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Vitamin D in Prevention of the Diseases

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Abstract: ***Vitamin D, a fat-soluble vitamin with well-established roles in calcium and bone metabolism, has garnered significant attention for its potential extra-skeletal effects, particularly in the prevention of various acute and chronic diseases. This review synthesizes current evidence from epidemiological studies, randomized controlled trials, and meta-analyses regarding the association between vitamin D status and the risk of musculoskeletal, metabolic, cardiovascular, autoimmune, infectious, and malignant diseases. While observational data consistently demonstrate inverse associations between serum 25-hydroxyvitamin D concentrations and the incidence or severity of several disorders, interventional studies yield mixed results, with clear benefits primarily observed in populations with established deficiency. The immunomodulatory, anti-inflammatory, and cell-regulatory properties of vitamin D are explored as potential mechanisms underlying these associations. Despite widespread interest and biological plausibility, robust evidence supporting routine vitamin D supplementation for primary prevention of non-skeletal diseases in the general population remains limited. Current guidelines recommend targeted supplementation for individuals at risk of deficiency, while ongoing research aims to clarify the role of vitamin D in disease prevention and to identify subgroups most likely to benefit from intervention.***

Keywords: 25-hydroxyvitamin D (25(OH)D); cardiovascular diseases; epidemiology

1. Introduction

Vitamin D, traditionally recognized for its pivotal role in calcium homeostasis and bone health, has emerged as a subject of intense research interest due to its potential involvement in the prevention of a wide spectrum of acute and chronic diseases.[1-6] The discovery of vitamin D receptors in numerous tissues and the identification of its immunomodulatory, anti-inflammatory, and antiproliferative properties have expanded the scope of investigation beyond skeletal outcomes.[1-6] Epidemiological studies have reported associations between vitamin D deficiency and increased risk of cardiovascular disease, diabetes mellitus, autoimmune disorders, certain malignancies, and infectious diseases.[7-8] These findings have prompted hypotheses that optimizing vitamin D status may confer protective effects against these conditions.[7-8] Despite compelling observational data, randomized controlled trials and meta-analyses have produced inconsistent results regarding the efficacy of vitamin D supplementation in disease prevention, particularly in populations without established deficiency.[9-13] The complexity of vitamin D metabolism, variability in study designs, and differences in baseline vitamin D status contribute to the ongoing debate about its role in clinical practice.[9-13] This review aims to critically examine the current evidence on vitamin D and its potential role in the prevention of various diseases, elucidate underlying biological mechanisms, and discuss the implications for clinical management and future research directions.

Vitamin D and the Prevention of Diabetes

Vitamin D has been extensively studied for its potential role in the prevention of both type 1 and type 2 diabetes mellitus. Several biological mechanisms support a plausible link between vitamin D status and glucose homeostasis. [3,14] Vitamin D receptors (VDR) and the enzyme 1α-hydroxylase, which converts 25-hydroxyvitamin D to its active form, are expressed in pancreatic β-cells and various immune cells. [15-16] Experimental studies indicate that vitamin D may enhance insulin synthesis and secretion, improve β-cell survival, and modulate immune responses implicated in the pathogenesis of diabetes. [15-17] In type 1 diabetes, vitamin D is thought to exert immunomodulatory effects that may reduce autoimmune destruction of pancreatic β-cells. Observational studies have reported an inverse association between vitamin D status in early life and the risk of developing type 1 diabetes, although interventional data remain limited. [18-20] For type 2 diabetes, vitamin D may improve insulin sensitivity in peripheral tissues and reduce systemic inflammation, both of which are central to the development of insulin resistance. [18-20] Epidemiological studies consistently demonstrate that low serum 25-hydroxyvitamin D levels are associated with increased risk of incident type 2 diabetes. [21-23] Randomized controlled trials and meta-analyses have shown that vitamin D supplementation can modestly improve glycemic parameters- such as fasting glucose, HbA1c, and HOMA-IR—particularly in individuals with prediabetes, vitamin D deficiency, or elevated baseline glycemic indices. However, the effect size is generally small, and the benefit is most pronounced in high-risk subgroups. [21-23]

Despite these findings, large-scale trials in unselected populations have not consistently demonstrated a significant reduction in diabetes incidence with vitamin D supplementation. [9,24] Current evidence suggests that vitamin D may have a preventive role in diabetes primarily among individuals with established deficiency or those at high risk, rather than as a universal preventive strategy. [9,24]

