Vitamin D- It's Deficiency & Implications

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***Abstract*—It is now well established that vitamin D plays significant roles beyond its well-known effects on bone and calcium homeostasis(1). Vitamin D has the ability to function autocrinely in a local immunologic milieu since the vitamin D receptor is expressed on immune cells (B cells, T cells, and antigen-presenting cells), and these immune cells can all synthesize the active antioxidant(2). Both the innate and adaptive immune responses can be influenced by vitamin D. Increased autoimmunity and an increased vulnerability to infection are linked to vitamin D deficiency(3). The benefits of vitamin D supplementation for autoimmune disease patients may go beyond the effects on bone and calcium homeostasis because immune cells in these conditions respond to the protective effects of vitamin D(4). By fostering protective immunity and preserving self-tolerance, the immune system protects the body from alien, invading organisms. In the setting of vitamin D insufficiency, there seems to be an increased sensitivity to infection and a diathesis in a genetically predisposed host to autoimmunity(5). The effects of vitamin D deficiency on the immune system have become more apparent in recent years(6). Vitamin D's traditional functions include supporting bone health and calcium balance. Vitamin D promotes osteoclast development, calcium reabsorption of bone, and improved calcium absorption in the small intestine(7). In addition, vitamin D encourages the mineralization of bone's collagen matrix(8). Vitamin D is either produced in the skin or acquired from diet in humans(9). Latitude, season, sunscreen use, and skin pigmentation all affect the synthesis of vitamin D, which is synthesized cutaneously upon exposure to UV Blight(10). UVB rays are absorbed by melanin, which prevents 7-dihydrocholesterol from being converted to vitamin D(11). The liver then hydroxylates this inactive initial vitamin D molecule to become 25 OH vitamin D3 (25 D)(12). Although 25 D is likewise an inactive substance, it is the most accurate indicator of a person's vitamin D levels(13). 1-α-hydroxylase (CYP27B1), an enzyme activated by PTH, transforms it in the kidney into the active molecule 1,25 dihydroxy vitamin D (1,25 D) or calcidiol(14). 24-hydroxylase (CYP24) has the ability to further metabolize 1,25 D to the inert 1,24,25 vitamin D(15). A negative feedback loop strictly regulates 1,25 D levels. 1,25 D keeps blood levels within certain bounds and stops excessive vitamin D activity and signaling by inhibiting renal 1-α-hydroxylase and stimulating 24-hydroxylase enzymes. 1,25 D enhances calcium reabsorption in the gut and encourages osteoblast development and matrix calcification in the bone(16). By attaching itself to the vitamin D receptor (VDR), the active hormone affects these tissues. The 1,25D-VDR-RXR heterodimer moves to the nucleus when this complex dimerizes with the retinoid X receptor (RXR)(1). There, it binds to vitamin D responsive elements (VDRE) in the promoter regions of vitamin D responsive genes and causes these genes to express themselves(2). The VDR is expressed by cells in the bone marrow, brain, colon, breast, and malignant and immunological cells, among other tissues besides the skeletal and intestinal(3). This suggests that vitamin D may have purposes beyond calcium and bone homeostasis(4). Furthermore, 1-α-hydroxylase is expressed in organs other than the kidney and can convert 25 D to 1,25 D in non-renal compartments(5). Consequently, vitamin D may have paracrine or autocrine effects in addition to its endocrine ones(6). The ability to sustain tolerance and foster protective immunity are two of the most recently identified non-classical activities of vitamin D, along with impacts on cell proliferation and differentiation and immunologic effects(7). Since T cells, B cells, and antigen-presenting cells (macrophages and dendritic cells) have the resources to produce and react to 1,25 D, vitamin D may have either an autocrine or paracrine effect on the immune system(8). Furthermore, because local regulation of the enzymes producing and inactivating vitamin D differs from the controls originating in the kidney, local levels of 1,25 D may differ from systemic, circulating levels(9). In contrast to renal hydroxylase, the extrarenal 1-α-hydroxylase enzyme in macrophages is not controlled by PTH (10). Rather, it depends on the amount of 25 D in the blood or can be brought on by cytokines like TNF-α, IL-1, or IFN-γ (11). Additionally, there is no negative feedback of local 1,25 D synthesis by 1,25 D because the macrophage 24 hydroxylase enzyme is a non-functional splice variation(12)**

