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The Power of Vitamin D: from Osteoporosis to Cancer

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Abstract
Vitamin D is an important nutrient that exerts a tremendous role in maintaining physiological function as well as bone health [1]. Its initial role in calcium homeostasis and bone metabolism has already been established well, especially with regards to osteoporosis prevention and management. Nonetheless, recent studies have broadened its significance beyond skeletal well-being, showing its possible function in immune modulation, cardiovascular health, and cancer prevention. Deficiency of vitamin D has been associated with a higher risk of osteoporosis, fractures, and musculoskeletal disease. In addition, new evidence indicates that proper vitamin D levels can lower the risk of certain cancers, such as breast, colorectal, and prostate cancer, by modulating cell growth, differentiation, and apoptosis. In spite of these encouraging results, issues continue to surround optimal vitamin D levels, strategies for supplementation, and its exact mechanisms in disease prevention. This review discusses the multi-aspect role of vitamin D, ranging from its traditional role in bone health to its newly emerging role in cancer prevention, with a focus on the necessity of additional clinical trials to define absolute therapeutic recommendations.

Keywords: Vitamin D, Osteoporosis, Cancer, Bone Health, Immune System, VDR Polymorphisms, Inflammation, Precision Nutrition, Supplementation, Public Health, Chronic Disease Prevention

1. Introduction

Vitamin D is an oil-soluble vitamin crucial for preserving bone health, maintaining calcium homeostasis, and general physiological function. Historically acknowledged as a way of preventing rickets and osteoporosis, vitamin D has been increasingly recognized for a wider range of health benefits across the body. It is mainly obtained from skin synthesis when exposed to sunlight and foods, with supplementation usually advised to avoid deficiencies.Over the last few years, there has been a lot of research into the function of vitamin D in several diseases, widening its importance from bone health to immune function, cardiovascular health, and even preventing cancer. Research has indicated that vitamin D deficiency is not just a primary risk factor for fractures and osteoporosis but is also linked to a higher incidence of chronic disease, such as autoimmune diseases and cancers like breast, colorectal, and prostate cancer. The possible mechanisms by which vitamin D has its protective action include cell proliferation, differentiation, apoptosis, and inflammation modulation, all of which are key to disease progression.

In spite of encouraging results, there are controversies surrounding the best levels of vitamin D for disease prevention and the efficacy of supplementation. Geographical position, lifestyle, age, and genetic factors

affect vitamin D status and render it a multifaceted issue in public health and clinical investigation. This review intends to discuss the multifaceted role of vitamin D, ranging from its established utility in bone metabolism to its newly emerging role in cancer prevention, with emphasis on the necessity for more studies to establish its therapeutic role.

2. Vitamin D and Calcium Metabolism

Vitamin D is involved in calcium metabolism that is vital to bone health, muscle function, and overall physiological homeostasis. The role of vitamin D in calcium homeostasis is to control the absorption, distribution, and excretion of calcium so that it is sufficient for cellular and skeletal processes.

Absorption of Calcium

Vitamin D increases calcium absorption from the small intestine, mainly the duodenum. In the absence of dietary calcium, the active vitamin D hormone calcitriol (1,25-dihydroxyvitamin D_3) induces the messenger RNA synthesis of calcium-binding proteins like calbindin, which enables calcium movement across intestinal epithelial cells into the bloodstream. Without vitamin D, just a limited amount (10–15%) of calcium from the diet is absorbed, while with normal levels of vitamin D, calcium absorption can be up to 30–40%.[6]

2. Regulation of Blood Calcium

- Vitamin D acts in association with the parathyroid hormone (PTH) to regulate calcium homeostasis. When the blood calcium levels fall
- Parathyroid glands secrete PTH, which activates the formation of active calcitriol from inactive vitamin D (25-hydroxyvitamin D) in the kidneys.
- Calcitriol increases the absorption of calcium from the intestines.
- PTH and calcitriol activate the resorption of bone, whereby osteoclasts dissolve the bone tissue releasing calcium into the blood.
- The kidneys retain more calcium, minimizing calcium excretion in urine.On the other hand, when blood calcium is elevated, PTH secretion is lowered, decreasing vitamin D activation, intestinal absorption, and bone resorption, thereby regulating calcium balance.

