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Review Regarding the Impact of Vitamin D Deficiency on the Function of Immune System

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Abstract

The long-held knowledge regarding vitamin D is that it could affect both the homeostasis of calcium and bone metabolism. It is a vital immune regulator that has an impact on the immune system's innate and adaptive components, as it is based on mounting data. Research has shown that vitamin D deficiency is linked to several immune-mediated illnesses, infection, vulnerability, and cancer. The objective of this article is to highlight the importance of this vitamin and clarify the relationship between the immune system and it in general, in addition to the innate and acquired immunity in particular.

Keywords: Deficiency of vitamin D, Immune system disease, Autoimmune disease, and Vitamin D.

1. Introduction

The immune system's role is to provide the body with defensive resistance and guard it against the outside-attacking germs [1]. Later, light has been shed on the risks that vitamin D deficiencies may have on the immune system [2]. In case of vitamin D insufficiency, disorders are more susceptible to take place in a hereditarily inclined autoimmunity [3]. It has two conventional capacities, which are bolstering calcium homeostasis and bone health. In addition to advancing osteoclast separation and calcium reabsorption of bone, vitamin D promotes the assimilation of calcium in the small intestine. In addition, it makes a difference in regard to the collagen framework in bones as it mineralizes it. Various cell sorts, including resistant cells, including Monocytes, T cells, B cells, and antigen-presenting cells, all incorporate vitamin D receptors and proteins for metabolizing vitamin D [4].

2. Sources of the Vitamin D

It has been found that vitamin D has three conceivable sources, which are: dietary sources, UVB-dependent endogenous synthesis, and supplementation [5]. A little amount of vitamin D in people comes from food; however, the lion's share is delivered in the skin through UVB introduction [6]. There are exceptionally few non-fortified types of food that contain noteworthy amounts of either of the two main forms of cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2), such as greasy angle (liver oil from salmon, mackerel, sardines, and cod). Other fountains of such nourishments involve a few types of mushrooms (Shiitake), especially when they are sun-dried [7].

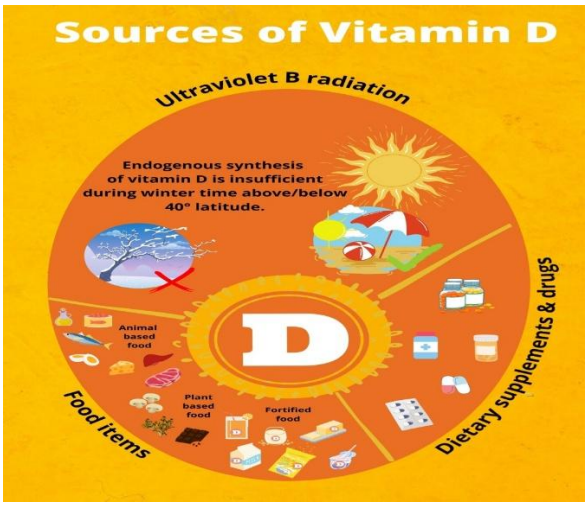

Fig.1. Main sources of vitamin D [5]

3. Vitamin D's Mode of Action

Examine the genomic activities. The VDR mediates all of the genomic actions of 1,25(OH)2D. VDR is a transcription factor and a member of the nuclear receptor family of steroid hormones [8] and [9]. Three domains comprise it: the ligand binding domain at the C-terminus, the hinge region connecting these two domains, and two zinc fingers on the N-terminal DNA binding domain, which clings to the DNA grooves at certain locations (VDREs) [10]. Crystallography using X-rays has been employed in order to resolve the ligand-binding domain's structure. There are twelve helices in it. The terminal helix aids in VDR's binding to its heterodimer partner, usually RXR, and acts as a regulating system by surrounding the incorporated ligand and establishing a coactivator interface [11]. Directly repeating hexanucleotides with a 3 nt gap between the half sites, or a DR3 motif, make up almost all of VDREs with the highest affinity for VDR, despite the fact that the sequence of VDREs varies greatly. Complexes of coregulators necessary due to their genetic action are then recruited by VDR binding to its VDRE [12].

