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Role of vitamin D deficiency on Autoimmune Diseases Flares

[1]Dr. Zainab Mousa Al. Nemer, [2]Dr. Layla Hassan Al. Nosair,
[3]Dr. Thara Alawi Al. Sharfa, [4]Dr. Zainab Zaki Al. Jaffer

Abstract: **This study was aimed to focus on reviewing the evidence and discussing the interaction roles of Vitamin D on the autoimmune disease, we intended to overview most common systemic autoimmune diseases and we excluded specific organ autoimmune disease. Comprehensive dilated search was performed of the literature through several medical science databases; MIDLINE (PubMed), Embase, for relevant studies which published in English up to December, 30. 2016 with human subjects. several Mesh terms were used in search methods among databases which are: "Vitamin D" AND "Autoimmune diseases" combined with "Systemic lupus erythematosus" AND "Rheumatoid arthritis" AND "Multiple sclerosis". Studies references in the identified articles were searched for more relative studies to be included in our review. Epidemiological, genetic, and standard studies suggest a potential function of vitamin D in the pathogenesis of specific autoimmune diseases, the majority of which show a connection in between low levels of vitamin D and disease appearance or manifestations of these disease. Vitamin D has important functions beyond those of calcium and bone homeostasis which include modulation of the innate and adaptive immune responses.**

Keywords: **Autoimmune Diseases Flares, Systemic lupus erythematosus.**

1. INTRODUCTION

The fact of autoimmunity is consisted of a complicated interaction in between endogenous and exogenous factors such as genetic, hormone, and environmental ones, which vitamin D has been acknowledged as both an exogenous and endogenous gamer [(1)]. Vitamin D is a fat-soluble prohormone found in considerable quantities in particular fish and in small amounts in other active ingredients of the Western diet. It is manufactured in big amounts in skin exposed to UV rays of sunlight. Following the syntheses of vitamin D, it is transformed in vivo into biologically active metabolites specifically 25(OH)D and 1,25(OH)D [(2)]. The latter regulate various functions in numerous cell types, through binding to vitamin D receptors (VDR) on both calcemic and noncalcemic tissues [(2)]. Thus, upon activation of VDRs, they not only control calcium metabolic process however likewise generates a variety of biological actions, which affect cellular growth, expansion, apoptosis, and immune modulation [(3, 4)].

Many tissues other than the skeletal and intestine reveal the VDR consisting of cells in the bone marrow, brain, colon, breast and immune cells and malignant cells recommending that vitamin D might have functions other than calcium and bone homeostasis [(5)]. Additionally, tissues besides the kidney reveal 1-α-hydroxylase and are capable of transforming 25 D to 1,25 D, in non-renal compartments [(6,7)]. For that reason, in addition to its endocrine functions, vitamin D might act in a paracrine or autocrine way. A few of the more just recently acknowledged non-classical actions of vitamin D include impacts upon cell proliferation and distinction as well immunologic results leading to an ability to maintain tolerance and to promote protective immunity. As antigen presenting cells (macrophages and dendritic cells), T cells and B cells have the needed machinery to react and manufacture to 1,25 D, vitamin D might act in a paracrine or autocrine manner in an immune environment. Furthermore, local levels of 1,25 D may differ from systemic, circulating levels as regional guideline of the enzymes inactivating and manufacturing vitamin D are various from the controls coming from the kidney. Nevertheless, the implications of vitamin D deficiency on the immune system have actually become clearer recently and in the context of vitamin D shortage, there appears to be an increased susceptibility to infection and a diathesis, in a genetically prone host to autoimmunity [(8)]. Additionally, both humoral and cellular adaptive actions are affected by vitamin D. Decreased expansion and antibody production by B cells have been documented following direct exposure to vitamin D (9). While the later effect on the cellular action is consisted of a switch from Th1 to Th2 cytokine profile, ameliorating Th17 path via transcriptional modulation of interleukin-17A, as well as induction of T regulative cells and immune tolerance [(10,11)]. In this context, seasonal variation in vitamin D levels was reported to parallel modifications in peripheral blood human T cell compartment [(12)] Thus, vitamin D has actually been accepted as one of the natural immune modulators and regulator of various immune-mediated procedures [(13)].

