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Review Article

Deficiency of Vitamin D and Related Disorders

Nadira A Al-Baghl[1]*, Amani Hashim Mahdi[2], Ghada Fareed Hussain Qutub[3], Ahmed Abdulrahman Alanazi[4], Mohammed Sameer Alabbad[5], Hassan Abdulrahman Eissa[6], Maram Abdulrahman Aldahoos[7], Futun Thamer Almutiri[8], Bayan Lafi Altamimi[9], Mohammed Ahmed Alqubali[10], Zainab Jaffer A Alshaikh[7], Kawther Ahmed Al Rebh[11], Abdulmajed Mohammad A. Alrawail[12] and Nouf Khalid Alalshaikh[13]

[1]Director of Public Health Network, Dammam, Saudi Arabia
[2]National Guard Hospital, Jeddah, Saudi Arabia
[3]Umm Alqura University, Makkah, Saudi Arabia
[4]Medical University of Lublin, Poland
[5]Aljafer General Hospital, Alahsa, Saudi Arabia
[6]Khafji General Hospital, Khafji, Saudi Arabia
[7]Safwa General Hospital, Safwa, Saudi Arabia
[8]Maternity and Children Hospital, Al Kharj, Saudi Arabia
[9]King Fahad Hospital, Madinah, Saudi Arabia
[10]Prince Sultan Military Medical City, Riyadh, Saudi Arabia
[11]Alaqrabya Primary Healthcare, Khobar, Saudi Arabia
[12]Northern Border University, Arar, Saudi Arabia
[13]King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia

***Corresponding Author:** Nadira A Al-Baghl, Fellowship Family and Community Medicine, Master Professions Medical Education - Public Health, Director of Public Health Network, Dammam, Saudi Arabia.

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Abstract

Introduction: Vitamin D is responsible for maintaining the metabolism of calcium and phosphate and preserving a healthy, mineralized skeleton. Also known as an immunomodulatory hormone. The active form of vitamin D, 1,25-dihydroxy vitamin D, has been demonstrated in experimental experiments to exhibit immunologic effects on a number of innate and adaptive immune system components as well as endothelial membrane integrity. Low serum 25-hydroxyvitamin D levels have been linked to an increased risk of acquiring a number of immune-related conditions and diseases, including psoriasis, type 1 diabetes, multiple sclerosis, rheumatoid arthritis, TB, sepsis, respiratory infection, and COVID-19. As a result, a number of clinical trials with varying results have been carried out to ascertain the effectiveness of administering vitamin D and its metabolites for the treatment of these diseases. Recent research reveals that certain people may benefit from vitamin D supplementation more or less than others. Vitamin D administration has been shown to significantly alter broad gene expression in human peripheral blood mononuclear cells. Although the ideal level of serum 25-hydroxyvitamin D is still up for debate, it is advised to increase vitamin D intake and get enough sunlight exposure to keep serum 25-hydroxyvitamin D levels at least at 30 ng/mL (75 nmol/L), and ideally at 40 - 60 ng/mL (100 - 150 nmol/L), in order to reap the most benefits for your overall health.

Aim of the Study: The aim of the present review is to understand various disorders related to Vitamin D deficiency.

Methodology: Comprehensive research of the various disorders related to Vitamin D deficiency. PUBMED engine was the database used for the search process, and articles were collected from 2011 to 2022. The term used in the search were: Vitamin D, immune diseases, depression, infection.

Conclusion: Unquestionably, vitamin D is crucial for maintaining the metabolism of calcium, phosphate, and bone. Once a $1,25(OH)_2D$ is created, it modulates the innate and adaptive immune systems in an autocrine and paracrine manner. Additionally, there is some proof that vitamin D may modify immune activity in a non-genomic way by maintaining endothelium membranes. The majority of the available research points to the necessity of maintaining a healthy vitamin D status for controlling the body's immune system. Many immune-related diseases, including autoimmune disorders and infectious diseases, are linked to low serum levels of 25(OH)D. With a few exceptions noted in this study, there is less compelling evidence that vitamin D is a useful therapeutic option for autoimmune illnesses and infectious diseases. Based on inconsistent results from clinical trials, it is still debatable whether vitamin D therapy is beneficial as an additional immunomodulatory drug for treating the majority of illnesses.

