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Potential Role of Vitamin D in Health and Disease: A literature Review

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In Loving Memory of Late Professor Doctor ""Mohamed Refaat Hussein Mahran""

Abstract

Vitamin D, a fat-soluble prehormone, crucially maintains calcium and phosphorus balance. Global concern surrounds its deficiency, prevalent in various populations. While vital for bone health, emerging evidence suggests broader effects beyond bone mineralization. Deficiency links to diverse diseases and higher mortality rates. Supplementation, deemed safe and cost-effective, aims to enhance health, especially in vulnerable groups. Clinical trials often fail to consistently demonstrate positive effects across diseases due to design limitations. This review examines vitamin D's potential mechanisms in discussed disorders, emphasizing trials and meta-analyses. Despite extensive research, addressing challenges remains crucial. Future studies should comprehensively evaluate the vitamin D endocrine system rather than focusing solely on 25-hydroxyvitamin D levels. Employing physiologically relevant dosages, categorizing by achieved vitamin D levels, and ensuring extended follow-up are critical. These strategies will refine our understanding of vitamin D's impacts, particularly regarding supplementation on health outcomes. Overcoming these challenges is vital for effectively gauging the potential benefits of vitamin D supplementation in diverse health conditions.

Keywords: Vitamin D, Role in Health, supplementation, immunity, respiratory tract

1. Introduction

Vitamin D, classified as a fat-soluble prehormone, plays a crucial role in maintaining calcium and phosphorus homeostasis [1]. Deficiency in this essential nutrient poses a significant global health concern due to its potential to induce osteomalacia, a condition characterized by insufficient mineralization of bones in humans [2]. Research emphasizes the extensive repercussions of vitamin D insufficiency, establishing connections with diverse health conditions, notably infectious diseases like COVID-19 and upper respiratory tract infections [3-5]. Furthermore, investigations have revealed correlations between insufficient levels of vitamin D and a spectrum of other disorders, encompassing muscle weakness, diabetes, hypertension, cancers, autoimmune diseases, and cardiovascular disorders and an increased risk of hip or vertebral fractures in later life [6-9]. The sources of vitamin D include exposure of the skin to ultraviolet B radiation (UVB), dietary intake (such as, Cod liver oil, Fatty fish, and Eggs, and fortified foods), The recommended dietary intake of vitamin D can vary based on age, sex, and specific health conditions, the human body relies on ultraviolet B (UVB) radiation from sunlight to produce a substantial portion of its vitamin D requirements [10]. Vitamin D exists in two forms: vitamin D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D3 is synthesized by the skin following sun exposure and is also obtainable from animal sources, whereas vitamin D2 is a synthetic form commonly present in fortified foods and derived from plants. However, numerous factors contribute to the risk of vitamin D deficiency, including air pollution, geographical latitude, seasonal variations, sunscreen usage, sedentary occupations, and dietary patterns, among others [11].

2. Vitamin D assessment

The assessment of vitamin D status in the body commonly relies on the measurement of total serum 25(OH)D levels. However, defining the cut-off points for vitamin D deficiency varies among different consensus recommendations. The US Institute of Medicine (IOM) established a classification system wherein serum 25(OH)D levels below < 30 nmol/L indicate vitamin D deficiency, while 30–50 nmol/L suggest insufficiency, and ≥50 nmol/L are considered

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sufficient [12]. Conversely, the Endocrine Society set different thresholds based on circulating parathyroid hormone levels. They defined vitamin D deficiency as ≤ 50 nmol/L, insufficiency as 50–75 nmol/L, and normal levels as ≥75 nmol/L [13, 14]. Moreover, a consensus among these guidelines is evident in recommending that serum 25(OH)D levels < 25 or 30 nmol/l should be avoided across all age groups to prevent adverse health effects [15].

