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Research Article

The Medical Benefits and Risks of Vitamin D Supplementation

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Abstract:

In addition to its well-known role in maintaining bone and calcium homeostasis, vitamin D plays a significant role in maintaining human health. The numerous medicinal advantages of vitamin D supplementation, as well as the possible hazards associated with it, are investigated in this detailed analysis. The biological routes of vitamin D metabolism are investigated, as well as the critical functions that vitamin D plays in the control of the immune system, the operation of the cardiovascular system, and the development of the nervous system. In this review, the data that supports the preventative benefits of vitamin D against illnesses such as rickets, osteoporosis, multiple sclerosis, and certain malignancies is highlighted. On the other hand, it highlights the dangers that are connected with taking an excessive amount of supplements, such as toxicity, hypercalcemia, and unfavorable medication interactions. The findings highlight the need of developing unique dosing strategies for each individual. depending on criteria such as age, health condition, and risk factors, in addition to the significance of monitoring blood 25(OH)D levels in groups who are susceptible to the disease. The purpose of this review is to provide a comprehensive analysis of the most recent scientific information in order to formulate clinical and public health recommendations that ensure the safe and effective use of vitamin D in both preventative and therapeutic settings.

Keywords: Vitamin D, Bone and calcium homeostasis, Immune system, Supplementation benefits, Toxicity, Hypercalcemia, Individualized dosing

1-Introduction

Vitamin D is a vitamin that transforms into a multipurpose secosteroid hormone essential for human health, reproduction, and the sustenance of life. Due to insufficient dietary intake of vitamin D, people rely on vitamin D generated in the skin. The synthesis rate in the skin is influenced by several factors, including melanin density, the application of sunscreen and UV-blocking products, clothes, as well as the time of day, month, and duration of sun exposure.(1) Furthermore, the dermal production of vitamin D diminishes in aging populations due to aging or damaged skin. Simultaneously, sunshine supplies vitamin D, which is crucial for humans and offers various multi-system advantages, many of which remain inadequately comprehended. (2) The principal components of the vitamin D group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). (3) Cholecalciferol and ergocalciferol may be ingested with meals. Following the consumption of food, vitamin D2 experiences two separate metabolic pathways. Initially, vitamin D2 undergoes metabolism in the vital organ called liver to generate 25-hydroxy.vitamin D, which is then transformed in the kidney by the enzyme25-hydroxyvitamin D-1alpha-hydroxylase (cytochrome P 27B1) into its active form, 25-dihydroxyvitamin D (calcitriol). (4) Calcitriol connect to the vitamin D receptor (VDR) to facilitate its various physiological effects. (5) Vitamin D's main bodily function is often linked to maintaining the musculoskeletal system. However, this very simple chemical has many more biological functions besides maintaining calcium-phosphorus balance. (6) Sunlight is the principal source of vitamin D, which can also be acquired from certain foods, including fatty fish and fortified margarine. Vitamin D possesses a cholesterol backbone and exhibits steroidal effects. It is the lipophilic hormone that is crucial for neurological health. (7) 1,25-di hydroxy cholecalciferol (calciferol) is the most active metabolite of vitamin D and a powerful immune modulator crucial for pathogen defense. (8) The interaction of calcitriol with its receptor facilitates the translocation of the receptor complex to the nucleus, where it binds to the genome and regulates around 1200 genes. (9) In combination with calcium and phosphates. Ergocalciferol (vitamin D2) is predominantly gained from botanical sources or plant-derived products, while cholecalciferol (vitamin D3) is mostly found in animal sources such as tuna. (10) Vitamin D supplementation can prevent and treat nutritional rickets in newborn and children (11) The Institute of Medicine advises a daily intake of 600 IU of vitamin D to satisfy the requirements of the majority of individuals aged 1 to 70 years. Individuals over 70 years may require 800 IU daily, (12) decreased the level of Vit D in blood is recognized as a causative factor for two metabolic bone disorders: rickets in children and osteomalacia in adults.(13) Vitamin D

deficiency constitutes a worldwide health issue primarily resulting from inadequate sunshine exposure. Approximately 1 billion individuals globally are believed to suffer from vitamin D deficiency or insufficiency, with a particular prevalence among the older population. (14) Vitamin D insufficiency may arise from several factors, potentially impairing one or more phases of vitamin D activation. The subsequent variables are of fundamental importance:

- Reduced food consumption or absorption: Specific malabsorption diseases, including celiac disease, short bowel syndrome, and gastric bypass, may result in vitamin D insufficiency. Older persons are more inclined to consume reduced quantities of vitamin D orally (15)
- Reduced sun exposure: Approximately half an hour sunlight exposure, with over 40% of skin free clothes, is necessary to avert the decrease the level of vit D.(16)
- Decreased endogenous synthesis: Individuals with chronic liver diseases, such as cirrhosis, may have impaired 25-hydroxylation, resulting in a shortage of active vitamin D.(17) Defects in 1α-25-hydroxylation can be seen in renal failure and hypoparathyroidism.
- Enhanced hepatic catabolism: Pharmaceuticals include phenobarbital, carbamazepine, dexamethasone, nifedipine, spironolactone, clotrimazole, and rifampin stimulate hepatic P450 enzymes, hence expediting the conversion of vitamin D into inactive metabolites.(18)
- End-organ resistance: Hereditary vitamin D-resistant rickets may induce end-organ resistance to this nutrient.(19)

Objective

This review aims to critically analyze the medical benefits and potential risks associated with Vitamin D supplementation. With growing interest in its role beyond bone health, Vitamin D has been widely studied for its effects on immune function, chronic disease prevention, and mental health. However, while supplementation is often promoted as a preventive or therapeutic measure, emerging evidence highlights concerns regarding inappropriate dosing, toxicity, and unclear clinical outcomes in certain populations. By synthesizing current scientific literature, this review seeks to provide a balanced understanding of the efficacy, safety, and limitations of Vitamin D supplementation across various health contexts, thereby guiding evidence-based clinical and public health decisions.

2-Medical benefit of vitamin D

Vitamin D is a critical vitamin for osseous development and the regulation of calcium equilibrium. It is essential for skeletal growth and also performs other significant biological functions in neurodevelopment and operation.

2.1 Bone and muscle health

Vitamin D facilitates the absorption of calcium and phosphate in the intestine, promotes osteoclast development, accelerates calcium reabsorption from bone, and supports the mineralization of the bone matrix. (20)

Vit D has a critical role in the prevention of many conditions: -

2.1.1 Sarcopenia: -

In the past ten years, more and more research has shown how important vitamin D is in sarcopenia, a condition in which skeletal muscle mass and strength decrease over time due to aging processes. Muscle strength, muscle growth, and neuromuscular function are all affected by vitamin D. Previous research has shown that as people get older, their muscle mass decreases. This is strongly connected to lower amounts of vitamin D in the blood, which makes older people more likely to fall. (21) Vitamin D needs to bind to the VDR in order to have an effect on skeletal muscle through the genomic route.(22) This agrees with what Campbell and his colleagues found: a loss of certain vitamin D receptors on muscle cells is directly linked to getting older and losing muscle strength and function. This fits with the reality that people whose serum 25(OH)D levels are higher have better muscle strength in their lower limbs than people whose serum levels are lower. (23)

2.1.2 Rickets: -

Rickets, which is caused by not getting enough vitamin D, can be avoided by eating foods that contain enough vitamin D(24). Even though people know this, babies still get rickets in the US and other Western countries because they don't get enough vitamin D or enough time in the sun. This is especially true for children who are only fed breast milk and children with darker skin.(25) Rickets is not confined to infancy and early childhood, as demonstrated by reports of vitamin D deficiency-induced rickets in teens. Rickets exemplifies severe vitamin D insufficiency, with a peak incidence occurring between 3 and 18 months of age. (26)

2.1.3 Osteoporosis: -

Reduced bone mass and microarchitecture-related bone deterioration are hallmarks of osteoporosis, a chronic, progressive disorder that makes bones more brittle and more prone to fractures. (27) 1,25 dihydroxy vitamin D is the biologically active form of vitamin D, primarily responsible for creating the appropriate microenvironment for bone mineralization. Foods may be fortified with vitamin D, or vitamin D may be supplemented.