Keywords: *Vitamin D; Immune Diseases; Depression; Infection*

Introduction

Vitamin D is a fat-soluble vitamin that is crucial for maintaining calcium homeostasis and bone metabolism. Insufficient vitamin D can cause osteomalacia, rickets, and osteomalacia in adults as well as in children. Rickets was successfully eradicated from the world in the 1930s because of the fortification of milk with vitamin D. Vitamin D is an international concern. Around 1 billion people globally lack enough vitamin D, and 50% of people are vitamin D deficient. The elderly, obese, nursing home residents, and hospitalized patients are the groups with the highest prevalence of vitamin D insufficiency patients. Regardless of latitude or age, the prevalence of vitamin D deficiency was 35% greater in obese people. With a global prevalence of up to 1 billion, subclinical vitamin D insufficiency is still prevalent in both industrialized and developing nations. Subclinical vitamin-D insufficiency is linked to fragility fractures, osteoporosis, and an elevated risk of falls. Vitamin D insufficiency is now linked to cancer, cardiovascular disease, diabetes, autoimmune illnesses, and depression, according to numerous contradicting recent research [1].

It is a hormone that modulates immunity in addition to being crucial for maintaining a healthy mineralized skeleton. Immune cells such as lymphocytes, monocytes, macrophages, and dendritic cells all express the vitamin D receptor (VDR) and metabolizing enzymes. Vitamin D has considerable physiologic effects on the innate and adaptive immune systems, according to experimental investigations. According to studies conducted on animals, administering vitamin D or its metabolites alters the onset and course of several immune-related disorders. This corroborates clinical and epidemiological evidence linking vitamin D to the occurrence and severity of numerous diseases, including infectious diseases, multiple sclerosis, rheumatoid arthritis, psoriasis, and multiple sclerosis [2].

Etiology

Ergocalciferol (D2) and cholecalciferol (D3) are primarily obtained through dermal synthesis and diet (fatty fish livers, fortified foods), respectively. In the liver, the enzyme hepatic enzyme 25-hydroxylase converts both of these substances into 25-hydroxy-vitamin D2 (25-OH-D2) and 25-hydroxy-vitamin D3 (25-OH-D3). The kidney's 1-alpha-hydroxylase enzyme then changes both 25-OH-D2 and 25-OH-D3 into vitamin D's most active form, 1,25 dihydroxy vitamin D. This 1,25-dihydroxy vitamin D, which is active, reduces renal excretion of calcium and phosphate while increasing intestine absorption of calcium and bone resorption. A lack of vitamin D can have many different reasons [3].

Some of the major reasons for vitamin D deficiency:

1. Decreased dietary intake and/or absorption
2. Decreased sun exposure
3. Decreased endogenous synthesis
4. Increased hepatic catabolism
5. End organ resistance.