I. VITAMIN D AND IMMUNITY PROTECTION

Before the development of potent antibiotics, vitamin D was utilized (unknowingly) to cure illnesses like

tuberculosis In sanatoriums, patients with tuberculosis were treated by being exposed to sunshine, which was believed to destroy the disease directly(13). Rich in vitamin D, cod liver oil has also been used to treat tuberculosis and provide extra protection against infections in general(14). Numerous cross-sectional studies have linked higher infection rates to lower vitamin D levels(15). Between 1988 and 1994, about 19,000 participants were examined in one report(16). Even after controlling for factors like season, age, gender, body mass, and race, people with lower vitamin D levels (<30 ng/ml) were more likely to self-report a recent upper respiratory tract infection than people with adequate levels(1). The amount of vitamin D varies throughout the year(2). The correlation between lower serum vitamin D levels and illness persisted throughout the year, despite seasonal infection rates fluctuating, with the lowest rates occurring in the summer and the highest in the winter(3). Serum vitamin D levels were used to stratify men in another cross-sectional research of 800 Finnish military recruits(4). Compared to recruits with greater vitamin D levels (over 40 nmol), those with lower vitamin D levels missed noticeably more days of active duty due to upper respiratory illnesses(5). Numerous more cross-sectional studies have examined vitamin D levels and influenza rates, along with rates of other illnesses like HIV and bacterial vaginosis(6). All have noted a link between higher infection rates and decreased vitamin D levels(7). Studies examining the possible advantages of giving vitamin D to reduce infection have shown inconsistent results, most likely as a result of several methodologic issues(8). According to a recent well-designed prospective, double-blind placebo study, administering a therapeutic dose of vitamin D and using nasopharyngeal swab culture (rather than self-report) as an objective outcome, reduced the incidence of influenza infection by a statistically significant 42%.Vitamin D's positive effects on the innate immune system contribute to its protective immunity benefits(9). It is known that lipopolysaccharide LPS, a proxy for bacterial infection, is recognized by macrophages via toll-like receptors (TLR)(10). When TLRs are engaged, a series of events results in the production of peptides including beta defensin 4 and cathelocidin that have strong bacterialcidal properties(11). These peptides have strong anti-microbacterial properties and colocalize with infected bacteria inside phagosomes, where they rupture bacterial cell membranes(12). An essential component of the innate antimicrobial response is vitamin D. Both the 1-α-hydroxylase and the VDR are expressed more when TLR binding occurs(13) . Consequently, the 1,25 D-VDR-RXR heterodimer binds to the beta defensin 4 and cathelocidin VDREs, causing the transcription of these proteins(14). A substantial amount of 25 D is essential necessary for cathelocidin transcription(15). It is now evident that NFkB binding to the proper response regions on the beta defensin 4 RNA is necessary for transcription of beta defensin 4(16). NFkB is translocated to its binding site as a result of TLR 2-1 signaling facilitating IL-1 receptor interaction(1).

II. VITAMIN D AND IMMUNE SYSTEM DISORDERS

Multiple sclerosis (MS), rheumatoid arthritis (RA), diabetic mellitus (DM), inflammatory bowel disease, and systemic lupus erythematosus (SLE) are among the autoimmune illnesses for which there is growing epidemiologic evidence that vitamin D deficiency is linked(2). Low serum vitamin D levels have been linked to the future onset of autoimmune diseases, including RA, MS, and autoimmune diabetes mellitus(3). Additionally, there is evidence that islet cell autoimmunity and reduced vitamin D exposure during pregnancy are related(4). A statistically higher chance of pancreatic autoimmunity in the offspring is linked to reduce in utero exposure, as measured by a lower maternal intake of vitamin D during pregnancy, in mothers whose potential child was at risk of developing autoimmune diabetes mellitus(5).

It has also been demonstrated that vitamin D speeds up the course of pre-existing autoimmune diseases(6). 161 patients with an early undifferentiated connective tissue illness were monitored for an average of more than two years in one study(7). The majority of patients stayed in an undifferentiated state and did not advance(8). While 126 individuals did not advance, 35 patients (21%) went on to acquire a specific rheumatologic diagnosis, such as Sjogren's disease, RA, SLE, or Mixed Connective Tissue Disease(9). The two groups' initial features were comparable(10). Crucially, the group that had a conclusive condition had a considerably lower mean vitamin D level(11).