This study was aimed to focus on reviewing the evidence and discussing the interaction roles of Vitamin D on the autoimmune disease, we intended to overview most common systemic autoimmune diseases and we excluded specific organ autoimmune disease.

2. METHODOLOGY

Comprehensive dilated search was performed of the literature through several medical science databases; MIDLINE (PubMed), Embase, for relevant studies which published in English up to December, 30. 2016 with human subjects. several Mesh terms were used in search methods among databases which are: "Vitamin D" AND "Autoimmune diseases" combined with "Systemic lupus erythematosus" AND "Rheumatoid arthritis" AND "Multiple sclerosis". Studies references in the identified articles were searched for more relative studies to be included in our review.

3. RESULTS

- ***Vitamin D contribution in Immunologic Function:***

The systems underlying the assumption that vitamin D is related to autoimmunity are its immunomodulatory and anti-inflammatory functions, along with the existence of VDRs on the majority of immune cells. In addition, numerous epidemiological observations support this concept. Possibly the most established link in between environmental factors and autoimmunity lies with the interactions in between infections and autoimmunity [(14)]. Vitamin D sets off the inherent action to infection including the activation of Tolllike receptors, anti-bacterial peptides (i.e., cathelicidin), and cells of the inherent action [(15)]. One may suggest that by reducing infections, vitamin D modulates autoimmunity. Another example of this triangular link is the connection in between Epstein-- Barr virus (EBV), autoimmunity, and vitamin D. EBV is thought about one of the most notorious contagious agents while considering induction of autoimmunity [(16)]. Furthermore, EBV was allied with downregulation of VDR expression and vitamin D useful impacts [(17)].

There is increasing epidemiologic evidence connecting vitamin D shortage and autoimmune diseases consisting of numerous sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease and systemic lupus erythematosus (SLE) [(18)]. Reports of low serum vitamin D anticipating advancement of autoimmune disease in the future have actually been published for MS, autoimmune DM and RA [(19,20)]. There is likewise data linking decreased in utero exposure to vitamin D and islet cell autoimmunity [(21)]. Lower in utero exposure examined by a lower maternal consumption of vitamin D during pregnancy in women whose potential child was at risk of developing autoimmune DM is related to a statistically increased risk of the child developing pancreatic autoimmunity [(21)].

Vitamin D has many impacts on cells within the immune system. It prevents B cell proliferation and blocks B cell differentiation and immunoglobulin secretion [(9,22)]. Vitamin D additionally reduces T cell expansion [(23)] and leads to a shift from a Th1 to a Th2 phenotype [(24)]. It impacts T cell maturation with a skewing away from the inflammatory Th17 phenotype [(25)] and helps with the induction of T regulatory cells [(26)]. These impacts lead to reduced production of inflammatory cytokines (IL-17, IL-21) with increased production of anti-inflammatory cytokines such as IL-10 (**Figure 1A**). Vitamin D also has effects on monocytes and dendritic cells (DCs). It hinders monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-12, and TNFα [(27)]. It additionally inhibits DC distinction and maturation with conservation of an immature phenotype as evidenced by a decreased expression of MHC class II particles, co-stimulatory molecules and IL12 [(28,29)] (**Figure 1B**).