3. Role in Bone Health

Vitamin D insures that calcium is sufficient for mineralization of bones. In the absence of enough vitamin D, the bones are weakened and become brittle, causing conditions such as rickets in children and osteomalacia in adults. Deficiency in vitamin D also leads to chronic osteoporosis, which results in heightened risk of fractures.

4. Calcium Metabolism Outside Bones

Aside from bone health, vitamin D-regulated calcium metabolism is involved in:

- Muscle function: Muscle contraction requires calcium, and vitamin D deficiency is associated with muscle weakness.
- Nervous system: Calcium plays a crucial role in the release of neurotransmitters and nerve conduction.
- Immune function: Vitamin D regulates immune function and inflammation and indirectly influences calcium-dependent immune responses[2]

5. Osteoporosis and Fracture Prevention

1. Understanding Osteoporosis

Osteoporosis is a chronic bone disease where bone mass declines and the bone microarchitecture is deteriorated, which increases the fragility of the bones and risk of fracture. It predominantly occurs in elderly individuals, especially postmenopausal women, as a result of hormonal imbalances that lead to rapid loss of bone mass. Risk factors also include deficiency of vitamin D, poor intake of calcium, physical inactivity, heredity, and certain illnesses or drugs.[7]

2. Vitamin D's Role in Bone Health

Vitamin D is essential for bone strength through the regulation of calcium and phosphate metabolism. It increases intestinal calcium absorption, stimulates bone mineralization, and ensures serum calcium levels by acting in concert with the parathyroid hormone (PTH). Without vitamin D, calcium absorption is reduced, causing lower bone density and a higher risk of osteoporosis and fractures.

3. Osteoporosis and Vitamin D Deficiency

Low vitamin D levels have been closely linked to decreased bone mineral density (BMD) and an increased risk of fracture. Deficiency can cause:

- **Osteomalacia** in adults, resulting in bone pain and weakness.
- **Bone resorption**, with the body trying to replace insufficient calcium by destroying bone tissue.
- **Increased risk of falls,** since vitamin D deficiency also leads to muscle weakness, impairs balance, and contributes to falls, which are the most common cause of fractures among older adults.[4]

Fracture Prevention Strategies

Proper Vitamin D Intake

- Recommendations for the daily amount of vitamin D depend on age, but it typically ranges from 600–800 IU/day, with greater amounts required for those at risk of deficiency.
- Sunlight exposure in the range of approximately 10–30 minutes a few times per week allows the body to naturally synthesize vitamin D.
- Fatty fish, fortified milk, egg yolks, and supplements when needed are dietary sources.

Adequate Calcium Intake:

- Calcium is vital to have healthy bones, with adequate daily intake between 1000–1200 mg/day based on age and gender.
- Good dietary sources of calcium are dairy products, leafy greens, nuts, and fortified foods.
- Regular Weight-Bearing and Strength Exercises:
- Exercises like walking, jogging, resistance exercises, and yoga aid in improving bone density and decreasing fracture risk.

Fall Prevention Strategies:

- Proper home lighting, clearance of tripping hazards, and balance training exercises can all help to decrease the risk of falls.

Medical Interventions:

- Bisphosphonates, selective estrogen receptor modulators (SERMs), or denosumab can be prescribed by healthcare professionals for high-risk patients to decrease bone loss.
- Bone mineral density (BMD) monitoring using DEXA scans can be used to estimate osteoporosis risk and monitor treatment.

6. Immune Regulation and Inflammation

Vitamin D is also a regulator of the immune system, both innate and adaptive immunity. Calcitriol (1,25-dihydroxyvitamin D_3), the active form of vitamin D, interacts with the vitamin D receptor (VDR) in multiple immune cells, i.e., macrophages, dendritic cells, T cells, and B cells. The binding between calcitriol and VDR modulates the immune responses to strike a balance between immune activation and suppression to avoid over-inflammation and autoimmune response.[6]

Vitamin D and Innate Immunity

- The innate immune system is the initial defense of the body against infection. Vitamin D supports innate immunity by:
- Increasing antimicrobial peptide expression: Calcitriol stimulates cathelicidin (LL-37) and β-defensin expression, which combat bacterial, viral, and fungal infections.
- Increasing macrophage and monocyte function: These cells are more efficient at identifying and eliminating pathogens when vitamin D status is adequate.
- Modulating dendritic cell function: Vitamin D facilitates a tolerogenic phenotype of dendritic cells, limiting excessive immune activation and inflammation.

