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THE ROLE OF VITAMIN D DEFICIENCY IN THE PREVALENCE AND SEVERITY OF DISEASES: A FOCUS ON NON-AUTOIMMUNE OUTCOMES – LITERATURE REVIEW

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ABSTRACT

Vitamin D is a steroid hormone essential to a broad spectrum of physiological processes. Synthesized in the skin via UVB exposure and obtained from dietary sources, it plays a central role in calcium and phosphorus homeostasis and is critical to cardiovascular, musculoskeletal, neurological, metabolic, and reproductive health. Owing to its pleiotropic effects, vitamin D deficiency can lead to widespread systemic dysfunction and has been associated with increased all-cause mortality. According to a position statement of the European Calcified Tissue Society from 2019 its prevalence is between 30–60% in Western, Southern and Eastern Europe. The 2023 Polish recommendations titled *"Vitamin D deficiency in developmental age – the scale of the problem, prevention, treatment, and the latest 2023 guidelines for Poland"*, state that approximately 90% of adults and nearly all adolescents in Poland are affected by vitamin D deficiency. High-risk groups include older adults, individuals with obesity, pregnant women, and those with limited sunlight exposure or chronic diseases. Although traditionally associated with autoimmune conditions, growing evidence links vitamin D deficiency to a range of non-autoimmune disorders. As a modifiable factor implicated in diverse chronic diseases, vitamin D deficiency underscores the need for standardized diagnostic criteria and targeted clinical trials. This review synthesizes molecular, clinical, and epidemiological findings to evaluate the systemic consequences of vitamin D deficiency. It identifies key research gaps, methodological inconsistencies, and the absence of standardized diagnostic criteria. The need for personalized supplementation strategies and large-scale randomized trials is emphasized to clarify causal relationships and inform evidence-based clinical guidelines.

Keywords: Vitamin D, vitamin D deficiency, avitaminosis D, functional vitamin D deficiency, cholecalciferol

INTRODUCTION

Vitamin D (VitD) belongs to the group of steroid hormones which are fat-solvable [1], [2]. There are several forms of VitD, with the most common being ergocalciferol, (vitamin $D_{2)}$ which is produced by

plants and cholecalciferol (vitamin D_3), which is synthesized in humans' skin [3], [4]. Both D_2 and D_3 might be supplied through dietary sources [5].

Cutaneous exposure to the sunlight, specifically UVB rays, induces the transformation of 7-dehydrocholesterol to previtamin-D3. Through thermal isomerization, it is further transformed into vitamin D_3. Upon absorption in the skin or in the gastrointestinal tract, the next step happens in the liver, where the hydroxylation of the vitamin D_3 to 25-hydroxycholecalcicferol D (25[OH]D_3), known as calcifediol occurs. A subsequent hydroxylation transpires in the kidneys where the active form of VitD: 1,25-dihydroxycholecalciferol D (1,25[OH]$_2D_3$), also known as calcitriol, is formed [3]. VitD and its metabolites are transported to their target tissues thanks to vitamin-D-binding protein (DBP) or group-specific component (Gc-globulin). After the crossing from the bloodstream into the cells, VitD binds to the vitamin D receptor [6], [7], [8].

Vitamin D exerts its biological effects through its active metabolites – calcifediol and calcitriol, which, thanks to steroid receptors located in the cell's nucleus, can regulate the mechanisms of transcription and translation. Due to its involvement in the synthesis of the proteins responsible for calcium absorption, and those that determine the mineral processes in bones, cholecalciferol plays a pivotal role in calcium and phosphorus homeostasis. The significance of this compound stems from its participation in several processes: augmentation of the absorption of calcium and phosphates in the digestive system, promoting renal calcium reabsorption, and elevating blood calcium and phosphates levels [7], [8], [9].

Vitamin D deficiency is a condition characterized by decreased serum 25-Hydroxyvitamin D [25(OH)D] levels [10]. It is a recognized disease classified under the International Statistical Classification of Diseases and Related Health Problems (ICD-10) with the code E55, while E55.9 denotes unspecified vitamin D deficiency [11], [12].

The exact threshold at which vitamin D deficiency leads to physiological symptoms and their prevalence remains uncertain [13], [14]. The U.S. National Institutes of Health (NIH) Office of Dietary Supplements defines deficiency as a 25(OH)D level below 12 ng/mL and considers levels under 20 ng/mL inadequate for bone and overall health [10]. Similarly, the Institute of Medicine (IOM) / National Academy of Medicine (NAM) defines deficiency as levels below 20 ng/mL [15]. However, a recent study by Fabregat-Bolufer et al. (published in March of 2025) used big data analysis with an intent to establish sufficient serum vitamin D reference intervals. They examined retrospectively 130,030 samples and although acknowledged further need to investigate the topic due to study limitations, concluded that vitamin D deficiency might be indicated by levels below 12–14 ng/mL (25–30 nmol/L) when clinical symptoms appear [16].