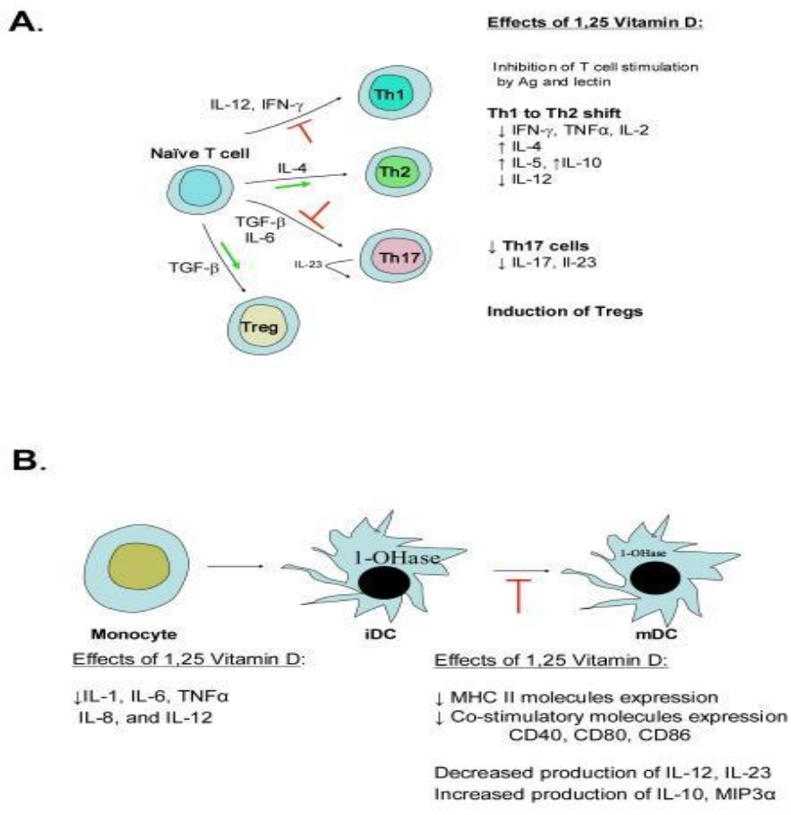

Figure 1: A. Effects of 1,25 Vitamin D on T cells include suppression of T cell proliferation, a shift from Th1 to a Th2 development, inhibition of Th17 cell development and facilitation of T regulatory cells. B. Effects of 1,25 Vitamin D on monocytes and dendric cells include inhibition of inflammatory cytokine production by monocytes and inhibition of dendritic cell differentiation and maturation. [(29)]

- ***Roles of Vitamin D in systemic autoimmune diseases:***

A. Roles of Vitamin D in Systemic Sclerosis;

Systemic sclerosis (SSc) is a chronic progressive systemic autoimmune disease of unidentified etiology. The disease is identified by excess synthesis and deposition of collagen and other extracellular matrix parts in a variety of organs and tissues. This results in vasomotor disturbances, fibrosis, atrophy of the skin and subcutaneous tissue, and multi-organ involvement. Vitamin D shortage in SSc might be associated with several factors, including inadequate sun exposure due to disability, reduced vitamin D production in the skin due to fibrosis and thickening of the skin in addition to insufficient consumption because of gut participation and malabsorption. On the other hand, low levels of vitamin D might play a role in the occurrence of the disease itself. Vitamin D deficiency was reported in numerous studies concerning patients with SSc from various locations around the globe including patients from sun-exposed location as the south of Spain and Morocco [30,31,32]. A plausible association with direct exposure to the sun was likewise recommended by Seriolo et al. [33] who reported on seasonal variations in serum levels of 25- hydroxyvitamin-D in these patients. Age and vitamin D shortage were determined as risk factors of osteoporosis and fractures in SSc patients. In addition, vitamin D status has actually been related to specific symptoms of SSc. We have actually just recently found a correlation in between vitamin D shortage and skin thickening (determined by Rodnan's Score) in SSc patients [34]. Others reported a link in between vitamin D levels and seriousness of joint pain, immunological status [30] or longer disease duration, lower DCLO, greater pulmonary arterial pressure, and greater inflammatory markers [35]. Vitamin D shortage seems to be extremely typical amongst SSc populations independent of their geographic origin. This shortage is related to osteoporosis in addition to SSc disease symptoms.