Vitamin D and the Prevention of Cardiovascular Diseases

Vitamin D has been implicated in cardiovascular health through several biological and epidemiological pathways. [3,25] The presence of vitamin D receptors (VDR) in cardiomyocytes, vascular smooth muscle cells, and endothelial cells suggests a direct role in cardiovascular physiology. [3,25] Mechanistically, vitamin D is thought to modulate the renin-angiotensin-aldosterone system (RAAS), reduce vascular smooth muscle proliferation, inhibit inflammation, and improve endothelial function. [26-27] These effects may collectively contribute to blood pressure regulation, attenuation of atherosclerosis, and stabilization of vascular integrity. [26-27]

Observational studies have consistently demonstrated an association between low serum 25-hydroxyvitamin D levels and increased risk of hypertension, coronary artery disease, heart failure, atrial fibrillation, and stroke. [28-29] Vitamin D deficiency is also linked to adverse cardiovascular risk profiles, including dyslipidemia, insulin resistance, and increased systemic inflammation. [28-29] Experimental data suggest that vitamin D may suppress renin expression, thereby lower blood pressure, and exert anti-inflammatory effects that could reduce the progression of atherosclerotic plaque. [30-31] Additionally, vitamin D may enhance endothelial nitric oxide production, improve vascular reactivity and reduce arterial stiffness. [30-31]

Despite these mechanistic and observational findings, randomized controlled trials and meta-analyses have yielded mixed results regarding the efficacy of vitamin D supplementation in reducing major adverse cardiovascular events. [32-36] Most large-scale trials have not demonstrated a significant reduction in myocardial infarction, stroke, or cardiovascular mortality with vitamin D supplementation in unselected populations. [32-36] However, some subgroup analyses suggest potential benefit in individuals with baseline vitamin D deficiency or those at high cardiovascular risk. [32-36]

In summary, while vitamin D may influence several pathways relevant to cardiovascular disease prevention, current evidence does not support routine supplementation for cardiovascular protection in the general population. [1] Ongoing research is focused on identifying specific populations that may derive cardiovascular benefit from targeted vitamin D intervention. [1]

Vitamin D and Musculoskeletal Health

Vitamin D plays a central role in musculoskeletal health through its regulation of calcium and phosphate homeostasis, which are essential for bone mineralization and skeletal integrity. [3,37] The active form of vitamin D, 1,25-dihydroxyvitamin D, enhances intestinal absorption of calcium and phosphate, supports normal bone remodeling, and maintains serum calcium levels within a narrow physiological range. [3,37] Deficiency in vitamin D leads to impaired mineralization, resulting in rickets in children and osteomalacia in adults, and contributes to the development of osteoporosis and increased fracture risk in older adults. [1,38]

Beyond its effects on bone, vitamin D receptors are expressed in skeletal muscle tissue, where vitamin D is thought to influence muscle strength, function, and balance. [39-42] Observational studies have consistently shown that low serum 25-hydroxyvitamin D levels are associated with reduced bone mineral density, increased risk of falls, and higher incidence of fractures, particularly in the elderly. [39-42] Severe deficiency can result in proximal muscle weakness and increased susceptibility to falls, further compounding fracture risk. [39-42]

Randomized controlled trials and meta-analyses have demonstrated that vitamin D supplementation, particularly when combined with adequate calcium intake, can reduce the risk of fractures and falls in individuals with vitamin D deficiency or at high risk, such as institutionalized elderly populations. [1,43,44] However, in community-dwelling adults with sufficient baseline vitamin D status, the benefit of supplementation for fracture or fall prevention is less clear, and recent large-scale studies have not shown significant reductions in these outcomes with routine supplementation. [36,45]

In summary, maintaining adequate vitamin D status is critical for optimal bone and muscle health, particularly in populations at risk for deficiency. [11,46] While supplementation is effective in preventing musculoskeletal complications in deficient individuals, universal supplementation in the general population is not currently supported by robust evidence for primary prevention of fractures or falls. [11,46] Targeted assessment and correction of vitamin D deficiency remain key strategies in the prevention of musculoskeletal disease. [11,46]