These complexes have the ability to be both cell-specific and gene-specific, which allows 1,25(OH)2D to function deliberately on many kinds of cells. A subunit of these complexes typically connects with the VDR directly by means of an LXXLL motif [13]. Other subunits that contain enzyme activity include nucleosomal remodeling activity that contains ATPase (SWI/SNF), RNA polymerase II (Mediator complex) connections, methyl transferases and demethylases, and histone acetyl transferases (coactivators like the SRC family) or deacetylases (corepressors like SMRT and NCoR) [14].

Our understanding of the genome-level mechanism of the effects of vitamin D has significantly increased thanks to the more recent methods of ChIP-chip, ChIP-seq, and microarray. For example, 1,200 sites of binding for VDR were discovered in the mouse osteoblast below the basal circumstances (i.e., without 1,25(OH)2D). In contrast, 8,000 sites were discovered after 1,25(OH)2D was administered [15]. In a different investigation, there were 2,776 VDR binding sites found to change the expression of 229 genes in 1,25(OH)2D-treated human lymphoblastoid cell lines [16]. Particularly, in the process of reviewing evidence with varying period courses, the combination of VDR binding sites and genes activated varies from cell to cell with a certain, but not much, overlap upon

exposure to 1,25(OH)2D [17]. Furthermore, these VDR binding sites may be located thousands of base pairs away from regulation, or anyplace else in the genome [18]. Usually, these locations are linked to other transcription factor binding sites [19]. These include, among others, C/EBPa, C/EBPb, and RUNX2 in osteoblasts. These locations frequently exhibit a unique epigenetic histone signature that includes lysine either acetylation or methylation in H_3 and H_4 [20].

4. Immune System and Vitamin D

Vitamin D has notable impacts on calcium homeostasis and bone. It can work in an area of immunologic milieu since its receptor is expressed within safe cells (B cells, Lymphocytes, and antigen-presenting cells). These protected cells can all combine the vivacious vitamin D metabolite [21].

Immune system cells have been found to communicate the vitamin D receptor (VDR), while dendritic macrophages and cells have been shown to communicate the 1a-25(OH) vitamin D3 hydroxylase [22]. These discoveries indicate that privately combined $1,25(OH)_2D_3$ has both paracrine and autocrine capacities in the location of irritation [23].

The 1a hydroxylase, which acts as a catalyst, changes the $25(OH)D_3$ to $1,25(OH)_2D_3$, which seen as essential for the production of active vitamin D. $1,25(OH)_2D_3$'s attachment to the VDR, a transcription factor which controls gene expression in a tissue-specific way, mediates its activities [24]. Many different types of immune cells constitutively express the VDR. An atomic transcription factor is a part of the steroid/hormone superfamily. Low quantities of VDR are expressed by resting T-cells; they are levels are upregulated after activation [25].

According to some reports, the dynamic form of vitamin D, known as $1,25(OH)_2D_3$, with capabilities as an immunosuppressive medication, subsequently relieving the pathogenesis of immune system problems interceded by T helper 1, like IBD and experimental autoimmune encephalomyelitis (EAE), is a mouse model of multiple sclerosis [26]. Moreover, in three unmistakable animal models, there is evidence that deficiencies in vitamin D and VDR could deteriorate exploratory IBD. One clarification for $1,25(OH)_2D_3$ ability for decreasing autoimmunity has been put forward: it builds T regulatory cells both in vivo and in vitro. Furthermore, enormous screening techniques display that VDR polymorphisms are related to a higher

possibility of Crohn's disease and ulcerative colitis in human patients [27].