3. Vitamin D: physiology and metabolism

When cholesterol is converted to 7-dehydrocholesterol (7-DHC), vitamin D production begins. After that, this substance is sent to the skin, where it is stored in the keratinocyte and fibroblast cell membranes of the epidermis. In the skin, 7-DHC undergoes photolysis via UVB radiation to form pre vitamin D, subsequently converting into vitamin D through photolysis-mediated thermo-isomerization. For its biological activation, the liver and kidneys go through a series of enzymatic changes when vitamin D is obtained via food or cutaneous synthesis [16–18]. The vitamin D binding protein binds to the vitamin D and carries it to the liver. The primary circulating form of vitamin D, 25-hydroxyvitamin D (Calcidiol), is produced in the liver by the cytochrome P450 enzyme 25-hydroxylase (CYP2R1), which catalyzes the addition of a hydroxyl group at carbon 25 [19–22]. At position 25, CYP2R1 demonstrates the capacity to hydroxylate both vitamin D2 and vitamin D3 [23]. Mutations in the CYP2R1 gene have been linked to rickets. The inactive 25-(OH)D metabolite circulates in the bloodstream bound to vitamin D binding protein and necessitates further hydroxylation in the kidney tubules to acquire hormonal bioactivity. The mitochondrial cytochrome P450 enzyme known as 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), located in the kidney, facilitates hydroxylation at position 1α, transforming 25-(OH)D into 1α,25-dihydroxyvitamin D (calcitriol). Calcitriol represents the most potent hormonal form of vitamin D and plays a pivotal role in maintaining mineral balance, contributing significantly to the spectrum of biological actions attributed to vitamin D [22, 24-30].

4. Vitamin D deficiency: risk factors, global and regional prevalence

Vitamin D deficiency exhibits significant regional variability across different WHO regions, with the Eastern Mediterranean region showing the highest prevalence. In Kuwait, 58.9% of individuals aged 10 were found to have serum 25(OH)D levels below 30 nmol/L, while in Oman, 44.3% of the population aged 18–55 experienced similar deficiencies [31]. The IOF Committee of Scientific Advisors (CSA) Nutrition Working Group arrived at analogous conclusions regarding this prevalence.

Despite ample sunshine in the Middle East, the prevalent vitamin D deficiency can be primarily attributed to cultural practices. Specifically, the habitual use of veils limits sun exposure among the population, significantly affecting their synthesis of vitamin D [32, 33].

Skin exposure to UVB rays is the main source of vitamin D, while other factors such skin pigmentation, social and economic status, and inadequate vitamin D supplementation may also play a role [34]. On the other hand, just 3.0% of Americans aged 2 and older had serum 25(OH)D levels below 30 nmol/L, making the Region of the Americas the least likely to be vitamin D deficient. High socioeconomic position, extensive vitamin D fortification of milk and food, more public knowledge of the health hazards associated with vitamin D deficiency, and proactive government initiatives are all responsible for this positive situation. [35].

However, it is noteworthy that some countries within the Region of the Americas still report a high prevalence of vitamin D deficiency. For example, 34.0% of the Chilean population aged 18 and older has serum 25(OH)D levels below 30 nmol/L. In the African Region, the prevalence is low, with 8.0% and 18.9% for serum 25(OH)D levels below 30 and 50 nmol/L, respectively. It is crucial to interpret these findings cautiously due to the limited number of studies and participants in Africa, potential regional variations in sunlight exposure, and an overrepresentation of young individuals in the included studies. Future large-scale, population-based studies are warranted to provide more reliable insights. The European Region, benefiting from a wealth of data (93 studies with 7,238,477 participants), reveals a higher prevalence of vitamin D deficiency, with 18.0% and 53.0% having serum 25(OH)D levels below 30 and 50 nmol/L, respectively [36, 37]. This trend is exemplified by the British population, with 25.9% and 55.3% presenting serum 25(OH)D levels below 30 and 50 nmol/L, respectively. Similarly, South-East Asia and the Western Pacific Regions also report a notable prevalence of vitamin D deficiency, with 22.0% of the South-East Asia population and 10.0% of the Western Pacific population exhibiting serum 25(OH)D levels below 30 nmol/L, consistent with recent studies [38-40]. Overall, these findings underscore a widespread high prevalence of vitamin D deficiency across various WHO regions, with individuals residing at higher latitudes more susceptible, likely due to inadequate sunlight exposure.