2.2 Cancer prevention

Emerging results indicate that vitamin D can modulate the entire cancer process, encompassing initiation, metastasis, and cell–microenvironment interactions. These mechanisms encompass the regulation of cellular activities including proliferation, differentiation, apoptosis, autophagy, and epithelial–mesenchymal transition (EMT), as well as the manipulation of cell–microenvironment interactions such as angiogenesis, antioxidant activity, inflammation, and immunological responses. Vitamin D exhibits anticancer characteristics in cells with established genetic alterations during the start stage by obstructing tumor propagation through the suppression of cell proliferation, activation of cell differentiation, and induction of cell death. (28) The Vitamin D receptor (VDR) is extensively expressed across various cell types; nonetheless, its expression diminishes progressively throughout dedifferentiation and tumor advancement in numerous cancer forms. VDR expression levels were compared in normal, benign, and malignant tissues of the skin, breast, ovary, and prostate. The results of this comparison revealed that there is an inverse relationship between VDR expression and the presence of tumors that are malignant.(29). There is a strong correlation between high VDR expression and a reduced chance of developing malignant prostate cancer and death from cancer.(29) There is a correlation between the expression of nuclear VDR and a better overall survival rate in patients with lung cancer. According to the findings of a recent research, a decreased expression of VDR protein is associated with a worse prognosis for patients who have urothelial bladder cancer. This finding was similar across all of the studies.(30). Based on the findings presented here, it seems that the expression of VDR has the potential to act as a substantial early diagnostic biomarker for at-risk groups. It is also possible that vitamin D plays a significant part in preventing the growth of cancer. As a result, cancer cells may actively undermine the tumor-suppressing effects of vitamin D by deploying a number of methods to reduce the expression and activity of VDR.

2.3 Cardiovascular effects of vitamin D

There is an relation between vitamin D insufficiency and elevated rates of cardiovascular mortality as well as total mortality, according to the most recent studies.(31) Anti-inflammatory and cardioprotective qualities are attributes that vitamin D has. Reducing blood pressure and, improving cardiac and maintaining endothelial health are the means by which the cardiovascular preventative benefits are accomplished.(32) Elevated blood PTH levels, commonly observed in secondary hyperparathyroidism linked to vitamin D deficiency, have been suggested as a contributing factor to the progression of cardiovascular disease (CVD). No correlation was found between blood vitamin D concentrations and lipid levels. In contrast, some studies report advantageous effects of vitamin D drugs on lipid profiles, notably a decrease in apolipoproteins Apo A1 and B. (33)

2.4 Immune function

Inappropriate immune-mediated destruction of particular biological tissues is the root cause of autoimmune diseases such as multiple sclerosis, Hashimoto's thyroiditis, and inflammatory bowel disease. Vitamin D has a role in the regulation of T-cell proliferation and activity, which means that it plays a role in the development of these diseases. Vitamin D, namely 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, are both involved in the process of immune system regulation.(34). Autoreactive T-cell activity becomes apparent when there is a lack of vitamin D and signals that are communicated via the vitamin D receptor. This is especially true in situations where there is insufficient 1,25(OH)2D and a reduction in the function of the vitamin D receptor cells. After attaching to the vitamin D receptor (VDR) in immune cells, vitamin D performs the role of a selective immunosuppressant, hence reducing the severity of autoimmune illnesses (35). When there is an adequate amount of vitamin D, the T-cell response is restored, and the autoimmune response is reduced. Serum 1,25(OH)2D levels are lower in individuals who suffer from chronic conditions such as type 1 diabetes,MS, and thyroid autoimmunity.