Vitamin D in Immune Function and Infections

Vitamin D plays a critical role in modulating both innate and adaptive immune responses, with implications for susceptibility to and outcomes of infectious diseases. [3,47] The active form of vitamin D, 1,25-dihydroxyvitamin D, exerts its effects through the vitamin D receptor (VDR), which is expressed in a variety of immune cells, including monocytes, macrophages, dendritic cells, and lymphocytes. [3,47] In the innate immune system, vitamin D enhances the antimicrobial response by upregulating the expression of antimicrobial peptides such as cathelicidin (LL-37) and defensins. [48-50] These peptides are integral to the first line of defense against a broad range of pathogens, including bacteria, viruses, and fungi. [48-50] Vitamin D also promotes autophagy and phagocytosis in macrophages, further supporting pathogen clearance. [48-50] Within the adaptive immune system, vitamin D modulates T cell responses by suppressing pro-inflammatory Th1 and Th17 pathways while promoting regulatory T cell and Th2 responses. [51-52] This immunoregulatory effect helps to limit excessive inflammation and may reduce the risk of cytokine-mediated tissue damage during infections. [51-52]

Epidemiological studies have consistently demonstrated an association between low serum 25-hydroxyvitamin Dlevels and increased susceptibility to acute respiratory tract infections, influenza, and other infectious diseases. [53-54] Randomized controlled trials and meta-analyses suggest that vitamin D supplementation can reduce the risk of acute respiratory infections, particularly in individuals with baseline deficiency or those at high risk. [53-54]

During the COVID-19 pandemic, interest in vitamin D's immunomodulatory properties intensified. [55-56] Observational data indicate that vitamin D deficiency is associated with increased risk of SARS-CoV-2 infection, severe disease, and adverse outcomes. [55-56] Proposed mechanisms include modulation of the innate immune response, attenuation of pro-inflammatory cytokine release, and maintenance of epithelial barrier integrity. [55-56]

In summary, vitamin D is a key immunomodulator that supports host defense against infections through multiple mechanisms. [1,54,57,58] While supplementation appears most beneficial in individuals with deficiency, maintaining

adequate vitamin D status may be an important component of infection prevention strategies, especially in populations at risk for hypovitaminosis D. [1,54,57,58]

Vitamin D in Pregnancy and Neonatal Outcomes

Vitamin D plays a critical role in maternal and fetal health during pregnancy. [3,59-61] Adequate maternal vitamin D status is essential for optimal calcium and phosphate metabolism, supporting fetal skeletal development and mineralization. [3,59-61] Vitamin D receptors are present in the placenta and fetal tissues, underscoring its importance in gestational physiology. [3,59-61] Epidemiological studies have consistently demonstrated that vitamin D deficiency in pregnancy is associated with an increased risk of adverse maternal outcomes, including preeclampsia, gestational diabetes mellitus, and preterm birth. [3,59-61] Mechanistically, vitamin D may modulate placental function, immune tolerance, and inflammatory pathways implicated in these complications. [62,63]

Randomized controlled trials and meta-analyses indicate that vitamin D supplementation during pregnancy can significantly reduce the risk of preeclampsia and preterm labor, particularly in populations with baseline deficiency. [64-66] Supplementation has also been shown to increase maternal and neonatal 25-hydroxyvitamin D concentrations and may modestly increase birth weight and reduce the incidence of small-for-gestational-age infants. [64-66] However, the impact on other neonatal outcomes, such as low birth weight and Apgar scores, remains less clear, with some studies showing no significant benefit. [64-66] Vitamin D deficiency in pregnancy has also been linked to impaired fetal bone development, increased risk of neonatal hypocalcemia, and a higher incidence of respiratory and neurodevelopmental disorders in offspring. [67-69] Some evidence suggests that adequate maternal vitamin D status may reduce the risk of childhood wheeze, asthma, and certain neurodevelopmental conditions, although further research is needed to confirm these associations. [67-69]

In summary, maintaining sufficient vitamin D levels during pregnancy is important for reducing the risk of several maternal and neonatal complications. [3,54.70] While routine supplementation is recommended for pregnant women at risk of deficiency, ongoing research continues to refine optimal dosing strategies and clarify the full spectrum of benefits for maternal and neonatal health. [54,70]

Vitamin D and Cancer Prevention

Vitamin D has been extensively studied for its potential role in cancer prevention, with both mechanistic and epidemiological evidence suggesting a protective effect. [3,71,72] The active form of vitamin D, calcitriol (1,25-dihydroxyvitamin D), exerts its biological effects through the vitamin D receptor (VDR), which is expressed in a wide range of tissues, including many epithelial and immune cells. [3,71,72] Upon activation, the VDR modulates the expression of genes involved in cell proliferation, differentiation, apoptosis, and DNA repair- processes central to carcinogenesis. [3,71,72] Preclinical studies demonstrate that vitamin D can inhibit tumor cell growth by inducing cell cycle arrest, promoting apoptosis, and suppressing angiogenesis and metastasis. [6,73] Additionally, vitamin D has immunomodulatory properties that may enhance antitumor immune surveillance, particularly through the activation of T cells and the reduction of chronic inflammation, which is a known risk factor for several malignancies. [6,73]