Numerous investigations on vitamin D levels in lupus patients have been conducted worldwide(12). Patients usually have lower vitamin D levels than healthy controls or those with the condition(13). Patients usually have lower vitamin D levels than healthy controls or those with the condition(14). It is not unusual for more than 50% of lupus patients to have vitamin D deficiency, and severe deficiency (vitamin D levels below 10ng/ml) is also prevalent(15). Numerous research, albeit not all of them, have demonstrated an inverse relationship between vitamin D and disease activity(16). In other autoimmune disorders like MS and RA, comparable associations between low vitamin D levels and disease activity and severity have been noted(1).

III. IMMUNOLOGIC FUNCTION AND VITAMIN D

Vitamin D affects immune system cells in a variety of ways(2). It prevents B cell differentiation, immunoglobulin secretion, and B cell proliferation(3). Additionally, vitamin D causes a change from a Th1 to a Th2 phenotype by inhibiting T cell growth(4). Additionally, it promotes the activation of T regulatory cells and influences T cell maturation with a skew away from the inflammatory Th17 phenotype(5). Additionally, it promotes the activation of T regulatory cells and influences T cell maturation with a skew away from the inflammatory Th17 phenotype(6). These effects lead to an increase in anti-inflammatory cytokines like IL-10 and a decrease in inflammatory cytokines like IL-17 and IL-21(7). Dendritic cells (DCs) and monocytes are also impacted by vitamin D(6). It prevents monocytes from producing inflammatory cytokines such TNFα, IL-1, IL-6, IL-8, and IL-12(8) . Additionally, as shown by a decrease in the production of MHC class II molecules, co-stimulatory molecules, and IL12, it prevents DC differentiation and maturation while maintaining an immature phenotype(9). In the context of autoimmunity and the loss of self-tolerance, inhibition of DC differentiation and maturation is especially crucial(10). A mature DC that presents an antigen to a T cell promotes an immunological response to that antigen, whereas an immature DC that presents an antigen promotes tolerance(10). In the normal state, self-antigens are numerous due to physiological cell turnover and death(11). However, immature DCs typically present these self-antigens in order to preserve self-tolerance(12). Whether or not the immune components in autoimmune disease are able to respond appropriately to vitamin D is a crucial question given the significance of vitamin D for a functioning immune system, the severe deficiency seen in autoimmune disease, and the association between deficiency and more active disease(13). The immunomodulatory effects of vitamin D seem to affect immune cells (B cells, T cells, monocytes, and DCs) from a variety of autoimmune illnesses(14). Here are some instances of how immunologic components in various autoimmune diseases respond to vitamin D,B cells(15). Vitamin D may partially restore B cell abnormalities in lupus patients(16). Pre-incubating B cells from individuals with active lupus with 1,25 vitamin D considerably reduces both spontaneous and induced immunoglobulin synthesis(1). Furthermore, spontaneous generation of anti-DNA antibodies is greatly reduced by about 60% when vitamin D is added prior to incubation(2). T cells: MS patients' T cells react to vitamin D(3). Following preincubation in increasing vitamin D concentrations, the proliferation of activated CD4 cells from MS patients and controls is likewise reduced(4). Furthermore, both MS patients' and controls' Th17 polarized T cells react to vitamin D incubation; both exhibit downregulated IL-17 and gamma interferon production(5). Monocytes: Vitamin D prevents monocyes from producing inflammatory cytokines (TNFα, IL-1)(6). Vitamin D dramatically reduces the generation of cytokines by monocytes from both healthy controls and autoimmune diabetes patients (type 1 or latent autoimmune diabetics)(7). Vitamin D exposure also inhibits TLR 4 stimulation by LPS or LTA (leipoteichoic acid)(2) . DCs: Vitamin D's effects can affect DCs with lupus(8). Preincubation with vitamin D inhibits LPS-induced DC maturation, which results in decreased production of co-stimulatory molecules and HLA class II(9). Vitamin D also inhibits the responsiveness of lupus cells to LPS stimulation(10). Additionally, the expression of the interferon (IFN) signature in SLE is influenced by vitamin D(11). Plasmacytoid DCs produce interferon; the increase of IFN α inducible genes in lupus patients' peripheral blood mononuclear cells (PBMCs) is known as the IFN signature(12). About 50% of patients have the signature, which is correlated with disease activity(13). We have found that lupus patients