several influential factors affecting the prevalence of vitamin D deficiency. Notably, a

higher prevalence was evident among females compared to males, highlighting the necessity for targeted preventive measures, like vitamin D supplementation, to address this gender disparity. Seasonal variation also played a significant role, with a higher prevalence noted in Winter–Spring compared to Summer–Autumn. This emphasizes the importance of vitamin D supplementation during winter for individuals at risk of deficiency. Age-specific prevalence analysis revealed distinct patterns, with serum 25(OH)D levels below 30 nmol/L observed at rates of 14.9%, 18.2%, 13.8%, and 15.3% among individuals aged <18, 19–44, 45–64, and 65 years and older, respectively. Particularly noteworthy was the higher prevalence among adults aged 19 to 44, possibly due to lower vitamin D supplementation despite a greater need linked to increased muscle mass and fiber development [41]. Socioeconomic status emerged as a significant factor, showcasing varying prevalence rates within World Bank income groups, ranging from 10.2% in Upper-middle-income countries to 26.7% in Lower-middle-income countries. This underscores the need for heightened attention to individuals residing in Lower-middle-income and Low-income countries. Furthermore, the diversity in detection assays significantly influenced prevalence rates. Harmonizing the use of detection assays across studies can enhance result comparability. Additionally, numerous other pertinent risk factors contributing to vitamin D deficiency, such as genetic traits, dietary intake, clothing styles, outdoor exposure, skin pigmentation, and more, have been identified [42-44].

5. Vitamin D: Classical Health Effects

5.1. Role of Vitamin D in Bone

The health of bones is impacted by vitamin D both directly and indirectly [45]. It serves as a key regulator of mineral homeostasis, facilitating the absorption of calcium and phosphorus in the intestine, critical for optimal bone mineralization. The firmly established knowledge dictates that variations, whether acquired or genetic, within the vitamin D endocrine system can result in conditions like rickets and osteomalacia. Conversely, adequate vitamin D supplementation prevents these skeletal disorders, including renal osteodystrophy [46]. However, the precise role of vitamin D in the skeletal health of adults and older individuals remains a subject of debate. The Vitamin D Assessment (VIDA) study, a significant randomized trial administering either 100,000 IU vitamin D3 or a placebo monthly, revealed that correcting severe vitamin D deficiency led to improvements in bone mass density (BMD) [47]. However, supplementation in individuals already replete with vitamin D did not show associated improvements in BMD or bone quality. Moreover, The VIDA trial yielded no discernible impact on fracture or fall risks in either the complete dataset or the vitamin D-depleted group when compared to the placebo [47]. In the Calgary study, which evaluated the long-term effects of varying doses of vitamin D supplementation (400, 4000, and 10,000 IU per day), participants receiving the highest dose exhibited reduced bone mineral density (BMD) at the radius and tibia compared to those receiving 400 IU daily. Noteworthy findings showed no significant differences between the 4000 and 400 IU groups. Importantly, the administration of very high doses of vitamin D (4000 and 10,000 IU/day) was linked to potential adverse effects such as hypercalciuria and/or hypercalcemia [48].The reduction in BMD with very high doses may result from increased bone resorption directly or indirectly through the activation of osteoblasts, subsequently promoting osteoclastogenesis [49, 50]. In a meta-analysis involving eight studies and 30,970 participants, combined vitamin D and calcium supplementation demonstrated a 15% reduction in the risk of total fractures and a 30% reduction in the risk of hip fractures [51].

5.2. Role of Vitamin D in Muscles

The association between Vitamin D deficiency (VDD) and musculoskeletal dysfunction is well-established, characterized by decreased muscle strength and size, alongside an increase in noncontractile tissue within muscles [52, 53]. A comprehensive meta-analysis, covering 29 randomized controlled trials (RCTs) with 5533 subjects, explored the impact of vitamin D supplementation on muscle strength. It revealed a modest yet noteworthy enhancement in overall muscle strength. Notably, there was a significant positive effect on lower limb muscle strength, while grip strength remained unaffected [54]. Subgroup analyses indicated that the improvement in muscle strength was more prominent among individuals with baseline 25(OH)D values < 30 nmol/L compared to those with 25(OH)D ≥ 30 nmol/L.

While this meta-analysis also investigated the impact of vitamin D supplementation on muscle mass and power, the available data were limited, encompassing only six and five studies with a total of 538 and 245 subjects, respectively. Notably, no evidence supported the idea that vitamin D supplementation enhances muscle mass or power [54]. However, the potential improvement in lower limb muscle strength stands out as a promising mechanism by which vitamin D supplementation might mitigate the risk of falls, particularly considering that quadriceps strength serves as a significant predictor of falls [55].

