriasis, autoimmune thyroid disease, polymyalgia rheumatica and inflammatory bowel diseases [22]. While a strong association exists between

vitamin D deficiency and an increased risk and progression of Multiple Sclerosis (MS), suggesting supplementation may lower MS risk by modulating immune genes, further research is needed due to some contradictory results [23]. Similarly, early-life vitamin D deficiency has been linked to an increased risk of Type 1 Diabetes, though conclusive evidence is still emerging [24]. In contrast, for Amyotrophic Lateral Sclerosis (ALS), despite vitamin D's influence on implicated genes and reported low levels with progression, recent meta-analyses show conflicting results, leaving its benefits for ALS patients unclear [25].

3.3. Vitamin D and Renal Function

Chronic Kidney Disease (CKD) disrupts vitamin-D metabolism, leading to a deficiency of calcitriol. This can worsen bone disease (renal osteodystrophy), increase parathyroid hormone (PTH) levels and, contribute to cardiovascular problems [26]. Calcitriol supplements, including intravenous forms, are used in CKD management to address these issues by reducing PTH levels and increasing calcium absorption [27]. Monitoring calcium and vitamin D levels is important, as higher concentrations could potentially increase the risk of kidney stones, though studies have not conclusively shown this in most people.

4. Cancer

The relationship between vitamin D and cancer is a complex and evolving area of scientific inquiry. While there's a compelling body of preclinical and observational evidence suggesting that vitamin-D may play a role in cancer prevention and progression, clinical trials have yielded mixed results, leading to a cautious approach in making definitive recommendations [28]. Due to the prevailing lack of firm evidence from robust clinical trials, health professionals currently do not recommend taking vitamin-D supplements specifically to reduce their general risk of cancer or to prevent cancer recurrence [29]. While a reduction in cancer mortality by approximately 6% with vitamin-D supplementation has been suggested in some analyses [30], this is still an area of ongoing research that requires further confirmation from well-designed clinical trials.

5. Cardiovascular and cardiometabolic diseases

5.1. Cardiovascular and Cardiometabolic Diseases

The widespread prevalence of vitamin-D deficiency and the global burden of cardiovascular and cardiometabolic diseases have led to extensive research into their potential association. Consistently shows a higher incidence of hypertension in individuals with vitamin-D deficiency. Some evidence suggests higher 25(OH)D levels might reduce hypertension risk, but very high doses of vitamin D can cause hypercalcemia [31]. Higher incidence of stroke in individuals with vitamin D deficiency but largely fail to show benefits of vitamin D supplementation on stroke events [32]. Higher incidence occurs in those with Coronary Heart Disease (CHD) and cardiovascular mortality of vitamin D deficiency. Low vitamin D is associated with an increased risk of major adverse cardiovascular events and all-cause mortality, even in patients with established CHD [33]. Ecological studies also suggest higher cardiovascular mortality in winter and regions with less UV-B exposure [34]. Despite strong observational links, a direct causal relationship between vitamin D deficiency and CVDs is not yet established; the overall evidence is considered inconsistent and inconclusive for proving cause and effect.

Metabolic Syndrome (MetS) is a cluster of disorders (central obesity, hypertension, hyperglycemia, elevated triglycerides and cholesterol, reduced HDLs, insulin resistance) significantly increasing the risk of CVD and type 2 diabetes. Reduced serum vitamin D levels are related to an increased risk of MetS [35]. Vitamin D receptors are present in pancreatic β-cells, musculoskeletal and adipose tissues [36]. Vitamin D deficiency may impair β-cell function, affecting insulin secretion and sensitivity. Observational studies consistently find a considerably greater risk of developing Type 2 Diabetes Mellitus **(**T2DM) and MetS among individuals with low serum 25-hydroxyvitamin D3 [37]. There's a strong, often bidirectional, relationship between vitamin D and obesity. Obese individuals may have less bioavailable vitamin D due to sequestration in fat. Some findings suggest vitamin D supplementation might positively affect obesity prevention and treatment [38]. Several studies indicate vitamin-D deficiency increases the risk of dyslipidemia (abnormal lipid levels), with inverse relationships observed between serum 25(OH)D levels and total cholesterol (TC), triglycerides (TG) and, LDL-C [39]. Surprisingly, many studies describe the benefits of vitamin D supplementation

for MetS outcomes, but randomized trials have generally failed to show benefits on incident diabetes.