Vitamin D deficiency is primarily associated with an increased prevalence of autoimmune diseases, including Multiple Sclerosis (MS), Rheumatoid Arthritis (RA), Type 1 Diabetes, Lupus (SLE), Inflammatory Bowel Disease (IBD) (such as Crohn's disease and ulcerative colitis), and Psoriasis [17]. Additionally, several studies have established that vitamin D deficiency contributes to dysfunction across multiple physiological systems and is linked to an elevated risk of all-cause mortality and non-autoimmune conditions such as cardiovascular diseases, metabolic syndrome, and neurodegenerative disorders [18], [19], [20]. These associations highlight the broad impact of vitamin D on systemic health, reinforcing its role beyond immunological disorders.

METHODS

This literature review was conducted using major biomedical databases, including PubMed, Scopus, and PMC. Articles were selected based on relevance to the topic of vitamin D deficiency and its implications for health. While no formal exclusion criteria were applied regarding publication date or study design, priority was given to peer-reviewed articles from reputable journals. Particular attention was paid to methodological rigor, study design, and relevance to current clinical and biological understanding. Older, widely cited studies were included when they provided foundational or mechanistic insights that continue to support current hypotheses.

RESULTS AND DISCUSSION

CARDIOVASCULAR DISEASES

Vitamin D deficiency and vitamin D receptor dysfunction have been consistently associated with a wide range of adverse cardiovascular outcomes. These include a more severe progression of heart failure, myocardial inflammation, left ventricular hypertrophy, structural remodeling of the left heart chambers, slow coronary flow, increased proteinuria, and both systolic and endothelial dysfunction [20], [21], [22], [23]. The duration of vitamin D deficiency also appears to play a role in disease severity, as demonstrated by Assalin et al. who reported a correlation between prolonged vitamin D deficiency and

worsened cardiac remodeling and dysfunction [22].

Experimental findings by Assalin et al. further clarified that cardiac changes due to vitamin D deficiency occur independently of calcium and parathyroid hormone disturbances, suggesting a direct effect of vitamin D [22]. Their rat model demonstrated that vitamin D deficiency led to altered cardiac substrate metabolism, increased inflammatory cytokines such as TNF-α and IFN-γ, elevated oxidative stress, reduced antioxidant enzyme activity, and myocardial fibrosis and apoptosis. These changes were more pronounced with longer durations of deficiency, supporting the hypothesis that vitamin D deficiency is an ongoing process with cumulative impact on cardiac structure and function. However, extrapolating these findings to humans must be approached cautiously due to inherent species differences and limitations of animal models. Bae et al. provided additional mechanistic insight by demonstrating that activation of the vitamin D receptor pathway confers cardioprotective effects, attenuating cardiac dysfunction, myocardial apoptosis, and the upregulation of proinflammatory cytokines following myocardial infarction [21]. In contrast, vitamin D receptor-deficient models exhibited accelerated heart failure progression due to the absence of this protective signaling. Their study also highlighted vitamin D's role in reducing cardiac fibrosis and extracellular matrix remodeling, likely through enhanced vitamin D receptor expression. Moreover, vitamin D signaling was shown to downregulate renin-angiotensin system components, reinforcing the connection between vitamin D receptor activation and modulation of neurohormonal pathways central to heart failure pathophysiology. As with other animal-based studies, the relevance of these mechanistic findings to clinical practice requires further validation in human populations.

Support for vitamin D's vascular effects is further provided by Verstuyf et al. who found that lower serum vitamin D levels were associated with increased blood pressure across normotensive and hypertensive individuals from multiple ethnic backgrounds [24]. These findings reinforce the multifactorial role of vitamin D in maintaining cardiovascular stability.

Oz et al. added clinical relevance through a cross-sectional observational study evaluating epicardial coronary flow rate, endothelial function, and subclinical atherosclerosis in 222 patients with suspected ischemic heart disease and normal or near-normal coronary arteries [23]. They found that nearly half of the cohort had insufficient vitamin D levels, and that this insufficiency was independently associated with slow coronary flow, impaired flow-mediated dilation, and increased carotid intima-media thickness. These findings support a link between vitamin D insufficiency and microvascular dysfunction, early atherosclerotic changes, and compromised endothelial function, emphasizing the broader impact of vitamin D beyond structural myocardial outcomes. However, as a cross-sectional study, causal relationships cannot be confirmed, and potential confounding factors may have influenced results.

Wang et al. proposed that the cardioprotective benefits of vitamin D are primarily mediated through downregulation of the renin-angiotensin-aldosterone system [20]. Zittermann added that activation of this system could underlie the relationship between vitamin D deficiency and hypertension [25]. Wang et al. further identified vitamin D's influence on cardiac remodeling, vascular health, inflammation, and glycemic control as contributing mechanisms [20]. Holick and Zittermann supported the role of vitamin D in reducing the risk of heart failure and atherosclerosis [25], [26].

In their comprehensive review, Wang et al. emphasized the widespread prevalence of vitamin D insufficiency globally and its strong epidemiological associations with cardiovascular diseases, hypertension, and metabolic syndromes [20]. They noted that while some prospective studies suggest that vitamin D deficiency increases the risk of ischemic heart disease, sudden cardiac death, and heart failure, randomized clinical trials have yielded inconsistent outcomes, often limited by methodological shortcomings. Notably, no large-scale clinical trials have yet confirmed the benefit of vitamin D supplementation on cardiovascular endpoints. Nonetheless, Wang et al. proposed several biologically plausible mechanisms for cardioprotection. They recommended targeted screening and supplementation in high-risk populations, such as elderly individuals, patients with osteoporosis or chronic illness, and African Americans with cardiovascular comorbidities. However, the lack of definitive interventional data continues to limit broad clinical recommendations.