In a 2014 trial that employed a sequential meta-analysis approach to mitigate the risk of false-positive effects, Bolland et al. conducted a thorough analysis of data from 20 RCTs involving 29,535 participants. Their findings indicated that vitamin D supplementation did not result in a reduction of the relative risk for falls by 15% or more. This lack of effect persisted even in sensitivity analyses, where the threshold for risk reduction was lowered to 10%. Furthermore, no discernible differences were observed between the effects of vitamin D supplementation alone and combined vitamin D and calcium supplementation on the risk of falls. As a result, the authors concluded that forthcoming trials were unlikely to change these negative conclusions concerning the impact of vitamin D supplementation on fall risk [56].

6. Vitamin D: Non-Classical Effects.

6.1. Vitamin D and Hypertension

Preclinical investigations have provided insights into the role of Vitamin D deficiency (VDD) in potentially contributing to hypertension. This association is elucidated through the upregulation of the renin–angiotensin–aldosterone system, leading to increased vascular resistance and vasoconstriction [57-59]. Conversely, the activation of the Vitamin D receptor (VDR) has been shown to inhibit intrarenal mRNA levels and protein expression of key components within the renin–angiotensin–aldosterone system [57].Accumulating evidence supports the efficacy of vitamin D supplementation in reducing blood pressure, particularly in individuals with both hypertension and VDD [60]. The mode of vitamin D supplementation plays a crucial role, with daily administrations [61-63] or weekly administrations [64] demonstrating positive effects on hypertension outcomes. In contrast, the use of large bolus vitamin D doses, such as 100,000 IU every 2 months, has proven ineffective in reducing blood pressure in subjects with vitamin D deficiency [65]. It is noteworthy that substantial vitamin D doses may also exert adverse vascular effects, leading to vascular calcification [66]. Conversely, vitamin D supplementation in individuals already replete with vitamin D has no discernible impact on lowering blood pressure [67]. Moreover, the influence of antihypertensive medications on the relationship between vitamin D supplementation and blood pressure warrants consideration. For example, Bernini et al. found no effect of acute or chronic vitamin D supplementation on renin–angiotensin–aldosterone system in patients with essential hypertension undergoing renin–angiotensin–aldosterone system inhibitor treatment [61].

6.2. Role of Vitamin D in Cardiovascular

The Vitamin D receptor is expressed in various cardiovascular tissues, including endothelial cells, vascular smooth muscle cells, and cardiac myocytes [68]. Vitamin D is integral in maintaining endothelial function by impeding the proliferation of vascular smooth muscle cells and decreasing oxidative stress, inflammation, and thrombogenesis [69, 70]. Moreover, there's a proposition that vitamin D can influence lipid metabolism by enhancing the activity of lipoprotein lipase in adipose tissue and diminishing fatty acid absorption [71, 72].Furthermore, the ability of vitamin D to decrease RAAS activity contributes to its blood pressure-lowering effects.

In a comprehensive meta-analysis encompassing nearly 850,000 individuals, participants were categorized into tertiles based on their 25(OH)D concentrations. Those in the lower tertile demonstrated an elevated risk of cardiovascular disease-related mortality in comparison to their counterparts in the upper thirds of 25(OH)D concentrations [73]. Another meta-analysis revealed a heightened risk of cardiovascular mortality in subjects within the lowest quintile of 25(OH)D concentration, especially notable in individuals without a history of cardiovascular disease, as well as those with a history of cardiovascular disease [74].A recent large cohort study involving 24,311 patients with type 2 diabetes and 67,789 subjects with prediabetes—both populations at an increased risk of cardiovascular disease (CVD)—established an inverse and independent association between 25(OH)D levels and the risk of incident cardiovascular outcomes and all-cause mortality. A dose-response analysis indicated that elevating 25(OH)D levels up to 50–60 nmol/L was associated with a decreased risk of mortality and cardiovascular events [75]. This evidence underscores the significant role of vitamin D in cardiovascular health and suggests its potential as a modifiable factor in reducing cardiovascular disease risk.