2.4.1 Infections:

Lacking enough quantities of vitamin D would make it difficult for the immune system to function properly. This results in an increased vulnerability to bacterial and viral infections, especially intracellular bacterial infections. This is a consequence of the situation. such as TB. There is a negative correlation between normal vitamin D levels and a decrease in the number of seasonal diseases. (36). As an additional benefit, it strengthens the immune system and the ability to fight off bacterial and viral illnesses. Sunlight is known to aid in the healing process of leprosy and other mycobacterial illnesses, such as TB.(37) Mycobacterial products have the ability to boost the activity of the 1α-hydroxylase enzyme in macrophages that are present in granulomatous tissues. This, in turn, leads to an increase in the levels of 1,25(OH)2D3 inside the cells as well as the expression of the vitamin D receptor receptor (VDR). Cathelicidin is a bactericidal protein that removes Mycobacterium tuberculosis and other related intracellular pathogenic organisms via its bactericidal capabilities. All of these factors work together to promote the expression of the gene that generates cathelicidin, which is a bactericidal protein. A high concentration of vitamin D receptors (VDRs) has been shown to be present in T-cells and macrophages, as demonstrated by research. (38). Increased activation of the vitamin D receptor leads to an increase in the production and release of bactericidal peptides, such as cathelicidin and defensins, while simultaneously reducing the production of inflammatory cytokines.(39)

2.4.2 Multiple Sclerosis

There was a reduction in the risk of acquiring multiple sclerosis in those who used vitamin D supplements.(40) and its use as an

adjunct therapy alongside interferon-β diminished disease activity (41) Recently study (42) An endogenous role for vitamin D in the suppression of active multiple sclerosis lesions was hypothesized. This was shown by the higher expression of VDR in the white matter of MS patients that seemed normal, as well as the elevated levels of VDR and CYP27B1 in chronic active MS lesions in comparison to tissue from healthy controls.

3-Vitamin D toxicity

Vitamin D toxicity seems to be an uncommon occurrence, despite the rising utilization of vitamin D supplements among the general populace.(43)According to Galior et al., instances of hypercalcemia resulting from excessive supplementation of exogenous vitamin D3 generally involve daily doses exceeding 50,000 IU for a duration of at least 2–3 months. Treatment modalities encompass intravenous fluids, loop diuretics, calcitonin, bisphosphonates, and glucocorticoids, the latter primarily utilized in pediatric cases. (44) Vitamin D3, being a fat-soluble vitamin, has a considerable distribution volume owing to its buildup in the liver, muscle, and adipose tissue, with no alternative clearance mechanism aside from enzymatic metabolism. (45) There is a possibility that the symptoms of VDT are similar to those orders caused by increase the calcium level . These symptoms such as neuropsychiatric characteristics such as, psychosis, and, in extreme cases, coma. A number of symptoms, including recurrent vomiting and peptic ulcers, , are reported to be associated with VDT in the gastrointestinal tract. In addition to bradyarrhythmia with first-degree heart block, and ST segment elevation are some of the cardiovascular indications that are associated with VDT. These signals may be seen on an electrocardiogram. Polyuria and renal failure are all elements that are included in the category of renal symptoms. Hypercalciuria is the early sign of renal dysfunction. The presence of hearing impairment, and painful periarticular calcinosis are additional symptoms of VDT that are brought on by hypercalcemia. (46) Excessive activation of the vitamin D system leads to hypercalcemia due to heightened intestinal calcium absorption and the stimulation of bone resorption .((47)) The heightened resorption resulting from excess vitamin D contrasts with the correlation between bone resorption and insufficient vitamin D levels, as increasing 25(OH)D concentrations from low levels are linked to decreasing levels of bone turnover markers .((47)) The hallmark symptoms of vitamin D poisoning are solely due to hypercalcemia, which encompasses nausea, thirst, and lethargy. In the absence of laboratory testing, several indicators of hypercalcemia have been misidentified as gastroenteritis.(47)

Vitamin D toxicity occurs when large amounts of "free" 1,25(OH)2D are released from its carrier protein, vitamin D-binding protein (DBP), due to a significant surplus of other vitamin D metabolites. Vitamin D3 supplementation may adversely affect lipid profiles in postmenopausal women. Administration of pure vitamin D3 was correlated with elevated serum LDL cholesterol levels. The advantageous effects of HRT on blood LDL cholesterol levels diminished when estradiol valerate was administered alongside vitamin D3. The significance of these relationships to cardiovascular morbidity has yet to be determined.