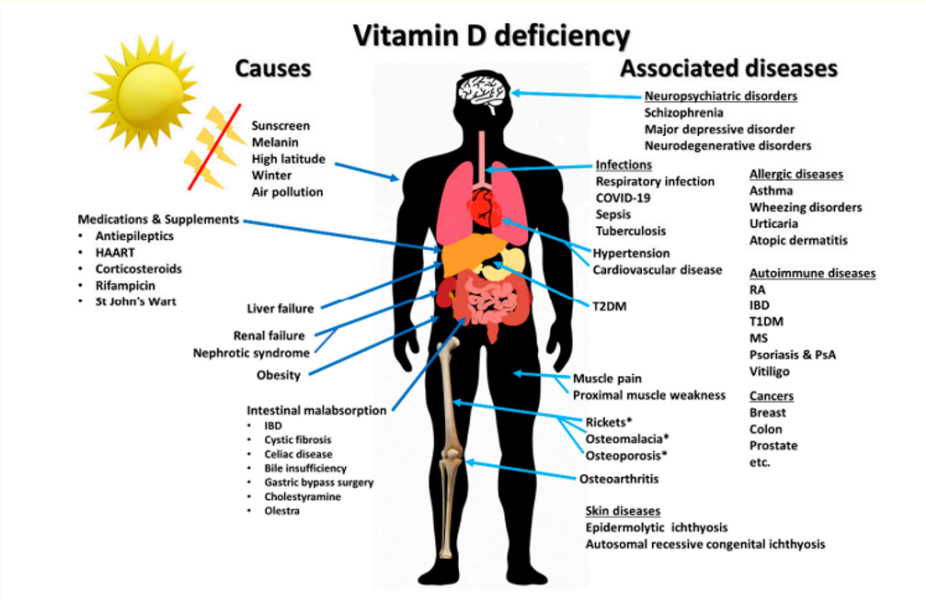

Figure 1: *An outline of diseases and conditions linked to vitamin D deficiency as well as its causes. Abbreviations: IBD: Inflammatory Bowel Disease, MS: Multiple Sclerosis, PsA: Psoriatic Arthritis, T1DM: Type 1 Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus; RA: Rheumatoid Arthritis [4].*

Vitamin D deficiency and related disorders

Type-I diabetes

The prevalence of type 1 diabetes is the maximum in Finland. Many explanations have been put out to explain the epidemic, including the development of autoimmunity being sparked by coxsackievirus B infections and exposure to specific hazardous compounds. It can be explained by the fact that Finland's population, particularly in northern Finland, has a high rate of vitamin D insufficiency due to a lack of exposure to sunlight. The winter, early spring, and late fall prevent Finns, like their northern counterparts, the Norwegians, from producing vitamin D3 in their skin through sun exposure for more than half a year. The earlier study that found that type 1 diabetes is more prevalent in regions with high latitudes and brief daytime periods also lends weight to this [5,6].

Although it is still unclear how type 1 diabetes develops, it is thought that autoreactive TH1 and CTL, as well as autoantibodies, cause the immune system to associate with the death of insulin-producing pancreatic cells. In the non-obese diabetic mouse model, $1,25(OH)_2D_3$

administration was reported to boost Treg and inhibit TH1, which resulted in a decrease in the prevalence of type 1 diabetes [60]. Furthermore, $1,25(OH)_2D_3$ directly stimulated insulin secretion by interacting with VDR in pancreatic cells. These processes confirm observational studies showing that increased vitamin D consumption for children was related to a lower risk of acquiring type 1 diabetes and assist in explaining how vitamin D has a potential protective and therapeutic role in reducing the risk of developing type 1 diabetes [5,6].

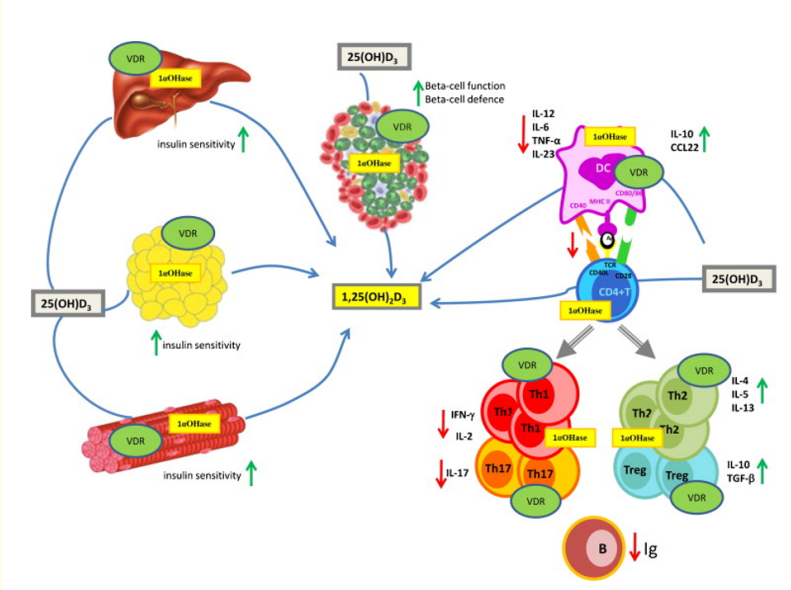

Figure 2: *Shows the direct secretion of insulin from $1,25(OH)_2D_3$ by interacting with VDR in pancreatic cells [7].*