Despite the compelling evidence, many of the foundational studies in this field are now more than a decade old. With ongoing advances in biomedical research and diagnostics, concerns have been raised about the current applicability of these earlier findings. A persistent challenge remains in establishing standardized serum thresholds for vitamin D sufficiency, which complicates interpretation across studies. Reflecting this uncertainty, Herrmann et al. initially questioned the role of vitamin D in cardiovascular protection, citing methodological and biological limitations in defining an optimal serum 25-hydroxyvitamin D concentration [27]. Nonetheless, their own data supported a protective role: individuals with vitamin D deficiency exhibited significantly higher cardiovascular mortality, greater prevalence of heart failure, and elevated NT-proBNP levels compared to individuals with adequate vitamin D status.

More recent research has reinforced the association between sufficient vitamin D levels and cardiac health. Peramaiyan et al. reported that vitamin D deficiency is associated with a heightened risk of

several cardiovascular conditions, including coronary artery disease, cardiac hypertrophy, myocardial infarction, fibrosis, cardiomyopathy, and heart failure [28]. Furthermore, vitamin D deficiency has been implicated in various arterial diseases such as aneurysm formation, arterial calcification, peripheral artery disease, hypertension, and atherosclerosis. The authors also highlighted links between vitamin D deficiency and cardiac inflammation, oxidative stress, metabolic energy alterations, structural changes in the left atrium and ventricle, systolic dysfunction, myocardial fibrosis, and apoptosis. Vitamin D's regulatory role over ST2—a receptor involved in binding interleukin-33 and modulating cardiac function—was noted as another pathway contributing to its cardiovascular effects. These cardioprotective benefits appear to be mediated via vitamin D's anti-inflammatory, anti-apoptotic, and anti-fibrotic mechanisms. However, the observational nature of these studies limits definitive conclusions regarding causality.

A 2025 study by Cheng et al. added further mechanistic insight by confirming the presence of vitamin D receptors in myocardial tissue, suggesting a direct regulatory role of vitamin D in cardiac function [29]. Cheng and colleagues examined the relationship between free vitamin D levels and cardiovascular outcomes, reporting that a two-fold increase in free vitamin D was associated with a 25% reduction in the risk of heart failure. Although no significant associations were found with other cardiovascular events, the authors proposed that vitamin D may enhance cardiac health through the regulation of calcium handling, reduction of oxidative stress, and anti-inflammatory activity within heart muscle cells. Importantly, they also noted the high intra-individual variability of free vitamin D, cautioning against the use of single-point measurements to predict long-term cardiovascular outcomes. This limitation reflects broader methodological challenges in accurately assessing vitamin D status and its clinical implications.

In conclusion, accumulating evidence supports a role for vitamin D in cardiovascular health through diverse biological pathways, including modulation of the renin-angiotensin-aldosterone system, reduction of oxidative stress, improvement of endothelial function, and prevention of myocardial remodeling and inflammation. However, the majority of available data come from observational studies or preclinical models, which restrict the ability to draw definitive causal inferences. Additionally, significant variability in methods used to assess vitamin D status and a lack of consensus on deficiency thresholds further complicate the interpretation of findings. While newer studies continue to reinforce earlier observations and provide greater mechanistic clarity, large-scale randomized controlled trials remain essential to determine whether vitamin D supplementation can effectively reduce cardiovascular morbidity and mortality in clinical practice.

BONE AND MUSCULOSKELETAL HEALTH

1. Bone Health

Vitamin D plays a central role in maintaining skeletal health by regulating calcium and phosphorus absorption in the intestines, suppressing parathyroid hormone (PTH) secretion, and modulating the activity of osteoblasts and osteoclasts—key cells involved in bone formation and resorption [20], [24], [30], [31]. These mechanisms collectively ensure proper bone mineralization and remodeling throughout the lifespan.

Vitamin D deficiency disrupts calcium-phosphate balance and undermines bone mineralization, leading to skeletal disorders such as rickets in children and osteomalacia in both pediatric and adult populations [32], [33]. Over time, chronic deficiency contributes to reduced bone mineral density, increasing the risk of osteoporosis and fragility fractures, especially in older adults and postmenopausal women [31], [34]. This increased risk may be partly explained by age-related declines in the expression of the vitamin D receptor, which reduces the body's responsiveness to vitamin D and its ability to regulate bone remodeling effectively [31].

A systematic review by Bischoff-Ferrari et al. assessed the effects of oral vitamin D supplementation on fracture outcomes in older adults. The review found that daily doses of 700–800 IU of vitamin D were more effective than lower doses in reducing hip and nonvertebral fracture risk. However, since most of these trials also included calcium supplementation, determining whether vitamin D alone contributed to these protective effects remained challenging [35]. The average supplementation duration across studies varied, with periods ranging from 12 to 60 months for nonvertebral fractures and 24 to 60 months for hip fractures.