5.2. Underlying Mechanisms (Biological Plausibility):

The widespread presence of vitamin-D receptors in various tissues, including vascular smooth muscle cells, endothelial cells and cardiomyocytes, provides a biological basis for its potential influence on cardiovascular health [40]. Active vitamin D (calcitriol) has been shown to inhibit vascular smooth muscle cell proliferation, regulate the renin-angiotensin system (RAAS), which influences blood pressure, decrease coagulation and exhibit anti-inflammatory properties. Cardiovascular risk is conceptualized as a triangulation of vitamin D deficiency, chronic inflammation and impaired regenerative capacity (e.g., low hematopoietic stem and progenitor cells - HSPCs). Chronic kidney disease appears to be a common factor linking these. Vitamin-D deficiency may also affect adipokines (e.g., leptin, adiponectin), influencing obesity and T2DM. It might also impact atherosclerosis by reducing inflammatory cytokines and inhibiting foam cell production [41]. There's a consistent body of observational studies showing correlations between vitamin D deficiency and increased incidence of hypertension, stroke, diabetes, CHD and cardiovascular mortality. Randomized controlled trials (RCTs) have largely failed to demonstrate significant benefits of vitamin-D supplementation on these specific cardiometabolic outcomes (blood pressure, incident diabetes, stroke, heart attack, or cardiovascular mortality). The consistent lack of positive findings in RCTs suggests that vitamin D supplementation may not be a primary preventive or therapeutic strategy for these conditions. It is plausible that low vitamin D levels might often be a marker of overall ill health or an unhealthy lifestyle rather than a direct, modifiable cause.

6. Infectious Diseases

Infectious diseases are a major global health concern and the body's immune system plays a critical role in combating them. Emerging research has highlighted the potential influence of vitamin D on immune function and, consequently, susceptibility to various infections [42][43].

6.1. Vitamin D and Overall Immune Function

For over a century, a link between vitamin-D status and susceptibility to infection has been investigated, with renewed interest following discoveries about vitamin-D's immunomodulatory properties. Nineteenth-century observations noted that children with nutritional rickets were more prone to respiratory infections, leading to the term, rachitic lung. The isolation of vitamin-D3 from cod liver oil, used to treat *Mycobacterium tuberculosis* (TB) in the 1930s, further underscored its potential role in infectious disease [44]. More recently, epidemiological studies have shown strong associations between seasonal variations in vitamin-D levels and the incidence of various infectious diseases, including septic shock, respiratory infection and influenza [45]. The discovery that the vitamin D receptor (VDR) and 1α-hydroxylase are present in immune cells has revolutionized the field of vitamin-D immunology. Calcitriol modulates gene expression involved in immune function and cytokine production by binding to the VDR. Seasonal associations between vitamin-D levels and the incidence of respiratory tract infections (RTIs) and influenza have been noted. Some positive studies in healthy, school-aged children found daily doses of vitamin D3 significantly decreased the risk of RTI, influenza A and asthma exacerbations [46]. In RTI-prone adults, daily vitamin-D3 supplementation for a year reduced infection rates and antibiotic use. However, other trials found no change in incidence or severity.

For patients with moderate to very severe Chronic Obstructive Pulmonary Disease (COPD), monthly vitamin-D3 supplementation improved lung function and reduced exacerbation rates, but only for participants who were vitamin-D deficient at baseline [47]. Individuals with Cystic Fibrosis (CF) are at increased risk of vitamin-D deficiency due to malabsorption of fat-soluble vitamins. Vitamin-D deficiency can contribute to bone disease and other complications in CF. Regular vitamin-D supplementation is often recommended [48]. Vitamin D deficiency is associated with an increased risk for all-cause and infection-related mortality in the general population, including from sepsis [49]. An increased prevalence of vitamin D deficiency has been observed in Human Immunodeficiency Virus (HIV) infected patients. While laboratory models have shown mixed results regarding vitamin-D's effect on HIV replication, the antimicrobial peptide cathelicidin, regulated by vitamin-D, may directly inhibit HIV replication [50]. Studies evaluating vitamin-D's impact on pneumonia largely yielded negative results regarding duration of illness, hospitalization or symptoms [51]. Vitamin D supplementation augmented the response to treatment in patients with chronic hepatitis C (HCV) [52]. There is limited direct research on the specific relationship between vitamin D and *Escherichia coli*