Vitamin D and Adaptive Immunity

- The adaptive immune system employs T and B lymphocytes, conferring long-term immunity. Vitamin D aids in regulating adaptive immunity by:
- Suppressing pro-inflammatory T cells: Vitamin D inhibits Th1 and Th17 cells, which secrete inflammatory cytokines IL-2, IL-17, and IFN-γ. This prevents excessive immune responses observed in autoimmune diseases.
- Augmenting regulatory T cells (Tregs): Vitamin D enhances Tregs, which impose immune tolerance and suppress autoimmune attacks.
- Regulating B cell function: It maintains antibody production under control, preventing excessive or self-reactive immune responses.

Vitamin D and Inflammation

- Vitamin D is important in regulating inflammation by inhibiting the production of pro-inflammatory cytokines and promoting anti-inflammatory cytokines:
- Decreases pro-inflammatory cytokines: Vitamin D inhibits TNF-α, IL-6, IL-12, and IL-17, which are responsible for chronic inflammation and autoimmune diseases.
- Increases anti-inflammatory cytokines: It increases the production of IL-10, which resolves inflammation and promotes immune homeostasis.

Vitamin D Deficiency and Autoimmune Diseases

- Low levels of vitamin D are associated with a higher risk of autoimmune and inflammatory disorders, including:
- Rheumatoid arthritis (RA)
- Multiple sclerosis (MS)
- Inflammatory bowel disease (IBD) (Crohn's disease, ulcerative colitis)
- Type 1 diabetes

Vitamin D supplementation has been found to decrease disease activity and inflammatory markers in certain autoimmune diseases, although more studies are required to establish optimal dosing and long-term effects.[5]

7. Vitamin D in Infectious Diseases

Sufficient vitamin D status is linked with improved outcomes in infections including:

Respiratory tract infections: Vitamin D increases lung immunity, lowering the risk and severity of pneumonia and influenza.

Tuberculosis (TB): Vitamin D was historically employed as a therapeutic agent for TB, and current research validates its immune defense against Mycobacterium tuberculosis.

COVID-19: Research indicates that vitamin D can modulate the immune response and alleviate the severity of COVID-19 by preventing excessive inflammation and cytokine storms.

8. Cancer Prevention: Epidemiological Insights

The Link Between Vitamin D and Cancer: Epidemiological research has increasingly implicated a possible role for vitamin D in cancer risk reduction and outcome improvement. Vitamin D acts through its active metabolite, 1,25-dihydroxyvitamin D_3 (calcitriol), which activates the vitamin D receptor (VDR) in many tissues. This binding modulates gene expression involved in cell cycle control, apoptosis, and immune function, thus suppressing tumor growth and progression.[10]

Epidemiological Evidence on Vitamin D and Cancer Risk: Several observational studies have investigated the relationship between vitamin D status and the risk of various cancers. Some of the main findings are:

Colorectal Cancer: Several large cohort studies suggest that increased serum 25-hydroxyvitamin D (25(OH)D) levels are linked with reduced risk of colorectal cancer.

Vitamin D is believed to decrease colorectal cancer risk by controlling cell proliferation, inflammation, and apoptosis in the intestinal epithelium.

Breast Cancer: Epidemiological evidence indicates that increased levels of vitamin D are associated with a lower incidence of breast cancer, especially in postmenopausal women.

Vitamin D could suppress tumor angiogenesis and inhibit estrogen-induced cell growth, which are essential in the development of breast cancer.[8]

Prostate Cancer: Evidence regarding the relationship between prostate cancer risk and vitamin D is inconsistent, with some reports indicating protection, whereas others demonstrate no appreciable correlation.

Variability in outcomes can be explained by differences in genetic factors, VDR polymorphisms, and study design.

Lung Cancer and Other Malignancies: Certain studies indicate a modest relationship between increased vitamin D levels and decreased risk of lung cancer and other malignancies, although outcomes are not always concordant.