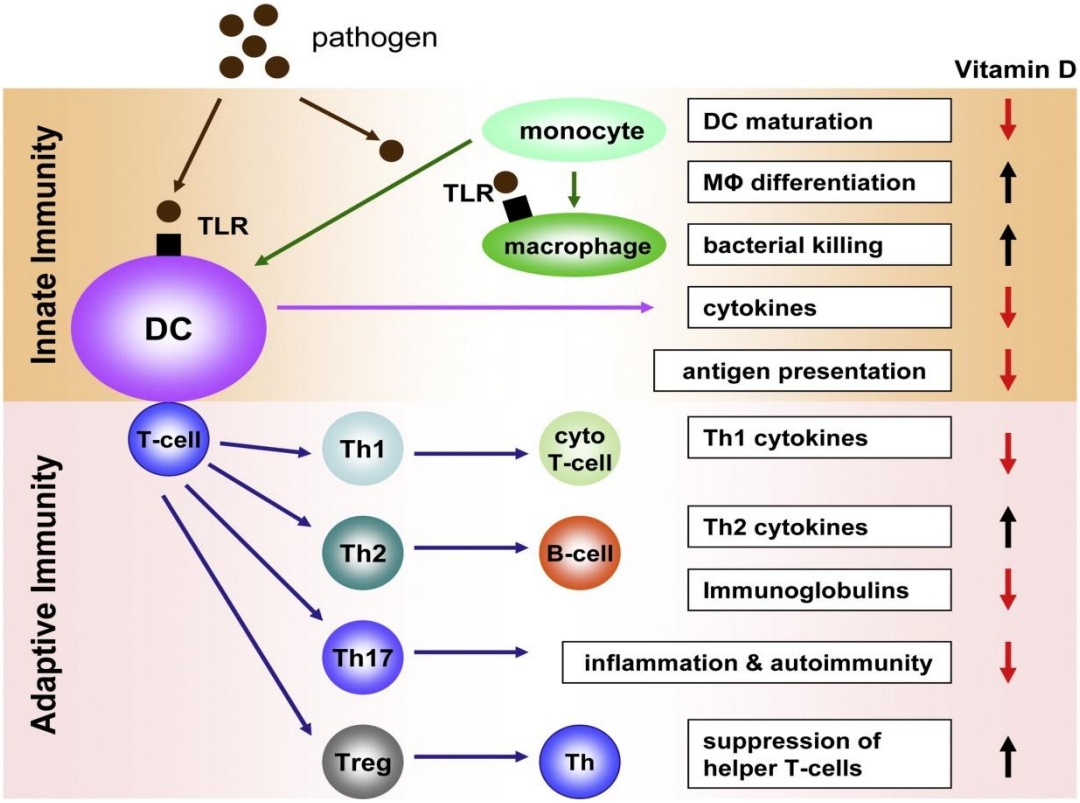

Fig.2. The impact of vitamin D on adaptive as well as innate immunity. The main innate and adaptive immunological reactions to a virus, as well as how vitamin D influences these reactions either favorably or unfavorably. [28].

5. Innate Immunity and Vitamin D

The stimulation of TLRs in polymorphonuclear cells, monocytes, macrophages, and other epithelial cells, including those in the colon, epidermis, gingiva, vagina, bladder, and lungs, makes up the innate immune response [29]. 10 are functional in human cells out of the 11 identified TLRs in mammals. A specific pathogen-associated molecular pattern (PAMP) initiates the host's innate immune response, which is released by infectious pathogens interacting with TLRs, resulting in a large family of transmembrane pathogen-recognition receptors that are not catalytic. Many TLRs transmit signals via adapter molecules, which include TIR domain-containing adapter, IFN-β (TRIF), and myeloid differentiation factor-88 (MyD88) [30].

TLRs 2, 4, 5, 7, and 9 signaling is mediated by MyD88, whereas TLRs 3 and 4 signaling is mediated by TRIF. Translocation of NF-κB into the nucleus is

a component of MyD88 signaling, triggering the synthesis and release of numerous cytokines that cause inflammation [31]. Interferon regulatory factor-3 is activated by TRIF signaling, inducing type 1 interferons like IFN-β, contrasting with TLR1/2, TLR4, TLR5, and TLR2/6, which react to bacterial ligands, while TLR3, TLR7, and TLR8 react with viral ligands [32].