infections. However, a higher mortality rate due to *E. coli* meningoencephalitis has been associated with vitamin D3 deficiency. Increasing vitamin D3 levels has been shown to increase the survivability of mice by effectively eliminating *E. coli* [53]. As vitamin D plays a role in overall immune function, it could potentially influence the body's response to bacterial infections in general.

Calcitriol induces several endogenous antimicrobial peptides (AMPs), such as cathelicidin LL-37 and defensins, in human monocytes, neutrophils and, epithelial cells. These AMPs inhibit infection by bacteria, viruses and, fungi [54]. Vitamin D also upregulates nitric oxide (NO) synthase, which enhances bacterial killing [55]. It can induce a T helper 2 (Th2) based immune response modulation to combat extracellular infections [56]. Calcitriol suppresses pro-inflammatory cytokines and up-regulates anti-inflammatory cytokines like IL-10, potentially reducing inflammation associated with infections that can increase clinical severity and mortality [57]. The strong biological plausibility for vitamin-D's role in immunity, stemming from the presence of VDRs in immune cells and its influence on antimicrobial peptides and cytokine production, initially suggested a broad therapeutic potential. However, clinical trials investigating vitamin D's effect on infectious diseases have shown high variability and mixed results. This variability arises from differences in individual responsiveness to vitamin D, the heterogeneity of study designs and, the complex nature of immune responses. Vitamin D's role as an immunomodulator involves both direct pathogen killing (via antimicrobial peptides) and dampening overly exuberant inflammatory responses that can contribute to disease severity [58]. This dual role means that its therapeutic benefit for specific infections might be limited to certain populations (e.g., those with severe deficiency or specific genetic polymorphisms) or particular contexts, rather than serving as a universal preventative or curative agent. Thus, while vitamin D undeniably supports general immune function, its direct impact on treating specific infections might be less pronounced or consistent than initial mechanistic studies might suggest.

7. Neurodegenerative Disorders

The relationship between Vitamin D and neurodegenerative disorders has been a topic of increasing research interest. Vitamin D, beyond its well-known role in bone health, acts as a

neurosteroid with widespread effects on the brain. Its deficiency has been linked to various neurological and mental health conditions. Low vitamin D levels have been associated with an increased risk of cognitive decline and neurodegenerative diseases such as Alzheimer's and Parkinson's [59].

7.1. Molecular Mechanisms of Vitamin D in Brain Function

Vitamin D exerts its effects in the brain by binding to the Vitamin-D Receptor (VDR), which is abundantly present throughout various brain regions, including the cortical and hippocampal areas crucial for cognition, learning and memory. This binding, in conjunction with the retinoic acid X receptor (RXR) forms a complex that moves to the nucleus and binds to Vitamin-D Response Elements (VDREs) in the promoters of vitamin-D sensitive genes, thereby regulating their expression [60]. Vitamin D deficiency during development can deregulate, including those involved in oxidative phosphorylation (e.g., cytochrome b5 [61][62], cytochrome P450 [63][64]), synaptic plasticity (e.g., Apolipoprotein B), mitochondrial function, neuroplasticity, calcium homeostasis, neuronal signaling, chaperoning and post-translational modifications (PTMs) [65]. The presence of VDR in the substantia nigra highlights vitamin D's significance in dopaminergic neurons, potentially preventing their degeneration in Parkinson's disease [66]. Furthermore, vitamin D is involved in the release of Nerve Growth Factor (NGF), a protein vital for the survival of cortical and hippocampal neurons [67]. 25(OH)D levels have been associated with brain volume [68]. Genome-wide association studies (GWAS) have identified numerous genetic variations linked to 25(OH)D levels, suggesting a genetic influence on vitamin D status [69][70]. Besides its genomic actions mediated by nuclear VDR, vitamin D also has rapid, non-genomic effects through surface receptors like PDIA3 (Protein Disulfide Isomerase Family A Member 3) found on almost all brain cell types [71][72]. These non-genomic functions are regulated by calcium and kinase signaling pathways.