Psoriasis

Numerous cultured malignant cells, including prostate cancer, colon cancer, breast cancer, and leukemia cells, have shown that $1,25(OH)_2D$ is a very effective hormone for slowing proliferation and inducing terminal differentiation. But $1,25(OH)_2D$ and its analogs have never been created for the effective treatment of any malignancy. In an effort to treat preleukemia, $1,25(OH)_2D_3$ was used; however, not only did this result in unfavorable hypercalcemia, but eventually, the leukemic cells developed a resistance to the antiproliferative effect. However, psoriasis is a chronic inflammatory condition that affects 2 - 3% of the world's population and is a non-malignant hyperproliferative illness of the skin. The epidermis is the primary location for the cutaneous synthesis of vitamin D3, as has been well-documented. These findings led to the hypothesis that a $1,25(OH)_2D$ dosage may be developed to treat a hyperproliferative skin condition like psoriasis [8,9].

Multiple sclerosis

In nations with higher latitudes, where people are more prone to vitamin D deficiency comparable to what has been shown with type 1 diabetes, the prevalence of multiple sclerosis (MS) is higher. During the first 10 years of life, there is a 50% lower risk of acquiring MS if you live below latitude 35. The incidence of MS dropped by 41% for every 20 ng/mL (50 nmol/L) increase in serum 25(OH)D levels over 24 ng/mL (60 nmol/L), according to Munger., *et al*. result's in a prospective nested case-control study of 148 MS patients and 296 controls (odds ratio, 0.59; 95% CI, 0.36 - 0.97). Women who consumed more than 400 IUs of Vitamin D each day had a 41% lower risk of having

MS, according to the same study group. Accordingly, it is thought that a lack of vitamin D contributes to the production of dysregulated T helper cells, CTL, NK cells, and B cells, which leads to the autoinflammation of the central nervous system and the damage to neurons and oligodendrocytes seen in MS. People who have particular human leukocyte antigen (HLA) alleles, such as HLA-DRB1*1501, are far more likely to develop multiple sclerosis (MS). It's interesting that vitamin D response elements have been discovered in the HLA-DRB1 gene's promoter region and that activation of VDR by $1,25(OH)_2D$ can change how the gene expresses itself [10].

Inflammatory bowel disease

Osteomalacia, osteoporosis, and fragility fractures are all more common in people with inflammatory bowel disorders (IBD) because they are more likely to be vitamin D deficient. This is due to their inability to effectively produce micelles and chylomicrons in their gastrointestinal tracts to absorb vitamin D. To attain a normal blood 25(OH)D level of at least 30 ng/mL (75 nmol/L), these patients should be tested for vitamin D deficiency and treated with a greater dose of vitamin D. New data suggests that there may be a bidirectional association between vitamin D levels and IBD. Nurses in lower latitudes had a continuously reduced risk of getting IBD than those in higher latitudes, according to data from two prospective Nurses' Health Studies. These findings were corroborated by a prospective cohort analysis of 72,719 Nurses' Health Study participants, which found that the highest projected quartile of serum 25(OH)D levels was related to a 46% lower risk of Crohn's disease (CD) and a 35% lower risk of ulcerative colitis (UC) [11,12].

IBD is a chronic, recurrent inflammatory condition of the gut brought on by a disordered innate and adaptive immune system, a compromised intestinal epithelial barrier, and an unbalanced intestinal microbiota. While UC is connected to a TH (T-helper)2 reaction, CD is thought to be primarily driven by a TH1 response. In both CD and UC, TH17 cells contribute to the inflammatory response. Numerous studies revealed that $1,25(OH)_2D_3$ enhances the expression of epithelial membrane junction proteins and intracellular pathogen recognition proteins, induces the production of antibacterial substances such as angiogenin, cathelicidin, and defensin by the intestinal epithelial cells, Paneth cells and intraepithelial lymphocytes and maintains the integrity of the intestinal mucosal barrier. These effects not only modulate T cell activity by promoting Treg and inhibiting TH1 and TH17 responses [11,12].