The protective actions of vitamin D might be influenced by tumor type, stage, and personal genetic predispositions.

3. Mechanisms of Cancer Prevention by Vitamin D

Vitamin D has several anti-cancer actions through various biological mechanisms, including:

Regulation of Cell Growth and Differentiation: Vitamin D prevents aberrant cell cycle progression to prevent uncontrolled cell proliferation—a key feature of cancer.

Through promoting normal cell differentiation, the risk of malignant transformation is reduced.

Induction of Apoptosis (Programmed Cell Death):

Calcitriol increases the level of pro-apoptotic proteins (e.g., BAX) and reduces that of anti-apoptotic proteins (e.g., BCL-2), facilitating the natural death of damaged or cancer cells.

Inhibition of Angiogenesis: Vitamin D inhibits the process of new blood vessel formation (angiogenesis) within tumors through the reduction of vascular endothelial growth factor (VEGF), which is essential for tumor survival.

Chronic inflammation is a major contributor to cancer development. Vitamin D suppresses inflammatory cytokines (e.g., IL-6, TNF-α) and oxidative stress, both of which are involved in carcinogenesis.[9]

Augmentation of Immune Surveillance: Vitamin D enhances anti-tumor immune responses by stimulating natural killer (NK) cells and regulating T-cell function, aiding in the recognition and destruction of cancer cells.

4. Vitamin D Supplementation and Cancer Prevention

- Randomized controlled trials (RCTs) of vitamin D supplementation and cancer prevention are mixed in their results. Some trials indicate a decreased cancer mortality, whereas others have found no appreciable effect on cancer incidence.
- Uncertainty surrounds optimal serum 25(OH)D for cancer prevention, although concentrations greater than 30–40 ng/mL are frequently linked to lower risk in epidemiological research.
- Genetic differences in the vitamin D receptor (VDR) and metabolic individuality can account for discrepancies in study results.

5. Future Directions and Research Needs

- Additional large-scale RCTs are required to provide firm recommendations on vitamin D supplementation for cancer prevention.
- Individualized strategies taking into account genetic susceptibility, initial vitamin D status, and lifestyle can maximize the protective effects of vitamin D against cancer.
- Examining the synergistic interactions of vitamin D with other nutrients (e.g., calcium, magnesium) and lifestyle factors (e.g., physical activity, diet) can offer additional information on cancer prevention.

6. Vitamin D and Tumor Microenvironment

1. Tumor Microenvironment (TME)

Tumor microenvironment (TME) is composed of cancer cells, immune cells, stromal cells, blood vessels, extracellular matrix (ECM), and signaling molecules that communicate with each other in favor of tumor growth, immune evasion, and metastasis. The TME is vital for cancer development, and targeting the TME is an attractive approach for cancer prevention and treatment.

Vitamin D has emerged as an important controller of the TME, acting on various constituents including immune response, inflammation, angiogenesis, and cell interactions. Its bioactive metabolite, 1,25-dihydroxyvitamin D_3 (calcitriol), is known to act as a protective molecule by influencing diverse cellular pathways within the TME.

2. Vitamin D's Function in Controlling the Tumor Microenvironment

Vitamin D has anti-tumor action through modification of the function of various constituents in the TME:

A. Regulation of Immune Cells within the TME

Boosts Anti-Tumor Immunity:

Vitamin D activates cytotoxic T lymphocytes (CD8+ T cells) and natural killer (NK) cells, which recognize and destroy cancer cells.

It augments interferon-gamma (IFN-γ) production, enhancing immune-mediated tumor inhibition.

Inhibits Immunosuppressive Cells:

Vitamin D inhibits the function of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), both of which inhibit anti-tumor immunity and facilitate cancer immune evasion.

It prevents tumor-associated macrophages (TAMs) from acquiring an M2-like, pro-tumorigenic phenotype and reverts them to an M1-like, tumor-destroying state.

B. Inhibition of Chronic Inflammation

Chronic inflammation in the TME supports tumor growth by enhancing oxidative stress, genomic instability, and immune suppression. Vitamin D reverses these effects by:

- Inhibiting pro-inflammatory cytokines (e.g., IL-6, IL-1β, TNF-α), which are associated with cancer progression.
- Enhancing anti-inflammatory cytokines (e.g., IL-10) to establish an immune-conducive environment.
- Inhibition of nuclear factor kappa B (NF-κB) signaling, a primary pathway promoting inflammation and tumor survival.