6.3. Role of Vitamin D in Respiratory Tract Infection

Vitamin D plays a pivotal role in regulating both the innate and adaptive immune responses. Vitamin D Receptor and CYP27B1 are expressed by virtually all immune cells, including macrophages, activated T and B cells, dendritic cells, and endothelial cells in the respiratory tracts. These cells possess the ability to convert 25(OH)D into its active form [76-78]. Although neutrophils express VDR, the absence of CYP27B1 implies their limited participation in this hydroxylation process [79].Extant evidence underscores the role of 1,25(OH)2D in regulating the innate immune response via a negative feedback loop on

macrophages and other immune cells. Specifically, IFNγ-activated macrophages prompt the release of 1,25(OH)2D, activating VDR on macrophages and subsequently suppressing the expression of crucial genes responsible for generating proinflammatory proteins [80]. In terms of adaptive immune responses, 1,25(OH)2D has been shown to restrain the proliferation and differentiation of activated human B cells, suppress T helper cells, and promote regulatory T (Treg) cells. The collective effect of these actions is a limitation of inflammatory processes. In the context of the influenza virus, exposing human lung A549 epithelial cells to 1,25(OH)2D before or after virus exposure has demonstrated a reduction in the production of TNF-α, IFN-β, and IFN-stimulated gene-15. Furthermore, it downregulates interleukin (IL-8 and IL-6 RNA levels [81].

A recent comprehensive review extensively explores the mechanisms through which vitamin D modulates and regulates immune responses [77]. Additionally, a large cross-sectional study involving 6789 subjects established a negative linear relationship between vitamin D levels and lung infections and function. For every 10 nM/L increase in vitamin D levels, the infection risk decreased by 7% [82]. Similar negative associations between vitamin D levels and the risk or severity of pneumonia have also been reported [83, 84].

6.4. Vitamin D and COVID-19

Various mechanisms have been proposed to elucidate the potential protective role of vitamin D against COVID-19. Firstly, by modulating the innate immune response, vitamin D triggers the synthesis of antimicrobial peptides such as cathelicidin (or LL-37) and β defensin, effectively impeding viral entry into cells [85]. Due to its influence on the adaptive immune system and its capacity to steer away from a proinflammatory state, vitamin D plays a crucial role in diminishing the risk of a cytokine storm, particularly significant in severe cases of COVID-19 [86]. Additionally, by regulating the renin–angiotensin–aldosterone system (RAAS), vitamin D exerts suppressive effects on angiotensin-converting enzyme (ACE) while concurrently inducing ACE2 expression. This dual action results in a reduction of angiotensin 2 and an elevation of angiotensin 1–7. These enzymatic alterations serve to rectify the ACE: ACE2 imbalance induced by SARS-CoV-2 infection, thus mitigating the risk of vasoconstriction and acute respiratory distress syndrome (ARDS) [86].Observational studies consistently reveal an increased risk of COVID-19 in patients with vitamin D deficiency (VDD) [87]. In the largest observational study conducted to date, it was established that vitamin D insufficiency or deficiency is associated with a 2.3–3.6 times higher risk of severe COVID-19, necessitating hospital admission [88]. Smaller, nonrandomized studies provided additional insights, demonstrating that the administration of high doses of vitamin D prior to SARS-CoV-2 infection correlated with milder manifestations of COVID-19 and improved survival rates, particularly among older frail patients [89, 90].

Pal et al. conducted a systematic review and meta-analysis [91] encompassing data from 13 studies. The evidence from this analysis suggests a correlation between vitamin D supplementation and enhanced clinical outcomes in COVID-19 patients, particularly a decrease in mortality rates. Notably, the positive effects were more pronounced when vitamin D was administered subsequent to the diagnosis of COVID-19. Drawing from these findings, the authors proposed the potential use of vitamin D as an adjunctive treatment in individuals afflicted with COVID-19. It is important to highlight, however, that the analysis primarily incorporated three studies in which vitamin D supplementation was initiated prior to the diagnosis of COVID-19 [91]. Despite these encouraging observations, it is imperative to acknowledge a critical aspect of the study, namely, the limited representation of pre-diagnosis vitamin D supplementation in their analysis. This calls for cautious interpretation of the findings, as the majority of the included studies focused on post-diagnosis administration. The overall heterogeneity among patients and the relatively modest sample sizes across studies could contribute to the observed disparities in the impact of vitamin D supplementation on COVID-19 outcomes.