with low serum vitamin D exhibit overexpression of interferon-inducible genes in comparison to those with normal serum vitamin D(14). Vitamin D supplementation may reduce the expression of these interferon-inducible genes in lupus patients(15). Indeed, we have found that vitamin D supplementation increases the likelihood of an IFN signature response, or the reduction in expression of IFN inducible genes, by 2.1 times (unpublished data Ben-Zvi, I)(15). Vitamin D may be able to reduce the interferon signature in SLE patients, according to a double-blind, placebo-controlled NIH-sponsored study (ClinicalTrials.gov identifier: NCT00710021)(16).

IV. DEFICIENCY OF VITAMIN-D

Introduction-

A fat-soluble nutrient, vitamin D is necessary for bone metabolism and calcium balance(1). A lack of this healthy ingredient can cause osteomalacia in adults and nutritional rickets in children(2). To end dietary rickets in children, North America started adding vitamin D to milk in the 1930s(3). Adults should consume between 400 and 800 international units (IU) per day(4). Up to 1 billion people globally, in both industrialized and developing nations, suffer from subclinical vitamin D insufficiency(5). Osteoporosis, a higher incidence of falls, and fragility fractures are all associated with subclinical vitamin D insufficiency(6). Vitamin D insufficiency may be linked to depression, autoimmune illnesses, diabetes, cancer, and cardiovascular disease, according to recent observational research(7). The ideal level of vitamin D in the blood is still up for debate(8). A blood total 25-hydroxyvitamin D level of more than 30 ng/mL (50 nmol/L) is considered to be vitamin D sufficient, using the 2019 Endocrine Society standards(9). A total 25-hydroxyvitamin D level below 12 ng/mL (30 nmol/L) is considered vitamin D deficiency, whilst a level between 12 and 20 ng/mL (30 to 50 nmol/L) is considered vitamin D insufficiency(10).

Causes-

The principal source of cholecalciferol (vitamin D3) is the dermal synthesis of vitamin D because few foods, such as fatty fish livers and fortified goods, are substantial sources of vitamin D(11). Hepatic 25-hydroxylase in the liver transforms cholecalciferol and ergocalciferol (vitamin D2) into their corresponding 25-hydroxy forms, 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3, respectively(12). The kidney's 1α-hydroxylase enzyme further transforms these forms into 1,25-dihydroxyvitamin D, the most active vitamin D metabolite(13). This active form decreases renal excretion of calcium and phosphate, increases intestinal absorption of calcium, and encourages bone resorption(14). All hydroxylation processes are catalyzed by cytochrome P450 mixed-function oxidases(15). Numerous factors can lead to vitamin D insufficiency, which may interfere with one or more phases of vitamin D activation(16). The most crucial elements are as follows:

Reduced dietary intake or absorption: Vitamin D deficiency can result from a number of malabsorption conditions, including cystic fibrosis, inflammatory bowel disease, gastric bypass, celiac disease, short bowel syndrome, and chronic pancreatic insufficiency(1). It is more common for older people to consume less vitamin D orally(2). Reduced sun exposure: To avoid vitamin D insufficiency, one must receive approximately 20 minutes of sunlight each day, with more than 40% of the skin exposed(3). But as people age, their skin produces less vitamin D(4). The cutaneous production of vitamin D is lower in people with darker skin(5). Vitamin D deficiency can also result from less sun exposure, as shown in patients who are institutionalized or stay in hospitals for an extended period of time(6). Regular sunscreen wearers limit their chances of getting enough UV exposure(7). Reduced endogenous synthesis: Defective 25-hydroxylation can result in a lack of active vitamin D in people with long-term liver diseases such cirrhosis. Both hypoparathyroidism and renal failure are associated with defects in 1α-25-hydroxylation(8).

Increased hepatic catabolism: Drugs like rifampin, phenobarbital, carbamazepine, dexamethasone, nifedipine, spironolactone, clotrimazole, and carbamazepine cause the decomposition of vitamin D into inactive metabolites more quickly by inducing hepatic p450 enzymes(10).