B. Rheumatoid Arthritis (RA) and Vitamin D:

RA is the most common autoimmune arthritis. The interactions between environment and genes are important in all stages of this autoimmune disease [36], of which vitamin D deficiency was found to be common in RA patients impacting approximately 65 % of them [37]. VDR polymorphism was discovered to be related to RA onset and activity [38], and experimental information showed that VDRs are present on macrophages, chondrocytes, and synovial cells from RA affected joints. Numerous studies addressed the issue of association between low vitamin D levels and RA disease. In certain research studies, RA activity, special needs scores, and scientific symptoms were related to vitamin D status [39,40]. Patel and colleagues [41] discovered a strong inverse association in between standard levels of serum 25(OH)D in patients with recently diagnosed inflammatory polyarthritis, 45 % of whom were classified as having RA at 1 year. In addition, vitamin D levels were related to standard disease activity, RA disease activity scores (DAS28), and health evaluation questionnaires scores. In another study, an inverse association between vitamin D status and pain was recorded [42]. Lastly, a recent discovery recommends that the minimized serum levels of vitamin D commonly seen in RA may increase fibroblast-like synoviocyte moderated cartilage and bone intrusion and erosions, hence supporting a possible function for vitamin D supplements to avoid or decrease bone and joint damage [43]. On the other hand, in a research study of 499 active RA patients, no correlation in between serum 25 (OH) vitamin D levels and disease activity was observed nor with reaction to therapy or radiographic progression [44]. Additional research study did not discover any link between vitamin D intake and the incidence of RA [45]. Nevertheless, it is widely accepted that treatment of vitamin D deficiency in patients with RA is relevant as deficiency prevails in this group of reasonably older patients. Vitamin D therapy might minimize the increased risk of falls and fracture in this group. Remarkably, climatotherapy at the Dead Sea induced considerable boost in 25-OHD serum levels and lowered musculoskeletal pain and disease severity [46]. While in murine designs of human arthritis, 1,25-dihydroxycholecalciferol hinders the progression of arthritis [47]. Taking it all together, although there is clinical uncertainty, one may suggest that in patients with RA, particularly older ones, and post-menopausal females, vitamin D supplementation might be useful [48].

C. Vitamin D interaction with Systemic Lupus Erythematosus (SLE);

SLE is an autoimmune disease primarily impacting ladies. The disease literally includes any of the body system or organ, while skin manifestations are among the most common. SLE patients are sensitive to sunshine exposure/ultraviolet radiation (i.e., photosensitivity) that may trigger worsening of the disease. For this reason, patients are routinely advised to prevent the sun and to utilize sunblocks thoroughly. These preventive techniques result also in obstructing UVB-induced synthesis of vitamin D3 (cholecalciferol) in the skin, and hence could be among the factors for vitamin D shortage amongst SLE patients [49]. Obviously, numerous case-control studies have shown a considerably lower level of serum vitamin D in SLE patients compared to matched healthy controls [50,51,52]. Being crucial to calcium-- phosphorus homeostasis, vitamin D shortage may contribute to osteopenia, osteoporosis, and renal disease in SLE patients likewise to healthy subjects [53]. However, the significance of vitamin D as an immune modulator raises the possibility of particular functions in SLE pathogenesis. In particular research studies, low serum concentrations of 25-OH vitamin D associated with SLE disease activity, additional supporting a pathogenic association between the two. For example, Amital et al. [54] recently studied vitamin D levels in an accomplice of 378 patients with SLE originating from Israel and Europe. In this study, a considerable inverse correlation between serum vitamin D levels and disease activity ratings as determined by the SLEDAI-2K and ECLAM scales was reported. Of note, inconsistencies regarding such association have actually been reported by other investigates [53,55], which might depend on factors such as different technique of assessment of SLE activity, time of evaluation of vitamin D level as well as geo-epidemiological and hereditary ones. Another function for vitamin D in SLE associates with SLE-associated cardiovascular disease. The excess cardiovascular risk in SLE cannot be described completely by standard cardiovascular risk factors [56]. In a current study, low vitamin D levels were considerably associated with fatigue and cardiovascular risk amongst SLE patients, although most of these associations can be discussed by BMI [57]. Therefore, whether the low levels of vitamin D are the outcome or the cause of advanced SLE disease is yet to be figured out. The many beneficial impacts of vitamin D and the high prevalence of vitamin D deficiency in SLE patients support vitamin D supplements in this group of patients [57].

4. CONCLUSION

Epidemiological, genetic, and standard studies suggest a potential function of vitamin D in the pathogenesis of specific autoimmune diseases, the majority of which show a connection in between low levels of vitamin D and disease appearance or manifestations of these disease. Vitamin D has important functions beyond those of calcium and bone homeostasis which include modulation of the innate and adaptive immune responses. Vitamin D deficiency prevails in autoimmune disease. Cells of the body immune system are capable of reacting and manufacturing to vitamin D. Immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D recommending that the helpful impacts of supplementing vitamin D lacking people with autoimmune disease may extend beyond effects on bone and calcium homeostasis. in between low levels of vitamin D and disease appearance or manifestations of these disease.

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