7.2. Vitamin D in Specific Neurological Disorders

Beyond its calcemic role, vitamin D deficiency is implicated in the pathophysiology of several neurological disorders such as Alzheimer’s disease (AD), Parkinson’s disease (PD), Autism spectrum disorder (ASD), Multiple Sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) [73]. Vitamin-D acts as a transcription factor and it regulates CNS genes by interacting with VDR. It helps prevent neuronal inflammation, enhances cognitive function and, reduces

oxidative stress. While VDR polymorphisms have been observed in AD, their mechanisms are not fully understood. Lower vitamin-D levels are linked to decreased cognitive function and worsened amyloid-beta pathology, as vitamin-D deficiency can reduce microglial-mediated amyloid-beta degradation and elevate memory impairment [74]. While some studies show no direct link between lower vitamin D and PD risk, decreased 25(OH)D levels are often observed as PD progresses, possibly due to reduced sun exposure. Vitamin D may exert neuroprotective effects by reducing inducible nitric oxide synthase (iNOS) levels, thereby decreasing reactive oxygen species (ROS) and, preventing alpha-synuclein aggregation [75]. Children with ASD often exhibit lower vitamin D levels compared to control groups. Genetic variations in vitamin D-modulating genes (e.g., *CYP2R1*, *VDR*) are hypothesized to play a pathological role in ASD. Lower vitamin D levels during gestation, postpartum and, early childhood are postulated to contribute to neurodevelopmental disorders like ASD [76]. Vitamin D deficiency is also linked to MS [77] and ALS [78].

7.3. Role of Vitamin D in Cognitive Function

Cognitive functions, encompassing rational thinking, recall, analytical skills, decision making and attention, are executed by brain regions like the frontal cortex, cerebellum and basal ganglia. Cognitive development is particularly critical from pregnancy to early infancy, and deficiencies during this period can impact functional ability [79]. The factors influence the cognition performance are age, sex, education, socioeconomic status, lifestyle (drinking, smoking, social life, profession, weight) and chronic diseases all influence cognitive performance. Neurodegenerative diseases like Parkinson's, Alzheimer's and Huntington's are well-known to cause cognitive decline. Vitamin D, after crossing the blood-brain barrier (BBB), is converted into its active form, $1,25(OH)_2D$, within neurons and microglia [80]. Diet significantly impacts cognitive performance, with vitamin D showing a notable influence. Vitamin-D plays a crucial role in modulating cognitive impairment across various neurological conditions. In Alzheimer's disease, lower serum vitamin D is associated with reduced hippocampal volume and accelerated disease progression, with deficiency linked to increased anxiety [81]. For Parkinson's disease, low vitamin D levels correlate with cognitive deficits and its neuroprotective effects may involve reducing inflammatory markers. Meta-analyses consistently show a significant link between vitamin D deficiency and an increased risk of developing dementia [82]. Furthermore, vitamin D deficiency is a known risk factor for ischemic stroke, with supplementation demonstrating benefits in cognitive and motor recovery

[83][84]. Finally, in epilepsy, vitamin D metabolism can be affected by antiepileptic drugs and higher vitamin D levels are associated with improved seizure control, making vitamin D3 a potential therapeutic target [85]. The role of vitamin D in various cognitive disorders may involve similar mechanisms, such as reducing oxidative stress, maintaining calcium levels and immunomodulation.