Rheumatoid arthritis

Numerous studies have demonstrated a link between low serum 25(OH)D levels and an increased risk of RA. In prospective cohort research, Merlino., *et al*. found that women in the highest tertile of vitamin D intake had a 33% lower chance of having RA than those in the lowest tertile. Low serum 25(OH)D levels have also been linked in several studies to increased disease activity in RA patients. Vitamin D and its metabolites are thought to have a therapeutic activity against RA based on the immunologic activities of $1,25(OH)_2D$ that suppress TH1 and TH17 responses and enhance Treg activity, despite the association being easily explained by the fact that these patients tend to have limited physical outdoor activities and sunlight exposure. The chronic synovial inflammation and symmetrical polyarthritis seen in RA are largely caused by overexpression of TH1 and TH17 as well as malfunctioning [13].

Clinical research on the use of vitamin D and its metabolites as an additional therapy for RA had varied results. In a randomized controlled trial (RCT), Gopinath., *et al*. showed that providing RA patients with 500 IUs of vitamin D3 daily in addition to disease-modifying anti-rheumatic medications (DMARDs) and calcium resulted in considerably greater pain alleviation than those getting DMARDs and calcium alone [13].

Tuberculosis

Finsen, who made the insightful observation that exposure to sunshine significantly alleviated cutaneous tuberculosis infection (lupus vulgaris) in the early 1900s, was awarded the Nobel Prize in 1903 for his discovery. As a result, solariums are being used as a successful TB treatment. Currently, tuberculosis is still a significant public health issue and the number one cause of morbidity and mortality in many underdeveloped nations. The condition known as latent TB occurs when the host immune system is able to create granulomas that can

envelop the *Mycobacterium* in an effort to restrict its growth. Patients develop symptoms and are identified as having active TB after the granuloma is unable to control mycobacterial proliferation. Vitamin D is crucial in the fight against tuberculosis [14].

Local antigen exposure causes activated macrophages and monocytes to create $1,25(OH)_2D$, which subsequently triggers the formation of cathelicidin, an antibacterial peptide that is effective against pathogens, including *Mycobacterium* TB. Low serum 25(OH)D levels have been observed in patients with active TB in numerous studies. Individuals with low serum 25(OH)D levels had a 63% greater risk of acquiring active TB, according to a nested case-control study by Aibana., *et al*. The risks of contracting tuberculosis (TB) were considerably greater (48%) in the vitamin D deficient group, according to a subsequent meta-analysis by the same group that included information from seven studies. It is believed that there is a bidirectional relationship between TB and vitamin D deficiency [14].

Sepsis and critical illness

Inpatients in the intensive care unit (ICU) commonly die from sepsis, a systemic inflammatory host reaction to a microbial infection. The prevalence of sepsis, as well as increased morbidity, mortality, and longer length of stay in the ICU in septic and critically sick patients, have all been linked to low levels of serum 25(OH)D in a number of observational studies. The actions of $1,25(OH)_2D$, which inhibits inflammatory cytokine upregulation and fosters antibacterial responses in innate immunity, could be used to explain the link. Furthermore, vitamin D3 and its metabolites have non-genomic effects on endothelial cells that might stop vascular leakage, which could potentially save lives in septic shock. Additionally, systemic inflammation may enhance 25-hydroxyvitamin D-24-hydroxylase activity and extravascular vitamin D-binding protein leakage, both of which may contribute to decreased serum 25(OH)D levels in sepsis and critical illness [15].

Respiratory disease

It is well known that influenza outbreaks are irregular and typically happen in the winter at higher latitudes, but they can happen at any time of the year in tropical regions. One of the hypothesized causes of the seasonal outbreak is a seasonal change in the blood levels of 25(OH)D, which are at their lowest in the winter. Numerous studies have shown an independent link between low levels of serum 25(OH)D and the frequency and severity of respiratory tract infections in both children and adults, supporting this notion. A prospective cohort study of healthy New England-based people revealed that those with serum 25(OH)D levels of 38 ng/mL (95 nmol/L) or higher had a two-fold lower chance of having acute respiratory tract infection (ARI) [16].

Infants who needed to be hospitalized for ARI had considerably higher risks of vitamin D deficiency than those with moderate ARI, according to a case-control study of children under the age of two. This demonstrates the defense against respiratory viral infection that a sufficient vitamin D level offers. Respiratory viruses cause cellular and tissue damage and activate innate and adaptive immune responses when they enter the respiratory epithelium through specific entry receptors, which leads to airway and systemic inflammation and, in severe cases, life-threatening sepsis or acute respiratory distress syndrome. By promoting cathelicidin release, altering toll-like receptor expression and NK cell function, and stifling proinflammatory cytokine overexpression, $1,25(OH)_2D$ exerts antiviral actions and modifies the inflammatory response to viral infection [16].