Building on these results, a newer study by Avenell et al. explored the effects of vitamin D supplementation with and without calcium [36]. The study concluded that vitamin D alone was ineffective in preventing fractures, including hip and new fractures, in the general population. In contrast, when combined with calcium, vitamin D resulted in a small but statistically significant reduction in hip fracture risk—particularly among high-risk groups such as institutionalized elderly individuals. Additionally, the combined supplementation modestly reduced the risk of non-vertebral fractures, although its effect on vertebral fractures remains uncertain. These findings underscore the importance of calcium co-supplementation in enhancing the efficacy of vitamin D in fracture prevention. However, one limitation of this review is that it does not specify the exact dosages of vitamin D or calcium used in the

trials, restricting the ability to assess dose-response relationships or determine optimal supplementation strategies. Furthermore, age-related declines in vitamin D receptor expression may mean that older individuals respond differently to supplementation than younger individuals, complicating the interpretation of results.

Epidemiological studies have consistently shown that low serum 25-hydroxyvitamin D [25(OH)D] levels are associated with decreased bone mineral density and a higher risk of skeletal complications, particularly in elderly populations where age-related physiological changes further impair vitamin D metabolism and bone remodeling. Although most studies focus on older adults due to their higher fracture risk, a growing body of research emphasizes the importance of establishing adequate vitamin D status earlier in life, when bone accrual is most active and peak bone mass is being established.

In adolescents, physical activity is a major determinant of both vitamin D status and bone strength. Recent research highlights the importance of vitamin D for skeletal development during adolescence. A systematic review by Devulapalli synthesized data from ten studies—including five cross-sectional, three population-based, one longitudinal, and one randomized controlled trial—focusing on youth aged 5–18 [37]. The review found a positive correlation between physical activity, serum 25(OH)D levels, and bone mineral content, although its largely observational design limits causal interpretation.

In summary, although vitamin D alone appears insufficient to prevent fractures, evidence supports its combined use with calcium—particularly among high-risk groups such as the elderly—for reducing fracture risk and preserving bone health. Additionally, maintaining adequate vitamin D levels from early life is essential for achieving optimal peak bone mass and supporting skeletal integrity throughout the lifespan. Further research is warranted to clarify the independent effects of vitamin D versus calcium and to determine optimal supplementation strategies across different age groups and risk profiles. These methodological challenges highlight the need for more rigorous, large-scale randomized controlled trials that isolate the effects of vitamin D in different populations. Such studies should control for potential confounders, standardize dosing and measurement of vitamin D levels, and examine long-term outcomes across diverse demographic groups.

2. Muscle Health

Beyond its well-established skeletal functions, vitamin D also plays a vital role in muscle health through both structural and functional mechanisms. Its effects are mediated by vitamin D receptors expressed in muscle tissue, where they regulate calcium transport, protein synthesis, and mitochondrial activity [14]. In addition to these roles, vitamin D facilitates phosphate metabolism, promotes phosphocreatine synthesis, enhances insulin sensitivity in myocytes, and further stimulates protein synthesis. Notably, Type II muscle fibers—critical for strength and power—exhibit a higher density of vitamin D receptors, suggesting that correcting vitamin D deficiency may preferentially enhance the function and recovery of these fibers [38].

While rickets and osteomalacia are traditionally associated with defective bone mineralization, these disorders also commonly present with muscular symptoms, including proximal weakness, hypotonia, and gait abnormalities [11], [32], [39]. Beyond their skeletal manifestations, vitamin D deficiency has been strongly linked to age-related muscle decline, particularly in the context of sarcopenia. Beaudart et al. observed that aging reduces vitamin D receptor expression and impairs 1,25(OH)D activity in muscle cells, compromising muscle cell survival and maintenance [40]. Contributing to this decline, aging muscle often exhibits increased adipose infiltration, which further diminishes muscle quality—though higher vitamin D levels may help counteract these degenerative changes. The InCHIANTI study by Houston et al. adds further support [41]. Individuals over 65 years old with lower serum 25-hydroxyvitamin D (25[OH]D) levels exhibited significantly reduced handgrip strength and poorer performance on the Short Physical Performance Battery (SPPB), regardless of sex.

Additional observational studies have strengthened the evidence linking vitamin D status to muscular strength. Stewart et al. and Vázquez-Lorente et al. found that higher serum vitamin D levels were associated with improved handgrip strength, greater lean mass, and more favorable muscle-to-fat ratios [42], [43]. Pereira da Silva Garcia et al. similarly reported reduced strength in vitamin D-deficient cancer patients [44]. In pediatric populations, Zeeb et al. noted that the benefits of vitamin D supplementation were observed only in children with normal or low body mass index (BMI), suggesting that individuals with higher baseline muscle mass may experience limited functional gain, likely due to ceiling effects [45]. Collectively, the evidence suggests that although vitamin D status is positively associated with muscle strength and composition across diverse populations, the extent of benefit derived from supplementation may be moderated by individual factors such as baseline muscle mass, age, body composition, and overall health status.