7.4. Vitamin D and Mental Health Conditions

Emerging research highlights vitamin D's role as a neuroprotective agent in mental health, influencing neuroinflammation, serotonin synthesis and brain plasticity [86][87]. Low vitamin D levels have been consistently linked to various mental health conditions, most notably depression and Seasonal Affective Disorder (SAD), with evidence suggesting that supplementation may alleviate depressive symptoms, particularly in winter, although research often suffers from methodological issues and inconsistent dosing. Individuals with depression frequently show lower vitamin D levels, likely influenced by lifestyle factors such as limited sun exposure and social withdrawal [88]. A significant correlation has also been observed between vitamin D deficiency and increased suicide risk, especially among military personnel and depressed individuals, with some studies indicating a protective effect from supplementation [89][90]. Cognitive decline has been associated with low blood levels of vitamin D [91] and similar deficiencies are implicated in schizophrenia [92]. In children with Attention-Deficit/Hyperactivity Disorder (ADHD), meta-analyses report significantly reduced vitamin D levels and adjunctive supplementation appears to improve symptoms [93]. Additionally, vitamin D may help reduce anxiety [94], as seen in patients with generalized anxiety disorder, prediabetes and premenstrual syndrome and is also found to be lower in individuals with Obsessive-Compulsive Disorder (OCD) [95] and Posttraumatic Stress Disorder (PTSD), the latter also showing possible genetic links through vitamin D-binding protein polymorphisms [96].

Overall, the strong biological basis for vitamin D's neuroprotective role, including the presence of VDRs in the brain, its influence on serotonin synthesis and its ability to reduce neuroinflammation, provides a compelling theoretical framework for its involvement in mental and neurological health. Consistent observational links have been drawn between low vitamin D levels and various mental and neurological conditions, including depression, cognitive decline and schizophrenia. However, research in this area is often complicated by

methodological limitations, such as a lack of baseline vitamin D testing or inconsistent dosing strategies. For instance, symptoms of depression, such as social withdrawal and isolation, can lead to reduced outdoor activity and, consequently, lower vitamin D synthesis from sun exposure. This creates a complex bidirectional relationship where the illness might exacerbate the deficiency, rather than the deficiency solely causing the illness. Therefore, while vitamin D supplementation may serve as a simple adjunctive intervention, particularly for individuals with documented deficiency, its role as a primary treatment or preventative measure for many mental health conditions requires more robust, well-designed trials. Such trials are needed to disentangle these complex bidirectional relationships and control for confounding factors, providing clearer guidance for clinical practice.