3.1 Lowering calcium levels is the primary goal of supportive clinical therapy for vitamin D intoxication.

Stop taking calcium and vitamin D supplements. Additionally, laying down must be forbid to prevent immobility-induced-hypercalcemia. To improve renal calcium excretion and treat dehydration, isotonic saline must be used.(48) In instances of significant intoxication resulting in increase the calcium level beyond 15milligram per decileter , the administration of calcitonin and bisphosphonates is indicated. The suggested dosage is outlined below:

- Calcitonin at 4 unit/kilogram IM should be given and reuse every 12 hours up to 48 hours.
- Intravenously bisphosphonates can be given together : Pamidronate 90 milligram Intravenous more than 2h and zoledronate 4 milligram Intravenous beyond 16 minutes. (49) administration of the drugs (calcitonin and bisphosphonates) has been shown to increase the efficacy of calcitonin.(50)

At the same time as the effects of bisphosphonates might last for a considerable amount of time, calcitonin has the potential to cause tachyphylaxis. Due to this, it is imperative that calcium levels be rigorously monitored during the process of administering these medications. Glucocorticoids are commonly administered intravenously for the purpose of managing vitamin D toxicity that is associated with granulomatous disease. However, the administration of these glucocorticoids is controversial. The levels of calcitriol are reduced by this medication, which in turn leads to a reduction in the amounts of calcium in the plasma. It does this by reducing the amount of calcium that is absorbed through the intestines and increasing the amount of calcium that is excreted via the urine.(51)

- Hydrocortisone 100 milligram/day or prednisone 40milligram/day for 5 day.
- Patients who are experiencing renal failure or repair refractory conditions may need hemodialysis to repair increase the level of calcium.

The patient's prescription list must be evaluated to modify future dosages of vitamin D supplements. Patient education is essential to prevent excessive consumption of vitamin supplements. The Endocrine Society recommends the surveillance of 25-hydroxy vitamin D and calcium serum concentrations in individuals undergoing high-dose vitamin D replacement treatment.

3.2 Other agent used to treat of VitD intoxication

- Through the stimulation of the hepatic microsomal enzyme, phenobarbital has the potential to be an effective therapy for vitamin D toxicity. This is accomplished by lowering the concentration of 25(OH)D.(52)

- By blocking cytochrome P450, CYP27B1, ketoconazole has the ability to lower the generation of active form of vitamin D by a non-specific manner. However, it is not suggested to take ketoconazole for an extended period of time since it inhibits a large number of other essential CYPs.(53)
- Aminoquinolines, which include chloroquine and hydrochloroquine, have the ability to reduce the formation of 1,25(OH)2D by stimulating mononuclear cells via a process that is not fully understood in granulomatous disorders.(54)
- In order to selectively stop the formation of 1,25(OH)2D, specific inhibitors of CYP27B1 (1α-hydroxylase) have been created. These inhibitors have the potential to be useful in preventing interference with other enzymes that include cytochrome P450.(55)
- The stimulation of certain enzyme that present in the liver(cytochrome P450 such as cytochrome P3A4 by an antibiotic that calledrifampin leads to an alternative catabolic destiny from the 24-hydroxylation route for vitamin D metabolites. This alternative fate enables the destroy of excess 1,25(OH)2D in individuals with idiopathic hepatitis (IIH).(56)

4-Vit D3 interactions

During the last several years, there has been a substantial rise in the amount of attention in the media about the purported effects of vitamin D and the possible health benefits of Vitamin D supplementation. Although this is the case, the possible influence that medicines might have on vitamin D levels is virtually ever addressed.(46)

- Vitamin D treatment has the ability to reduce the concentrations of atorvastatin and active metabolites, while simultaneously reducing cholesterol concentrations in a synergistic manner .(57)
- CNS agent like(Carbamazepineandphenobarbitaland phenytoin) all increase the hepatic breakdown of vitamin D to inactive metabolites, thereby decrease the absorption of calcium. (58)

Prolonged usage of carbamazepine for six months or more, particularly in conjunction with other enzyme-inducing anticonvulsants, has been noted to lead to hypocalcaemia and osteomalacia.
In a healthy kidney, cytochrome P24A1 activity predominantly governs the catabolism of 1,25(OH)2D and 25(OH)D, while cytochrome P3A4 activity is the primary contributor to this metabolic process in the liver and small intestine. Between 10% and 30% of individuals on phenobarbitone or phenytoin exhibit radiological or biochemical indications of diminished vitamin D levels. Osteomalacia may manifest within months following the commencement of anticonvulsant medication, and the simultaneous administration of many anticonvulsants is likely to have cumulative effects due to enzyme induction in the liver. The altering influences of solar exposure and nutritional consumption are also significant to consider. Vitamin D supplementation has been shown to enhance the aforementioned biochemical and radiological alterations.