CD14 is a coreceptor found in many of these TLRs. Reactive oxygen species and antimicrobial peptides are produced in case TLRs are activated; these substances finally destroy the organism [33]. Cathelicidin is one of the antimicrobial peptides. In the innate immune response, several functions of cathelicidin are involved. For hCAP18 to function, it has to cleave into its main peptide, LL-37 [34].

In addition to its antibacterial characteristics, LL-37 can cause the secretion of cytokines through the ERK/P38 pathway for IL-18 and G protein-coupled receptors for IL-6 and IL-10. It is also able to activate STAT-1 and STAT-3 by means of stimulating the epidermal growth factor receptor, prompting neutrophils, monocytes, macrophages, and T cells to move to the skin [35]. Ultimately, it has the ability to motivate keratinocyte migration and proliferation. Both myeloid and epithelial cells produce this antibacterial peptide, which is stimulated by $1,25(OH)_2D_3$ .Furthermore, in keratinocytes, $1,25(OH)_2D_3$ activates the coreceptor CD14 [36].

The expression of CYP27B1 is upregulated when TLR2 is stimulated in macrophages by an antimicrobial peptide or in keratinocytes by inflicting an epidermal wound. This, in turn, increases the synthesis of cathelicidin when there is sufficient 25(OH)D substrate [37]. The lack of ability of these cells to produce cathelicidin and/or CD14 in response to a challenge is blunted by the absence of the 25(OH)D substrate or CYP27B1 [38].

Patients with conditions like atopic dermatitis appear to be more helpless against microbial superinfections because their bodies produce less cathelicidin and other antimicrobial peptides. LL-13 and LL-4 are included in the Th2 cytokines that repress the acceptance of antimicrobial peptides [39]. Past their antibacterial capacities, such antimicrobial peptides have an essential role in laying out an association between the innate and acquired immune reactions [40].

6. Vitamin D and Adaptive Immune System

The responses of T- and B-cell immunological are calcitriol's tissue-

specific production, which is from circulating 25(OH)VitD. Having been activated, DCs cause 25(OH)VitD to become intracellularly activated. Such intracrine activity can then prevent DCs from maturing [41].

Accordingly, through intracrine and paracrine activities, the stimulation and regulation of the first Th-reaction becomes possible by $1,25(OH)_2$VitD. In such a case, $1,25(OH)_2$VitD reduces T-cell proliferation via functioning as a maturation inhibitor [42]. For polarizing the responses of Threg phenotypes or CD4+ T-cells toward a more regulatory Th2 (i.e., IL2, which activates humoral-mediated immunity by activating B-cells to produce neutralizing antibodies to promote defense against external pathogens), calcitriol signalling leads to repress the transcription of genes that encode Th1 response-like cytokine (i.e., INFγ, which stimulates cell-mediated immunity including macrophages, cytotoxic T-cells, and NK cells—and B-cell production of opsonizing antibodies to induce protection against intracellular pathogens) and Th17 (i.e., IL17, which provides anti-microbial immunity at epithelial and mucosal barriers) [43].

These final two features are seen to be essential to the ability of Vitamin D to inhibit Th1-driven immunological responses. Th17 cells are not only related to tissue damage and inflammation, but they also play an essential role in fighting off some infections, such as *Candida albicans, Helicobacter pylori, Cryptococcus neoformans, Staphylococcus, M. tuberculosis, and Klebsiella pneumoniae* [44]. Hence, $1,25(OH)_2$VitD could help to preserve self-tolerance through supporting protective innate responses and reducing too enthusiastic adaptive immune system responses. The precise processes of changes in VitD status may have an effect on T-cell functions [45].