In addition to population-level studies, individual case reports provide further clinical insight into the muscular consequences of vitamin D deficiency. Hazique et al. described a 13-year-old patient with severe deficiency who required seven months to fully regain muscle strength despite achieving

biochemical normalization within two months [46]. Likewise, Elwadhi et al. presented a case of a 3-year-old initially misdiagnosed with muscular dystrophy, later correctly identified as having vitamin D deficiency-related myopathy [47]. Although these cases emphasize the importance of assessing vitamin D status in patients with unexplained muscle weakness—especially in pediatric populations—they are inherently limited by their anecdotal nature and lack of control comparisons.

Randomized controlled trials examining the effect of vitamin D supplementation on muscle function have produced mixed results. Sanders et al. concluded that evidence suggests that vitamin D plays a crucial role in skeletal muscle function in the elderly [31]. Nevertheless, they reported a substantial variability in outcomes, which may reflect differences in study design, dosages, populations studied, and outcome measures. A meta-analysis by Beaudart et al., which included 30 randomized controlled trials, identified modest yet significant improvements in lower-limb strength following supplementation [40]. These effects were most pronounced in older adults, institutionalized individuals, and those with serum 25(OH)D concentrations below 30 nmol/L. Subgroup analyses indicated that the effect of supplementation was especially notable among individuals aged 65 and older and appeared more pronounced in frail populations compared to community-dwelling individuals. Interestingly, while vitamin D is often combined with calcium to support bone health, this analysis found no significant additive benefit of calcium for improving muscle strength, suggesting that calcium's role in muscular outcomes remains uncertain. However, no consistent improvements were observed for muscle mass or power, suggesting that the primary benefits of supplementation are functional rather than structural. The supplementation periods in the included studies ranged from 1 month to 60 months, with dosages varying significantly, highlighting the need for further research to determine the optimal duration and dosage of vitamin D supplementation for improving muscle function.

Several modifiable factors may influence the effectiveness of vitamin D on muscle outcomes. Co-supplementation with calcium has been shown to enhance bone mineralization and may augment muscle contraction efficiency. Adequate protein intake is essential for muscle repair and adaptation and may synergize with vitamin D to improve recovery and function [48]. Furthermore, regular physical activity—especially outdoor exercise—not only directly enhances muscle strength but also boosts endogenous vitamin D synthesis, potentially amplifying supplementation effects [49].

Taken together, the findings across molecular, clinical, and epidemiological domains emphasize the multifactorial nature of vitamin D's role in muscle health. In summary, vitamin D plays a critical role in maintaining skeletal muscle integrity through the regulation of calcium handling, protein synthesis, and mitochondrial function within muscle cells. Clinical, observational, and mechanistic evidence consistently supports the association between vitamin D deficiency and declines in muscle strength, particularly among older adults and individuals with functional limitations. Although results from supplementation trials remain mixed, improvements in lower-limb strength represent one of the most consistently observed outcomes. These effects appear most pronounced in populations with low baseline serum 25-hydroxyvitamin D levels, limited mobility, or institutionalized living conditions. The variability in findings across studies may reflect differences in study design, dosage, baseline vitamin D status, nutritional intake, and levels of physical activity. Moving forward, rigorously designed trials are needed to isolate the effects of vitamin D supplementation and to identify optimal dosing strategies for different population subgroups. Maintaining sufficient vitamin D status throughout life remains a promising approach to support musculoskeletal health and mitigate the risk of age-related functional decline.

NEUROLOGICAL DISORDERS

Vitamin D plays a significant role in nervous system. It has been demonstrated that vitamin D receptors are present in both neurons and glial cells, and that passive diffusion of serum vitamin D through the blood-brain barrier enables its activity within central nervous system [50], [51]. Vitamin D participates in processes such as neural differentiation, maturation, and regulation of neurotrophin [52]. Furthermore, vitamin D modulates the synthesis of several neurotransmitters, including acetylcholine, dopamine, and gamma-aminobutyric acid [52], [53].

Clinical trials conducted by Naveilhan et al. confirmed the occurrence of 1,25(OH)2D3 in metabolic processes within neuronal and glial cells, while Zehnder et al. validated this finding in the areas of cerebellum and cerebral cortex [51], [54], [55]. Moreover, Buell and Dawson-Hughes summarized the positive impact of the vitamin D on neuronal protection, based on studies confirming the protective function of vitamin D in the processes of detoxification and neurotrophin synthesis [56], [57], [58], [59]. Furthermore, according to Buell and Dawson-Hughes, considering the proven presence of vitamin D receptor in various regions of brain, the functional role of vitamin D in the human brain can be supported [56].

Alzheimer's disease, characterized by the accumulation of beta-amyloid plaques in the brain stem, is the most common neurodegenerative disease [60], [61], [62]. Balion et al. concluded that their analysis suggests that there is an association between lower vitamin D concentrations and poorer cognitive

function and a higher risk of Alzheimer's Disease [63]. Nevertheless, they point out that that there is no research which provides data from "sufficient period in a large at-risk population". They also suggested that further research needs to be conducted to confirm specific significance of vitamin D in nervous system and its potential benefits in this area [63]. On the other hand, Bivona et al. rejected the notion that vitamin D could be a reliable biomarker for Alzheimers Disease, arguing that "measuring the biomarker does not improve diagnosis or prognosis in these patients" [64]. Furthermore, they noticed that the absence of vitamin D measurement standardization in different studies makes the results unambiguous. For instance as vitamin D deficiency cut-off Afzal et al. used 25 nmol/L, when Aguilar-Navarro et al. used 20 ng/ml, and Duchaine et al. 50 nmol/L [65], [66], [67]. They have all came up with different conclusions in the following order – that lower vitamin D concentrations increase the risk of developing AD, that vitamin D is deficiency is associated with AD and that there is no association between vitamin D and AD. This is the reason why it is a demanding and unreliable task to compare past research. Bivona et al. stated that there is insufficient evidence to support the idea that low levels of vitamin D are a risk factor for Alzheimer Disease [64].