6.5. Vitamin D and Type 2 Diabetes

Preclinical investigations have suggested that vitamin D might exert influences on β-cell growth and differentiation, enhance insulin secretion [92, 93] elevate the expression of the insulin receptor [94], and augment insulin-mediated glucose transport [95]. Nevertheless, human studies employing rigorous methodologies to assess the impact of vitamin D supplementation on insulin secretion and action have not consistently supported these findings. Specifically, the Tromsö study, which incorporated both a case-control and a randomized controlled trial, involved 104 non-diabetic individuals with initially low serum 25(OH)D levels. These participants were randomly assigned to receive either 20,000 IU twice weekly or a placebo. Assessments conducted via a hyperglycemic clamp at baseline and six months post-treatment revealed that vitamin D supplementation did not result in a significant increase in first- or second-phase insulin secretion.

Furthermore, it did not enhance insulin sensitivity compared to the placebo group [96]. Barbarawi et al. conducted a meta-analysis, reviewing data from nine randomized controlled trials that encompassed a total of 43,559 patients. While the overall population did not exhibit a significant impact of vitamin D supplementation on the incidence of type 2 diabetes (T2D), post hoc analyses according to vitamin D dosage unveiled noteworthy trends. Individuals receiving ≥ 1000 IU/day exhibited a significantly reduced incidence of T2D. Moreover, non-obese patients undergoing high-dose treatment exhibited a reduced relative risk of developing T2D, whereas no notable benefit was observed among patients with obesity [97]. In a meta-analysis conducted by Barbarawi et al., involving data from nine randomized controlled trials with a collective sample size of 43,559 patients, the overall analysis did not reveal a significant impact of vitamin D supplementation on the incidence of type 2 diabetes (T2D). However, upon conducting post hoc analyses based on vitamin D dosage, a notable trend emerged. Individuals receiving doses of ≥ 1000 IU/day exhibited a substantially lower incidence of T2D (RR 0.88; 95% CI, 0.79–0.99; p = 0.03). Notably, non-obese patients receiving higher-dose treatments demonstrated a reduced relative risk of developing T2D (RR 0.68; 95% CI 0.53–0.89; p = 0.005), whereas no discernible benefit was observed among patients with obesity [97].

Exploring the impact of vitamin D supplementation on glycemic control in individuals with T2D, Wu et al. evaluated 24 studies. Their findings indicated that vitamin D supplementation led to improvements in HbA1c levels [standardized mean difference −0.25 (−0.45 to −0.05)]. Notably, this effect was more pronounced among patients initially presenting with vitamin D deficiency [SMD −0.39 (−0.67 to −0.10)], as well as in patients with a BMI < 30 kg/m2 [SMD −0.30 (−0.54 to −0.07)] [98]. In contrast, a subsequent systematic review and meta-analysis conducted by Li et al. reported divergent results. Their analysis indicated that while vitamin D supplementation did not notably impact fasting blood glucose, HbA1c, or fasting insulin levels, it did demonstrate an improvement in HOMA-IR (an index of insulin resistance) [99].

6.6. Vitamin D and Autoimmune Disorders

The activation of the Vitamin D Receptor by 1,25(OH)2D has been demonstrated to hinder the differentiation and proliferation of B and T helper lymphocytes, leading to a transition from an inflammatory state to a more immune-tolerant status [100]. Moreover, 1,25(OH)2D has shown the ability to suppress the production of pro-inflammatory Th1 cytokines while concurrently stimulating the activity of Th2 and regulatory T-cells [101]. These pathways have been implicated in the presumed protective role of vitamin D against autoimmune disorders. There's a hypothesis surrounding the presence of an acquired form of vitamin D resistance contributing to the onset of autoimmune conditions [102]. Vitamin D Deficiency (VDD) has been identified in various autoimmune disorders, encompassing rheumatoid arthritis, autoimmune thyroiditis, multiple sclerosis (MS), and type 1 diabetes [103-106]. In this context, our focus shifts primarily to multiple sclerosis given the extensive research on the effects of vitamin D in this realm, further supported by recent positive findings from the VITAL trial. Evidence suggests a potential connection between genetically induced Vitamin D Deficiency and an increased risk of MS [107, 108]. Multiple studies consistently reveal lower levels of 25(OH)D in individuals with multiple sclerosis compared to their healthy counterparts [109]. This assertion is strengthened by a comprehensive 2014 systematic review and meta-analysis that included 11 studies, involving a total of 1007 patients and 829 healthy individuals [110].