It was believed first that CD4+ T-cells could act as an indirect medium for the proliferative impact of B-cells, $1,25(OH)_2$VitD. However, in a recent research, it has been found that B-cells could respond intracrinally [46]. Moreover, 1,25(OH) can control B-cells expressing VDR. Due to 2VitD, the effects of vitamin D's active form on B-cells are evident, which are activated as opposed to those that are at rest; such impacts may vary as they are dependent on an individual's serum 1,25(OH)2VitD levels [47].

Providing the anti-proliferative impact, the VDR's increased activity mediates the inhibitory effects that require a specific degree of VDR engagement. Remarkably,

resting B-cells were also found to express CYP27B1 mRNA [48]. In addition, it was concluded that CYP24A1 was markedly upregulated when human B cells were incubated with 1,25$(OH)_2$VitD [49]. This indicates that the ability to break down the active molecule may have an impact on VitD activity in addition to VDR expression. B-cell stimulation does not change CYP24A1; this is in contrast with the VDR, a view which emphasizes the point showing 1,25$(OH)_2$VitD can directly cause a reaction in human B cells. Significantly, that B cells are more susceptible to a number of 1,25(OH)2D3 impacts, which may be owing to their up-regulation of VDR rather than CYP24A1. Similarly, 25(OH)VitD [50].

Ultimately, 1,25$(OH)_2$VitD has control over B-cell reactions and also stifles consistent B-cell expansion. Notwithstanding, in light of the fact that it stifles consistent B-cell expansion, which is essential for the separation processes to happen, it has the ability to influence the separation of plasma cells and memory cells. The chemokine receptor CCR10 and IL-10 are two supplemental B-cells that focus on 1,25$(OH)_2$VitD, demonstrating that B-cell reactions to VitD could extend to the control of mucosal immunity [51].

7. Autoimmune Disease Related with Vitamin D Deficiency

The role of vitamin D in bone metabolism is well known, but less is known about how it affects other organs or systems [52]. The vitamin D receptor (VDR) and its stimulating enzyme, 1-α-hydroxylase, are expressed by numerous kinds of cells in the kidney, pancreas, prostate, gut, platelets, as well as immune cells, indicating that vitamin D has an active function in these cell populations [53].

Over the past few decades, studies on epidemiology have shown a gradual rise in the occurrence of autoimmune disorders (ADs), particularly in Western nations. Loss of immunological tolerance, which causes healthy tissues to be destroyed, is a characteristic of Ads [54]. The most significant rise in endocrine, rheumatic, IDDM, MS, RA, SLE, and IBD and gastrointestinal ADs has been documented, and it has been connected to numerous causes, involving dietary modifications, stress, and pollution exposure in the environment [55].

Recently, inadequate vitamin D levels, which are crucial for the immune system, have been linked to ADs. Nevertheless, there is disagreement over the ideal dosages for both the management and avoidance of certain illnesses as well as the levels of vitamin D needed to maintain optimum health [56].

According to certain theories, vitamin D and its derivatives might be utilized to treat autoimmune illnesses in addition to preventing their onset [57]. Numerous experimental animal models, including those for SLE, type 1 diabetes, collagen-induced arthritis, and inflammatory bowel disease, autoimmune thyroiditis, and allergic encephalomyelitis, have demonstrated the healing benefits of taking supplements of vitamin D [50].