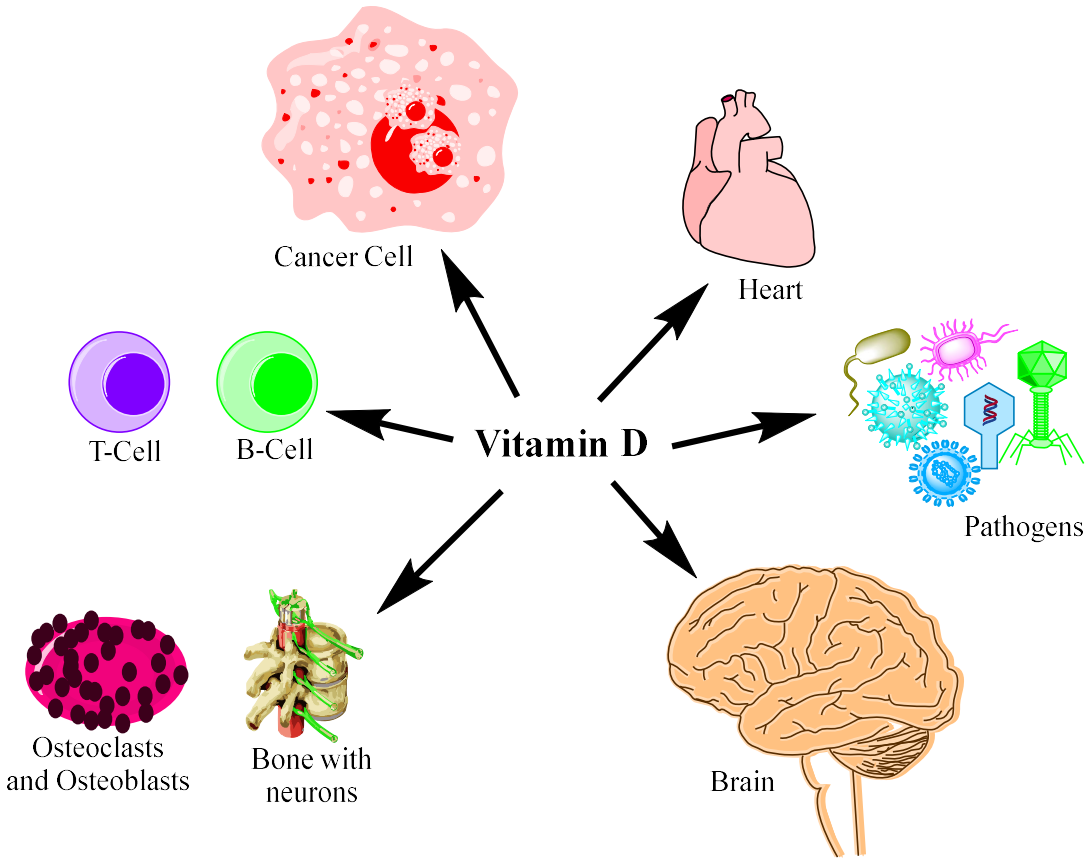

Fig. 2. Vitamin D affected organs and pathogens in the body

8. Conditions Affecting Vitamin D Absorption

Certain health conditions and medical interventions can significantly limit the body's ability to absorb fat-soluble vitamins, including vitamin D, thereby increasing the risk of deficiency. These include inflammatory bowel diseases such as ulcerative colitis and Crohn's disease, as well as celiac disease. Additionally, individuals who have undergone gastric bypass surgery may experience impaired vitamin D absorption. Obesity is another significant factor; due to higher fat mass, substantial amounts of vitamin D can become trapped in adipose tissues, making it less available in the bloodstream and leading to a volumetric dilution effect [97]. These conditions necessitate careful monitoring of vitamin D status and often require supplementation to maintain adequate levels.

9. Potential Adverse Effects of High-Dose Vitamin D

While vitamin D is essential, excessive intake can lead to toxicity, known as hypervitaminosis D, which can cause a range of adverse effects [98]. Taking more than 4,000 IU a day of vitamin D might result in symptoms such as upset stomach and vomiting, weight loss, loss of appetite and, muscle weakness. More severe effects can include impaired cognitive function (not being able to think clearly or quickly), heart rhythm issues, kidney stones and, kidney damage [99].

Furthermore, vitamin D can interact with a variety of medications, potentially leading to harmful effects or reducing the efficacy of either the vitamin or the drug. For instance, when taken with aluminum-containing phosphate binders commonly used in patients with kidney failure, vitamin D can cause harmful aluminum buildup in the body [100]. Anticonvulsants such as phenobarbital and phenytoin can accelerate vitamin D breakdown, impairing calcium absorption [101]. Vitamin D may interfere with the metabolism of atorvastatin, a cholesterol-lowering drug [102] and, should not be combined with calcipotriene [103], a vitamin D derivative used for psoriasis, due to the risk of elevated calcium levels [104]. Cholestyramine and orlistat, both of which impact fat absorption, can reduce the body’s ability to absorb vitamin D [105][106]. Caution is advised when using vitamin D with drugs metabolized by the CYP3A4 enzyme, such as lovastatin [107]. Additionally, high doses of vitamin D can increase the risk of life-threatening heart issues when combined with digoxin and may reduce the effectiveness of blood pressure medications like diltiazem [108]. Lastly, combining vitamin D with thiazide diuretics also increases the likelihood of hypercalcemia, underscoring the

importance of medical supervision when supplementing vitamin D alongside certain prescriptions [109]. These potential adverse effects and drug interactions underscore the importance of consulting a healthcare provider before initiating vitamin D supplementation, especially at high doses or in individuals with pre-existing conditions or those on other medications.