5- Vitamin D Dose Recommendations for Prophylactic and Therapeutic Use

Prophylactic (Preventive) Supplementation

- Infants (0–6 months): 400 IU/day from the first days of life, regardless of feeding method.(59)
- Infants (6–12 months): 400–600 IU/day, depending on dietary intake.(59)
- Children (1–10 years): 600–1000 IU/day,(59).
- Adolescents (11–18 years): 800–2000 IU/day,(59).
- Adults (19–65 years): 800–2000 IU/day,(59).
- Seniors (65–75 years): 800–2000 IU/day, as skin synthesis decreases with age(59).
- Eldest seniors (>75 years): 2000–4000 IU/day, due to further declines in skin synthesis and possible malabsorption(59).
- Pregnant and lactating women: 2000 IU/day is recommended if serum 25(OH)D cannot be measured; otherwise, dose should be individualized to maintain serum 25(OH)D >30–50 ng/m

These doses are adjusted for body weight and dietary intake; supplementation is especially recommended if adequate sun exposure is not achieved

Therapeutic (Treatment) Supplementation

Therapeutic dosing is indicated for individuals with laboratory-confirmed vitamin D deficiency, and is based on age and serum 25(OH)D levels:

- Infants (<1 month): 1000 IU/day for 3 months if 25(OH)D <25 nmol/L(59).
- Infants (1–12 months): 2000 IU/day for 3 months if 25(OH)D <25 nmol/L(59).
- Children (1–10 years): 3000–6000 IU/day for 3 months if 25(OH)D <25 nmol/L(59).
- Adolescents (11–18 years): 6000 IU/day for 3 months, or 50,000 IU/week for 1.5–2 months if 25(OH)D <25 nmol/L(59).
- Adults: 6000 IU/day for 3 months, or 50,000 IU/week for 2 months if 25(OH)D <25 nmol/L(59).(60)

For less severe deficiency (25–75 nmol/L), an increase of 1.5–2 times the prophylactic dose, or the highest prophylactic dose for the age group for 2–3 months, is recommended(59).
Maintenance After Correction

After achieving adequate serum 25(OH)D, maintenance dosing should follow age-appropriate prophylactic recommendations(59)(60)

Upper Tolerable Intake Levels

- Infants up to 6 months: 1000 IU/day(60).
- Infants 6–12 months: 1500 IU/day.(60)
- Children 1–3 years: 2500 IU/day.(60)
- Children 4–8 years: 3000 IU/day.(60)
- Everyone is over 8 years: 4000 IU/day(60).

Clinical Notes

- Dosing should be individualized, especially for those with risk factors such as obesity or malabsorption, who may require higher doses.
- Routine 25(OH)D screening is not recommended in the general population but is advised for risk groups(59).
- Vitamin D toxicity is rare but can occur at serum 25(OH)D levels >100 ng/mL, especially with excessive supplementation(59,60).

Conclusion

Vitamin D is a vital micronutrient that influences a wide range of physiological systems beyond its traditional role in bone and mineral metabolism. This review has highlighted the extensive benefits of vitamin D supplementation, including its critical functions in skeletal integrity, immune modulation, cardiovascular protection, and potential roles in cancer prevention and neuroprotection. However, it also underscores the importance of cautious and evidence-based supplementation, as inappropriate dosing can lead to serious adverse effects such as toxicity and hypercalcemia. Additionally, certain medications and health conditions may alter vitamin D metabolism, necessitating personalized dosing and close clinical monitoring. Ultimately, vitamin D supplementation should be tailored to individual needs, considering age, sunlight exposure, dietary intake, and underlying medical conditions. Public health strategies should aim to balance the prevention of deficiency with the avoidance of over-supplementation, ensuring optimal health outcomes across populations.

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