Parkinson's disease (PD) appears due to damage of cells producing dopamine in substantia nigra. It leads to significant diminution of the levels of the dopamine. Additionally, characteristic pathological feature of PD is the presence of Lewy bodies in substantia nigra and other regions of the brain. Parkinson's disease is classified as a progressive neurodegenerative disease and is the second most common condition within this category [68]. The clinical presentation of Parkinson's disease contains bradykinesia, rigidity and resting tremor [69], [70]. Evatt et al. came up with a conclusion that there is a significant vitamin D insufficiency in the group of patients with PD in comparison with healthy control groups and patients with AD. This result supports the thesis that there might be a possible impact of VitD insufficiency in PD [71]. Moreover, similar thesis was supported by Ding et al. proving that vitamin D levels "were deficient in 17,6% of patients with PD compared with 9,3% of controls" [72]. Both Evattt et al. and Ding et al. suggest that further research needs to be performed to fully understand the mechanism of this association and impact of VitD deficiency in patients with PD. Besides proven positive impact of VitD on neuronal cells, as neuroprotection, participation in neural differentiation and maturation, as it is described above, Fullard and Duda highlight that most of past studies show correlation between higher prevalence of vitamin D deficiency in PD in comparison to control groups [73]. Moreover, they noted that these observations might be caused by "reduced mobility and decreased sunlight exposure as PD progresses rather than disease modification by vitamin D".

Despite these associations, the National Centre of Nutritional Education in Poland (Narodowe Centrum Edukacji Żywieniowej) provides specific guidelines for vitamin D supplementation:

- Adults aged 19-65: 800-2000 IU (20-50 ug) per day in the autumn and winter season or throughout the whole year (depending on body weight and vitamin D intake in the diet), if during summer they do not spend time in the sun light for minimum 15 miuntes between 10:00 am and 3:00 pm with uncovered forearms and lower legs.
- Seniors ages 65-75: 800-2000 IU (20-50 ug) per day, during the whole year (depending on body weight and vitamin D intake in the diet).
- Seniors over 75 years old: 2000-4000 IU (50-100ug) per day, during the whole year (depending on body weight and vitamin D intake in the diet). [74]

METABOLIC DISORDERS

Among metabolic disorders, obesity, and type 2 diabetes (T2D) are of particular concern. According to projections published in 2023, by 2050, more than 1.31 billion people are expected to have diabetes [75]. Additionally, a March 2025 study estimates that by 2050, approximately 60% of adults and nearly one-third of children and adolescents worldwide will be overweight or obese [76]. Given the current and projected increasing trend in these conditions and their associated complications, both obesity and T2D represent a significant public health challenge.

Studies have shown an inverse association between circulating 25(OH)D levels and the incidence of type 2 diabetes [77], [78], [79]. However, these studies mainly establish a correlation rather than causality, as confounding variables and limitations in observational studies prevent definitive conclusions about causality. Meta-analyses suggest that higher levels of 25(OH)D may provide protective effects against the development of diabetes through mechanisms related to VitD receptor in pancreatic beta cells, which affect insulin secretion, and the role of VitD in calcium metabolism, which may influence insulin function. Additionally, 25(OH)D may provide protective pathways against beta-cell destruction mediated by systemic inflammation [80]. Nevertheless, these results do not establish a direct causal relationship—causality remains uncertain due to potential confounding variables inherent in observational studies. More recent studies propose improvement in insulin sensitivity and reduction of insulin resistance as the primary mechanisms of action and emphasize the role of VitD supplementation in reducing the risk of T2D [78], [81]. Randomized controlled trials (RCTs) and meta-analyses indicate that VitD

supplementation, especially in its active form, can reduce the incidence of T2D [81]. However, this effect varies across studies, with some showing minimal or no benefits, especially in populations without VitD deficiency. This effect seems particularly pronounced in individuals with prediabetes, where VitD supplementation has shown a 15% reduction in the risk of progression to full-blown diabetes in the general population, and up to 76% in individuals who maintained higher blood levels of 25(OH)D during follow-up. Furthermore, in patients already diagnosed with T2D, VitD supplementation significantly improves glycemic control, reducing fasting blood glucose (FBG), haemoglobin A1c (HbA1c), insulin resistance assessed by HOMA-IR, and fasting insulin levels. These benefits are particularly noticeable in patients with VitD deficiency, individuals with overweight, or those with an initial HbA1c level of 8% or higher [82].