C. Angiogenesis Regulation

Tumors are dependent on angiogenesis for the supply of oxygen and nutrients. Vitamin D suppresses angiogenesis by:

- Suppressing vascular endothelial growth factor (VEGF), a central pro-angiogenic factor involved in new blood vessel formation within tumors.
- Inhibiting endothelial cell proliferation and migration required for vascular network establishment in tumors.
- Stabilizing pericytes and blood vessel structure, resulting in enhanced drug delivery and decreased tumor hypoxia.

D. Regulation of Cancer-Associated Fibroblasts (CAFs) and ECM Remodeling

Cancer-associated fibroblasts (CAFs) are central components of the TME that promote tumor growth by remodeling the extracellular matrix (ECM) and secreting growth factors. Vitamin D:

- Suppresses CAF activation, diminishing their capacity to secrete tumor-promoting cytokines like TGF-β.
- Blocks stiffening of ECM, which is linked with higher invasiveness and metastasis of the tumor.
- Regulates matrix metalloproteinases (MMPs), which are enzymes that break down ECM constituents and enable cell migration of the tumor.

E. Metabolic Reprogramming within the TME

Tumor cells reprogram their metabolism to fuel high growth rate, usually through aerobic glycolysis (Warburg effect). Vitamin D normalizes metabolism within the TME by:

- Lowering glucose consumption and lactate secretion, creating a less permissive environment for tumor growth.
- Increasing oxidative phosphorylation (OXPHOS) in normal cells, favoring an anti-tumor metabolic balance.

3. Vitamin D's Effect on Tumor Growth and Metastasis

- Supresses epithelial-mesenchymal transition (EMT): EMT is a central mechanism of metastasis in which epithelial cancer cells develop migratory and invasive phenotypes. Vitamin D sustains epithelial cell integrity and suppresses EMT-related gene expression.

- Suppresses cancer stem-like cells (CSCs): CSCs are responsible for the recurrence of the tumor and drug resistance. Vitamin D has been proven to reduce CSC populations, rendering tumors more susceptible to treatment.
- Increases sensitivity to chemotherapy and immunotherapy: An advantageous TME induced by vitamin D enhances the efficacy of traditional therapies.

4. Clinical Implications and Future Directions

- Vitamin D as an adjuvant cancer treatment: Due to its capacity to regulate the TME, vitamin D supplementation can be used to increase the efficacy of cancer treatments, such as immunotherapy and chemotherapy.
- Personalized strategies: Future studies need to aim at optimizing vitamin D dosing according to individual genetic and environmental characteristics.
- Additional clinical trials: Additional randomized controlled trials (RCTs) are required to establish the degree of vitamin D's effect on the TME in various types of cancers.[5]

Conclusion

Vitamin D is important for overall health, with its effects ranging from bone metabolism to immune function and prevention of cancer. Its role in calcium homeostasis is firmly established, and it prevents osteoporosis and fractures, especially in the elderly. In addition to bone health, vitamin D is an important regulator of immune response and inflammation, preventing autoimmune diseases and chronic inflammatory disorders.

Epidemiological research indicates a positive correlation between vitamin D status and decreased risk of cancer, especially colorectal and breast cancer. Through its control of cell growth, apoptosis, angiogenesis, and immune surveillance, vitamin D is shown to have anti-cancer effects and modulate the tumor microenvironment (TME) by inhibiting inflammation, enhancing immune responses, and preventing metastasis.

Although promising, clinical trials on vitamin D supplementation and cancer prevention have yielded conflicting results, indicating the necessity of personalized strategies that take into account genetic, environmental, and lifestyle variables. Additional large-scale randomized controlled trials (RCTs) are needed to establish optimal vitamin D levels for disease prevention and therapeutic use.

Maintaining sufficient vitamin D intake through sun exposure, diet, or supplementation is an easy and efficient way to promote bone health, immune function, and possibly decreased cancer risk. With ongoing research, vitamin D remains a potent tool of preventive medicine, providing general health benefits that go beyond musculoskeletal well-being to systemic disease prevention and control.

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