In the VITAL trial, a meticulously designed study involving 25,871 participants, researchers utilized a randomized, double-blind, placebo-controlled approach with a two-by-two factorial design to assess the potential impact of vitamin D supplementation. Participants received 2000 IU of cholecalciferol daily, either alone or combined with omega-3 fatty acids (1 g/day) [111]. The study involved participants with an average age of 67 years and aimed to evaluate the effects on autoimmunity by monitoring the confirmed incidence of autoimmune diseases over a 5-year period. Annual questionnaires were used to track the emergence of new cases of rheumatoid arthritis, polymyalgia rheumatica, psoriasis, autoimmune thyroiditis, and inflammatory bowel disease (IBD). Results indicated that individuals receiving vitamin D supplementation showed a 22% reduced risk of developing new autoimmune diseases compared to those in the placebo group. Notably, upon excluding the initial 2 years of follow-up to assess the intervention's latency, the findings further confirmed the positive impact of vitamin D supplementation. It revealed a more pronounced effect, demonstrating a reduction in the incidence of autoimmune diseases [111].

6.7. Vitamin D and Neuroprotection

The Vitamin D Receptor (VDR) and 1α-hydroxylase, crucial enzymes in vitamin D metabolism, are widely expressed in the brain, notably in the substantia nigra and hippocampus, significant regions associated with Parkinson's disease and cognition, respectively [112, 113]. Vitamin D is posited to potentially confer

neuroprotection through various mechanisms, encompassing the regulation of neurotrophic factors, nerve growth, mitigation of cytotoxicity, and reduction of oxidative stress [114-116]. Additionally, vitamin D is implicated in modulating acetylcholine levels and the clearance of amyloid beta, further underlining its potential role in brain health [117]. Regarding Parkinson's disease, studies exploring the impact of Vitamin D Deficiency (VDD) have yielded conflicting outcomes. A substantial prospective study conducted in Finland (N = 3173) revealed that individuals in the highest quartile for baseline serum vitamin D levels showed a 65% lower risk of developing Parkinson's disease compared to those in the lowest quartile. This suggests a potential link between lower mid-life vitamin D levels and an elevated risk of the disease [118]. However, subsequent studies conducted in the USA with even larger sample sizes failed to validate this association [119].Conversely, consistent evidence in the literature associates vitamin D levels with the severity of Parkinson's disease. Cross-sectional studies consistently demonstrate a correlation between lower serum vitamin D levels and increased motor disability in Parkinson's disease: lower vitamin D levels are associated with worse motor function [120, 121].Yet, it remains unclear whether vitamin D directly modifies disease severity or if these associations stem from "inverse causality," where patients with more severe symptoms tend to be less mobile, receiving reduced sun exposure. In the realm of cognitive function, numerous studies highlight an association between low vitamin D levels and poorer cognition in the general population [122, 123]. However, intervention studies exploring the benefits of vitamin D supplementation in enhancing cognitive function, and anxiety [123-125].

6.8. Vitamin D and Cancer

Early investigations have demonstrated the potent antiproliferative and pro-differentiating effects of 1,25(OH)2D analogs on cancer cells in laboratory settings [126]. Vitamin D exhibits a multifaceted impact, diminishing tumor invasiveness, angiogenesis, and the tendency for metastasis [127, 128]. Systematic reviews and meta-analyses examining vitamin D levels and mortality outcomes in cancer patients indicate a protective association between higher vitamin D levels and several cancer types, including colorectal cancer [129]. breast cancer [130]. prostate cancer [131]. and various hematological malignancies [132]. However, these encouraging findings derived from observational studies may be influenced by potential biases stemming from overall better health status or healthier lifestyle choices among individuals with higher 25(OH)D levels. In the expansive VITAL randomized controlled trial (N = 25,871), participants underwent random assignment to either receive 2000 IU of vitamin D or a placebo daily, in conjunction with omega-3 fatty acids or a placebo. This was carried out using a two-by-two factorial design over a median follow-up period of 5.3 years [133]. It's noteworthy that participants included in the trial had no history of cancer, except for nonmelanoma skin cancer. The primary analysis did not reveal a significant reduction in the total incidence of invasive cancer with vitamin D supplementation. However, there was a notable trend indicating a potential decrease in total cancer mortality [133]. Considering latency by excluding events within the initial two years of supplementation, the intervention resulted in a significant reduction in the risk of mortality. The discernible impact of vitamin D supplementation on cancer mortality was evident in the cumulative incidence curves at the 4-year mark of supplementation.