As obese and Black individuals are known to have a higher risk for vitamin D deficiency, the COVID-19 pandemic's rise and the out-of-the-ordinary rates of symptomatic infection, morbidity, and mortality seen in African Americans and obese people suggest that vitamin D may have an impact on host response and susceptibility to the infection. In addition to its immunomodulatory and antiviral properties, $1,25(OH)_2D$ functions particularly as a renin-angiotensin pathway modulator and suppressor of angiotensin-converting enzyme-2, the host cell receptor that SARS-CoV-2 uses to infect cells. Therefore, it is suggested that vitamin D intake can lessen the likelihood and severity of COVID-19 infection [17].

Depression

It is unclear exactly how vitamin D and depression are related biologically. However, there are other potential mechanisms, such as an imbalance in the calcium homeostasis between intracellular and extracellular compartments, as well as a potential result of the dis-

equilibrium between the excitatory neurotransmitters glutamate and GABA. This then has an impact on cellular signaling. By controlling intracellular calcium storage and cellular signaling, vitamin D may be able to help correct this calcium and neurotransmitter imbalance as well as positively affect the beginning of depression [18].

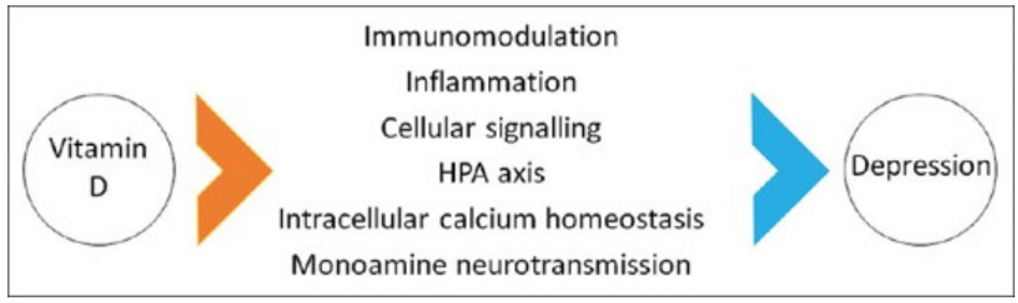

Figure 3: *Shows the biological link between vitamin D and depression [18].*

Rickets

Calcium or, more frequently, vitamin D deficiency is the defining feature of calcipenic (hypocalcemic) rickets. Due to vitamin D's ability to boost intestinal calcium absorption, this issue typically does not arise unless calcium intake is extremely low. The majority of children with calcium-deficient rickets had normal serum 25-hydroxyvitamin D concentrations (25(OH)D) and high serum 1,25-dihydroxy vitamin D concentrations ($1,25(OH)_2$] values, indicating appropriate vitamin D intake. Based on how they react to vitamin D supplementation, these kids may have higher vitamin D needs. As a result, children who are calcium deficient may have greater than normal vitamin D requirements. Additionally, reduced dietary calcium consumption raises serum $1,25(OH)_2D$ concentrations even in the absence of concurrent vitamin D insufficiency, decreasing 25(OH)D half-life, likely due to increased 25(OH)D catabolism [3].

Conclusion

Unquestionably, vitamin D is crucial for maintaining the metabolism of calcium, phosphate, and bone. Once a $1,25(OH)_2D$ is created, it modulates the innate and adaptive immune systems in an autocrine and paracrine manner. Additionally, there is some proof that vitamin D may modify immune activity in a non-genomic way by maintaining endothelium membranes. The majority of the available research points to the necessity of maintaining a healthy vitamin D status for controlling the body's immune system. Multiple immune-related diseases, including autoimmune disorders and infectious diseases, are linked to low serum levels of 25(OH)D. With a few exceptions noted in this study, there is less compelling evidence that vitamin D is a useful therapeutic option for autoimmune illnesses and infectious diseases. Based on inconsistent results from clinical trials, it is still debatable whether vitamin D therapy is beneficial as an additional immunomodulatory drug for treating the majority of illnesses.

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