The mechanisms underlying these effects involve multiple pathways, including reduced insulin resistance (as indicated by improvements in HOMA-IR following supplementation), anti-inflammatory effects that alleviate chronic low-grade inflammation, and impacts on glucose metabolism—all of which are key in the pathophysiology of T2D [78], [82], [83]. These mechanisms have been supported by experimental and observational studies; however, their clinical significance in large-scale interventions remains uncertain.

The association between obesity and vitamin D deficiency has been extensively studied, with evidence suggesting an inverse relationship between body fat percentage and circulating 25(OH)D levels [84].

Several mechanisms have been proposed to explain this relationship. One key hypothesis is vitamin D sequestration in adipose tissue, leading to lower bioavailability in circulation [85]. Additionally, volumetric dilution, reduced sun exposure, and altered vitamin D metabolism have been implicated as contributing factors [86]. Studies indicate that obese children and adolescents are at a higher risk of vitamin D deficiency, with lower serum 25(OH)D levels observed in individuals with increased abdominal fat and BMI [87], [88].

The impact of vitamin D deficiency in obesity extends beyond mere association. Experimental studies suggest that vitamin D influences adipocyte differentiation and lipid metabolism, though the clinical relevance of these findings remains debated [89]. Some research suggests that vitamin D plays a role in adipose tissue biology, influencing overall energy homeostasis. However, randomized controlled trials (RCTs) assessing the effect of vitamin D supplementation on weight management have produced mixed results. While some studies report modest improvements in BMI and metabolic parameters following supplementation, others fail to show significant changes in body weight or fat mass [90], [91]. Moreover, low vitamin D levels have been identified as a potential predictor of future obesity and metabolic complications [92].

VitD dosing in metabolic disorders should be individualized according to patient characteristics such as baseline VitD levels, body weight, age, and the presence of comorbidities. For healthy individuals, the National Academy of Medicine recommends 400–800 IU per day, with a tolerable upper intake level of 4000 IU daily; however, daily doses up to 10,000 IU have been used without safety concerns [93].

Patients with metabolic disorders, especially those with obesity, often require higher doses. Research indicates that obese individuals have circulating 25(OH)D levels approximately 20 nmol/L lower than those of normal-weight individuals, suggesting that they may need up to 2.6–3 times the standard dose to achieve similar serum levels [93]. In prediabetic patients, clinical trials have used VitD dosages ranging from 842 to 7543 IU daily (with a weighted average of around 3500 IU per day), and evidence suggests that such regimens can reduce the risk of progressing to diabetes by approximately 15% when doses are appropriately adjusted [94], [95]. Additionally, in gestational diabetes mellitus (GDM), VitD supplementation has been associated with improved lipid profiles and reduced risks of premature birth and neonatal complications [95].

Thus, when tailoring VitD supplementation for metabolic disorders, clinicians should consider a patient's BMI and metabolic status. For obese patients, for instance, it may be necessary to increase the daily dose to three times the standard recommendation, while prediabetic and GDM patients may benefit from doses around 3500 IU daily, always ensuring that supplementation remains within safety limits [93], [94], [95].

Beyond obesity and T2D, VitD deficiency has also been linked to other metabolic disorders, including hypertension and atherosclerosis, which are important contributors to cardiovascular disease. These associations are discussed in detail in the section on cardiovascular diseases.

PREGNANCY AND NEONATAL OUTCOMES

VitD plays a crucial role in maternal and fetal health during pregnancy. Its deficiency has been associated with numerous adverse health outcomes. Low VitD levels during pregnancy may increase the risk of preeclampsia, gestational diabetes, preterm birth, and postpartum haemorrhage, although study results are inconsistent—some findings suggest no clear association between vitamin D deficiency and postpartum haemorrhage, while others indicate an increased risk in women with low VitD levels [96],

[97], [98], [99], [100], [101], [102], [103]. Additionally, VitD deficiency may be linked to a higher likelihood of caesarean delivery (research in this area presents mixed findings—while some studies suggest that low VitD levels may increase the risk of caesarean delivery, others have found no significant association, highlighting the need for further investigation) [104]. One possible explanation for the inconsistencies observed in studies on VitD's effects during pregnancy and in newborns is the variability in the methodologies of different meta-analyses. These inconsistencies arise from the inclusion of studies conducted in diverse geographic regions, where factors such as sunlight exposure and baseline vitamin D levels may differ significantly. Additionally, the studies analyzed often use varying dosages of vitamin D supplementation and employ different research designs, including distinct criteria for measuring outcomes. These methodological discrepancies contribute to the divergent findings reported in the literature.

Maternal vitamin D deficiency also significantly impacts neonatal health, increasing the risk of low birth weight, impaired bone mineralization, and enamel defects [99], [102], [105]. Moreover, it may contribute to the development of neurological disorders, including attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), and childhood depression [106], [107], [108], [109], [110]. Recent studies suggest that maintaining VitD levels above 40 ng/mL may also help prevent respiratory infections and asthma in newborns [101].