Intriguingly, the authors also investigated potential interactions between baseline participant characteristics and supplementation outcomes, revealing a significant interaction with body mass index. Lean participants displayed a substantial reduction in cancer risk, while obese and overweight individuals did not observe the same effect [133].

7. Objectives for Vitamin D Supplementation

While the synthesis of vitamin D from 7-dehydrocholesterol in the skin due to sunlight exposure generally meets daily requirements, vitamin D deficiencies persist. Serum concentrations below 10 ng/ml (equivalent to 25 nmol/L) of 25(OH)D typically signify Vitamin D Deficiency. However, recommended target levels for ideal vitamin D vary among different organizations. According to the Endocrine Society Practice Guidelines, deficiency is indicated by a serum 25(OH)D level below 50 nmol/L, insufficiency falls within 52.5–72.5 nmol/L, and sufficiency is deemed optimal at levels of at least 75 nmol/L for musculoskeletal health [134]. These thresholds are supported by prominent organizations such as the American Association for Clinical Endocrinologists, American Geriatric Society, National Osteoporosis Foundation, and International Osteoporosis Foundation [135].In contrast, the World Health Organization and the current National Institute for Health and Clinical Care Excellence (NICE) guidelines in the UK define Vitamin D Deficiency as a serum 25(OH)D below 10 ng/ml (i.e., 25 nmol/L), with insufficiency identified between 25–50 nmol/L [136].

More aggressive supplementation is recommended, particularly among the elderly and individuals with limited sun exposure (such as dark-skinned individuals, those with cultural practices limiting sun exposure,) and poor nutrition. Although general guidelines exist, clinicians must customize vitamin D prescriptions based on various factors like obesity, nutritional status, diet, and sunlight exposure. A uniform approach to vitamin D supplementation is deemed ineffective. Studies indicate that patients with obesity may need two to three times higher vitamin D doses to address deficiency [137, 138]. Despite the rarity of vitamin D toxicity, moderation is advised. Notably, recent research has confirmed the clinical relevance of certain thresholds in mortality studies.

For instance, a Mendelian randomization study revealed elevated mortality risk below 25 nmol/L of 25(OH)D, stabilizing at 50 nmol/L [139]. Similar findings emerged from the Institute of Medicine, demonstrating a J-curve relationship between mortality and 25(OH)D levels. Mortality rates declined significantly as 25(OH)D approached 30 ng/mL, with a slight rise at 50 ng/mL [140]. However, some experts argue that higher mortality rates associated with 25(OH)D levels above 50 ng/mL might be due to prolonged past vitamin D deficiency that was subsequently treated [141].

8. Conclusion

Globally, the prevalence of vitamin D deficiency posing a significant burden on public health. This review seeks to provide a comprehensive overview of the current evidence concerning the therapeutic applications of vitamin D across various diseases. Despite the inherent complexities in assessing vitamin D supplementation effects in Randomized Controlled Trials, evidence suggests its potential in reducing acute respiratory infections, as well as extend to the incidence of Type 2 Diabetes and autoimmune diseases. These findings warrant further investigation. Moreover, it becomes evident that Vitamin D Deficiency correlates with adverse health outcomes, heightened morbidity, and increased mortality. However, when it comes to individuals already replete in vitamin D, supplementation doesn't seem to yield clinically significant benefits. Given the limitations associated with universal testing for vitamin D levels, which is both impractical and costly, the pragmatic approach in routine clinical practice leans towards recommending vitamin D supplementation. This approach is not only cost-effective but also well-tolerated and easily accessible. In research settings, it's pivotal to adopt a comprehensive approach while studying the impacts of vitamin D supplementation. This entails a holistic assessment of the entire vitamin D endocrine system, rather than solely concentrating on pre- and post-treatment levels of 25(OH)D. Employing appropriate and physiologically relevant vitamin D dosages, controlling the vitamin D supplementation received by subjects in placebo arms, and ensuring sufficiently extended follow-up periods are essential aspects that necessitate careful consideration in future studies.

Confirmation that all authors have approved the manuscript for submission

9. Conflicts of interest

There are no conflicts to declare

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None.

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