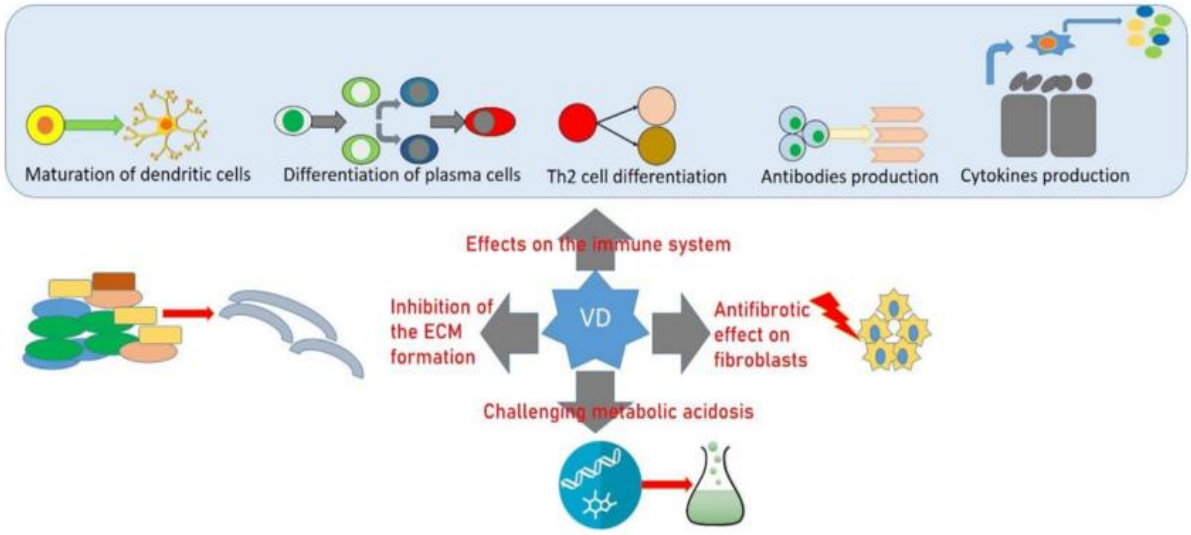

Fig.3.Autoimmune disorders, bone, and vitamin D. Th2: T helper 2 cells; ECM: extracellular matrix [40].

8. Conclusions and Recommendations

Historically, vitamin D has been considered a "panacea" for human health, helping many scientific studies to examine such a naturally occurring molecule that resembles a hormone or cytokine. Nevertheless, despite this compound's critical importance for human health, research on it has been conducted on the problem of its widespread deficiency in human populations.

The current view that $1,25(OH)_2$VitD and 25(OH)VitD are not only important participants in the development of bones is unquestionably valid. In addition to being objective regarding the the active vitamin D in its form, this review has unequivocally displayed that the immune system's two arms' cell components are also capable of activating circulating 25(OH)VitD, boosting the existence of intracrine and paracrine actions and the traditional endocrine pathway as well.

Numerous cellular systems have the ability to create vitamin D from substrates using the CYP450 family, which is highly

polymorphic. Yet, the increasing prevalence of goods made from plants that include antioxidants in daily diets, owing to the abundance of fruits and vegetables, may partially or completely replace the use of vitamin D as a tolerogenic, anti-inflammatory, and energetic and metabolic regulator. The basic question of whether vitamin D is really efficient in avoiding or treating inflammatory, metabolic, and degenerative diseases currently should be addressed in the domain of medicine so as to develop essential dietary and lifestyle recommendations for the right consumption of this essential molecule. Consequently, more investigation is required.

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مراجعة بشأن تأثير نقص فيتامين د على وظيفة الجهاز المناعي

هيام الغانم ماجد حمود هدى الحسيني

ملخص

من المعروف منذ زمن طويل أن فيتامين د يمكن أن يؤثر على توازن الكالسيوم واستقلاب العظام. وهو منظم حيوي للمناعة يؤثر على المكونات الفطرية والتكيفية للجهاز المناعي، كما يتضح من البيانات المتزايدة. وقد أظهرت الأبحاث أن نقص فيتامين د يرتبط بعدة أمراض مناعية، والعدوى، والضعف، والسرطان. الهدف من هذه المقالة هو تسليط الضوء على أهمية هذا الفيتامين وتوضيح العلاقة بين الجهاز المناعي وبينه بشكل عام، بالإضافة إلى المناعة الفطرية والمكتسبة بشكل خاص.

الكلمات المفتاحية: نقص فيتامين د، أمراض الجهاز المناعي، أمراض المناعة الذاتية، وفيتامين د.