VitD deficiency contributes to adverse pregnancy and neonatal outcomes through several biological mechanisms. One key pathway involves immune regulation—VitD enhances IL-10 production, an anti-inflammatory cytokine essential for immune tolerance, placental function, and fetal protection. Lower IL-10 levels in women with preeclampsia suggest that VitD deficiency may contribute to inflammatory dysregulation [102]. Additionally, VitD modulates the renin-angiotensin-aldosterone system (RAAS), helping regulate blood pressure. Its deficiency has been linked to increased renin activity, endothelial dysfunction, and a higher risk of preeclampsia. VitD deficiency may also impact labor by reducing pelvic muscle strength, increasing the likelihood of cesarean delivery. The presence of VitD receptors in muscle cells suggests a role in maintaining muscle function. For fetal development, VitD is crucial for skeletal mineralization, particularly in the third trimester, as it regulates placental calcium transfer. Furthermore, VitD supports respiratory health by modulating immune responses, reducing the risk of neonatal infections, and influencing lung development, potentially lowering asthma susceptibility [101].

Long-term maternal health risks associated with VitD deficiency extend beyond pregnancy. One emerging concern is its potential link to postpartum affective disorders. Studies indicate that VitD deficiency is associated with increased postpartum anxiety symptoms, particularly in women who do not take VitD supplementation. Deficient VitD levels have also been correlated with a higher risk of postpartum depressive symptoms [111].

Given the high global prevalence of vitamin D deficiency, ensuring optimal levels in pregnant women is of utmost importance. Different doses of vitamin D supplementation during pregnancy have been studied for their potential to reduce the risk of adverse maternal and neonatal outcomes. While there is no universal consensus on the optimal dosage, clinical trials have investigated a wide range of doses, from 600 IU to 5000 IU per day, with a weighted average of approximately 2500 IU daily. Studies evaluating the prevention of specific complications suggest that the estimated median vitamin D dosage for preeclampsia prevention was 3161 IU per day, while for intrauterine and neonatal mortality, the median dosages were 3375 IU and 2750 IU daily, respectively. Similarly, for preterm birth and SGA birth, median dosages of 3375 IU and 2750 IU per day were reported. These findings highlight the potential benefits of higher vitamin D intake; however, evidence remains inconclusive, and recommendations for supplementation during pregnancy are not yet standardized [94]. For newborns, VitD supplementation is particularly important due to the low VitD content in human milk, which typically provides less than 78 IU/L. The American Academy of Pediatrics (AAP) recommends a daily intake of 400 IU of vitamin D for exclusively and partially breastfed infants, starting shortly after birth and continuing until sufficient intake is achieved through fortified formula or whole milk. Despite these guidelines, adherence remains low, with less than one-third of infants meeting the recommended supplementation levels [10].

CONCLUSIONS

Vitamin D deficiency is a modifiable risk factor with broad implications across multiple physiological systems and non-autoimmune health outcomes. This review reaffirms its critical role in cardiovascular, musculoskeletal, neurological, metabolic, and reproductive health, while also highlighting key areas of ongoing uncertainty.

In cardiovascular health, it may influence myocardial remodeling, inflammation, endothelial function, and neurohormonal regulation. Although observational and mechanistic studies suggest strong associations, causality remains unconfirmed due to inconsistent findings from randomized trials and methodological limitations. Current guidelines support supplementation in high-risk individuals, but population-wide recommendations for prevention are not yet warranted.

For bone and muscle health, vitamin D supports calcium-phosphate homeostasis, bone remodeling, and muscle function. Deficiency is consistently linked to impaired mineralization, increased fracture risk, and reduced muscle strength—particularly in older adults. While combined supplementation with calcium shows modest benefits in fracture prevention, evidence for vitamin D alone remains limited. Likewise, its contribution to muscle strength is supported by observational data, though intervention trials report mixed results. Maintaining adequate levels across the lifespan appears essential, and future studies should focus on refining dosing strategies tailored to age, physical activity, and nutritional status.

In the neurological domain, vitamin D contributes to neuroprotection, neurotransmitter regulation, and neural differentiation. Low serum levels have been associated with cognitive decline, Alzheimer's disease, and Parkinson's disease; however, these findings are inconsistent due to variable definitions of deficiency and study heterogeneity. While biologically plausible mechanisms exist, current evidence does not support its use as a diagnostic marker or therapeutic agent for neurodegenerative disorders.

Deficiency is also strongly linked to metabolic disorders, particularly obesity and type 2 diabetes. Supplementation may improve glycemic control and insulin sensitivity, especially in individuals with prediabetes or low baseline levels. However, altered metabolism in obesity often requires higher dosing, and results from clinical trials remain mixed. While associations are compelling, individualized approaches remain necessary until stronger interventional evidence becomes available.

During pregnancy, adequate vitamin D status is crucial for both maternal and neonatal outcomes. Deficiency has been associated with preeclampsia, gestational diabetes, preterm birth, and impaired fetal development. Though observational and mechanistic data support these associations, clinical trials have yielded mixed results. Higher supplementation doses may be beneficial, but optimal regimens are not yet clearly defined. For infants—especially those who are breastfed—early supplementation is essential to prevent deficiency-related complications.

Despite growing recognition of its physiological relevance, substantial uncertainties persist. These include the lack of universally accepted serum 25(OH)D thresholds, inconsistent outcomes from supplementation trials, and variability in dosing recommendations across populations. Differences in study designs, geographical factors, and outcome measures further complicate interpretation. These persistent uncertainties underscore the need for standardized methodologies and international consensus to enable more consistent, evidence-based clinical guidance.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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