End-organ resistance: End-organ resistance to vitamin D may result from rickets that is inherited and resistant to this nutrient(11).

V. CARDIOVASCULAR DISEASE DUE TO DEFICIENCY OF VITAMIN-D-

A lack of vitamin D is associated with a higher risk of cardiovascular disease (CVD)(12). Low vitamin D levels have been linked in studies to a number of CVDs, including atrial fibrillation, heart failure, and coronary artery disease (CAD)(13). Furthermore, cardiovascular risk factors including diabetes and high blood pressure can be exacerbated by vitamin D insufficiency(14).

The Potential Impact of Vitamin D Deficiency on Cardiovascular Health:

• Elevated CVD Risk:

Low vitamin D levels have been linked in studies to an increased risk of CVD, which includes diseases including atrial fibrillation, heart failure, and coronary artery disease(15). • Cardiovascular Risk Factors: A lack of vitamin D can make pre-existing cardiovascular risk factors, such as diabetes and hypertension, worse, which raises the risk of CVD. • Endothelial Dysfunction: A lack of vitamin D can affect the endothelium's ability to function, which is essential for preserving normal blood flow and the inner lining of blood vessels(16).

The Vascular Stiffness Factor-

Increased vascular stiffness, which makes it more difficult for the heart to pump blood efficiently, has been related to low vitamin D levels(1).

• Inflammation: A lack of vitamin D can exacerbate inflammation, which is a major contributing factor to the onset and advancement of atherosclerosis, or the accumulation of plaque in the arteries(2).

• Heart Failure: Studies show that vitamin D insufficiency is common in heart failure patients and may be linked to worse outcomes for these patients(3).

• Abnormal Heartbeat: In severe circumstances, irregular heartbeats can be fatal. Low calcium levels, which can be caused by low vitamin D, may be a contributing factor(4)

VI. TREATMENT OF THE DEFICIENCY OF VITAMIN-D-

Vitamin D Supplementation: • Over-the-counter supplements: Cholecalciferol (vitamin D3) is a common vitamin D supplement that is easily accessible and can be used to treat a deficiency(5).

• Prescription-strength supplements: A physician may recommend greater dosages of vitamin D2 or D3 for more severe deficits(6).

• Amount: According to Yale Medicine, the right amount will change based on the degree of the deficiency, personal characteristics like age and weight, and the presence of other medical disorders(7).

• Types: There are two primary forms of vitamin D: D3 (cholecalciferol) from animals and D2 (ergocalciferol) from plants(8). According to the Cleveland Clinic, D3 is frequently used since the body absorbs it more easily(9).

2. Modifications to Diet:

• Foods high in vitamin D: Include items like egg yolks, fortified dairy products, and fatty fish (salmon, tuna, and mackerel) in your diet(10).

• Fortified foods: Make the choice of fortified foods such as breakfast cereals, plant-based milk substitutes, and milk(11).

3. Exposure to Sunlight:

• Safe sun exposure: Although exposure to the sun can aid in the body's production of vitamin D, it's crucial to do so in a way that minimizes damage, particularly during the hours of most sunlight(12). It can be advantageous to briefly expose a section of your skin to the sun(13). • Individual requirements: Skin tone, latitude, and season all affect how much sun exposure is required(14).

4. Observation & Monitoring:

• Blood tests: To be sure that treatment is working, routine blood tests can help track vitamin D levels(15).

• Speak with a healthcare practitioner: It's critical to collaborate with a healthcare provider to identify the most effective treatment plan and track your progress(16).

Allopathy

Cholecalciferol (vitamin D3) supplements are commonly used as an allopathic treatment for vitamin D insufficiency(1). Depending on how severe the deficiency is, this can be accomplished with prescription or over-the-counter oral supplements(2). A doctor may give higher dosages or different forms, such as ergocalciferol (vitamin D2), in more severe situations(3).

VII. CONCLUSION

Beyond maintaining calcium and bone homeostasis, vitamin D has a significant role in regulating both the

innate and adaptive immune systems. In autoimmune diseases, vitamin D insufficiency is common(4). Vitamin D can be synthesized and reacted to by immune system cells(5). Since immune cells in autoimmune disorders respond to vitamin D's ameliorative actions, vitamin D supplementation may provide advantages for autoimmune disease patients that go beyond improvements in calcium and bone homeostasis(6).

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