Epidemiological data have shown inverse associations between serum 25-hydroxyvitamin D levels and the incidence or mortality of certain cancers, most notably colorectal cancer. [26,36,74,75] Some observational studies also suggest potential protective effects against breast, prostate, and ovarian cancers, although findings are less consistent. [26,36,74,75] Randomized controlled trials and Mendelian randomization studies, however, have yielded mixed results, with most large-scale trials failing to demonstrate a significant reduction in overall cancer incidence with vitamin D supplementation in unselected populations. [76-78] Notably, some evidence indicates that vitamin D supplementation may reduce cancer mortality and may be more beneficial in individuals with baseline deficiency. [76-78]

In summary, while vitamin D exhibits several biological mechanisms that could plausibly reduce cancer risk, and observational data support an association between adequate vitamin D status and lower cancer risk, robust evidence from interventional studies remains limited. [13,79] Current guidelines do not recommend vitamin D supplementation solely for cancer prevention, but maintaining sufficient vitamin D levels may be considered as part of an overall strategy for reducing cancer risk, particularly in populations at risk for deficiency. [13,79]

Vitamin D in Aging and Longevity Outcomes

Vitamin D has emerged as a key factor in healthy aging, with growing evidence linking its status to longevity and the prevention of age-related diseases. [3,80,81] The biological plausibility for vitamin D's role in aging is supported by the widespread expression of vitamin D receptors (VDR) in multiple tissues, including bone, muscle, immune cells, and the cardiovascular system. [3,80,81] Vitamin D influences cellular processes such as proliferation, differentiation, apoptosis, and modulation of oxidative stress, all of which are central to the aging process. [3,80,81]

Epidemiological studies consistently demonstrate that low serum 25-hydroxyvitamin D levels are associated with increased all-cause and cause-specific mortality in older adults. [82-84] Observational data suggest that individuals with vitamin D deficiency have higher risks of cardiovascular disease, certain cancers, infections, cognitive decline, and frailty. [82-84] Notably, the risk of mortality appears to plateau at serum 25(OH)D concentrations of approximately 50–60 nmol/L, with little additional benefit at higher levels. [82-84]

Mechanistically, vitamin D may contribute to longevity by reducing chronic inflammation, enhancing immune function, preserving musculoskeletal health, and protecting against metabolic and vascular dysfunction. [85-87] Vitamin D's role in maintaining muscle strength and bone density is particularly relevant in the elderly, as it reduces the risk of falls, fractures, and associated morbidity. [85-87] Additionally, vitamin D may modulate pathways involved in cellular senescence and DNA repair, further supporting its potential role in delaying biological aging. [85-87]

Interventional studies and meta-analyses of vitamin D supplementation have shown mixed results regarding reductions in all-cause mortality and prevention of age-related diseases. [9,26,88] While some trials indicate a modest reduction in mortality, especially among individuals with baseline deficiency, others have not demonstrated significant benefits in unselected populations. [9,26,88] The heterogeneity in study populations, dosing regimens, and baseline vitamin D status may account for these discrepancies. [9,26,88]

In summary, maintaining adequate vitamin D status is associated with improved survival and reduced risk of age-related morbidity. [1,54] While routine supplementation for longevity in the general population is not universally recommended, targeted correction of deficiency in older adults remains an important strategy for promoting healthy aging and potentially extending lifespan. [1,54]

2. Conclusion

Vitamin D plays a fundamental role in musculoskeletal health and has important immunomodulatory, metabolic, and potential cardioprotective effects. While observational studies have linked vitamin D deficiency to a wide range of acute and chronic diseases including osteoporosis, fractures, falls, certain infections, adverse pregnancy outcomes, and possibly cardiovascular and metabolic disorders evidence from randomized controlled trials remains mixed regarding the efficacy of routine vitamin D supplementation for primary prevention in the general population. The greatest benefits of supplementation are observed in individuals with established deficiency or those at high risk, such as older adults, pregnant women, and individuals with limited sun exposure or malabsorption syndromes. Targeted assessment and correction of vitamin D deficiency remain essential components of preventive health strategies. Ongoing research is needed to further clarify optimal dosing, identify populations most likely to benefit, and elucidate the broader implications of vitamin D status in disease prevention.

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