10. The Role of Polymers with Vitamin D

Vitamin D is a fat-soluble nutrient that is sensitive to environmental factors like light, heat, and moisture. This sensitivity can lead to its degradation, affecting its bioavailability and shelf-life. This is where polymeric nanospheres come into play, as they are used to,

- **Improve Stability and Bioavailability:** Polymeric nanospheres can be used to encapsulate vitamin D, protecting it from degradation. This is particularly useful in food and pharmaceutical industries. Natural polymers like pectin and carboxymethyl cellulose can be used to create microgels and nanoemulsions that encapsulate vitamin D, increasing its stability and bioavailability [110].
- **Enhance Delivery:** Polymers can be designed to create specialized delivery systems for vitamin D. For topical applications, such as for the treatment of skin conditions like psoriasis, polymeric nanospheres can be used to deliver vitamin D3 more effectively into the skin while protecting it from photodegradation [111].
- **Create Drug Delivery Systems:** In medicine, hydrogels, which are a type of polymer, are being developed to encapsulate and protect vitamin D, facilitating its targeted delivery to specific absorption sites within the body. This can enhance its therapeutic efficacy, especially for conditions where vitamin D is used to regulate cell proliferation and differentiation [111].

Conclusions

The comprehensive investigation into diseases and health conditions associated with vitamin D levels reveals a complex and multifaceted picture. The evidence unequivocally establishes

vitamin D's direct and causal role in bone health and musculoskeletal conditions, including the prevention and treatment of rickets, osteomalacia and, its contribution to slowing bone mineral loss and reducing fracture risk in osteoporosis. This area represents a clear and clinically actionable domain where vitamin D supplementation has proven efficacy.

However, for a wide array of non-skeletal conditions, the relationship with vitamin D is far more intricate, often characterized by a significant observational-interventional discord. While numerous observational studies consistently report associations between low vitamin D levels and an increased risk of autoimmune diseases, various cancers, cardiometabolic disorders (hypertension, stroke, coronary heart disease, metabolic syndrome, type 2 diabetes) and, infectious diseases, randomized controlled trials (RCTs) have frequently yielded mixed or inconclusive results regarding the direct benefits of vitamin D supplementation for these conditions.

Vitamin D is a fat-soluble nutrient that is sensitive to environmental factors like light, heat, and moisture, which can cause it to degrade. To protect it and improve its effectiveness, polymeric nanospheres are used. These tiny spheres, often made from natural polymers, encapsulate vitamin D, shielding it from degradation and increasing its stability and bioavailability. This technology is crucial in the food and pharmaceutical industries, where it can also be used to create specialized drug delivery systems for topical treatments or targeted therapeutic applications within the body.

This disparity highlights a critical distinction: observational studies are valuable for generating hypotheses and identifying correlations, often supported by plausible biological mechanisms (e.g., vitamin D's role as a prohormone influencing immune function, inflammation and, cellular processes). However, these studies cannot establish causality due to the influence of numerous confounding factors such as lifestyle, diet, obesity, sun exposure and, genetic predispositions. The overall failure of many RCTs to confirm the benefits seen in observational studies suggests that for many non-skeletal conditions, low vitamin D levels might be a marker of underlying poor health or an unhealthy lifestyle rather than a direct, modifiable cause.

A notable exception to this discord is the VITAL study, which provided some of the first direct interventional evidence that daily vitamin D supplementation can reduce the incidence of specific autoimmune diseases like rheumatoid arthritis, psoriasis and, autoimmune thyroid

disease in older adults. This finding suggests that for certain populations and conditions, the relationship with vitamin D may indeed be causal, moving beyond a simple association.

In conclusion, while vitamin D is undeniably vital for overall health, particularly bone health, its broad therapeutic application beyond skeletal conditions requires further definitive research. The complexity of its systemic actions, the challenges in disentangling confounding factors and, the mixed results from robust clinical trials underscore that while promising associations exist, moving from correlation to proven causal interventions for many conditions remains an ongoing scientific endeavor. Individualized assessment of vitamin D status and cautious, evidence-based supplementation, especially considering potential adverse effects and drug interactions, are paramount for clinical practice.

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