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## Vitamin D and the Immune System

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### Abstract

It is now clear that vitamin D has important roles in addition to its classic effects on calcium and bone homeostasis. As the vitamin D receptor is expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all capable of synthesizing the active vitamin D metabolite, vitamin D has the capability of acting in an autocrine manner in a local immunologic milieu. Vitamin D can modulate the innate and adaptive immune responses. Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection. As immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D, the beneficial effects of supplementing vitamin D deficient individuals with autoimmune disease may extend beyond the effects on bone and calcium homeostasis.

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The immune system defends the body from foreign, invading organisms, promoting protective immunity while maintaining tolerance to self. The implications of vitamin D deficiency on the immune system have become clearer in recent years and in the context of vitamin D deficiency, there appears to be an increased susceptibility to infection and a diathesis, in a genetically susceptible host to autoimmunity.

The classical actions of vitamin D are to promote calcium homeostasis and to promote bone health. Vitamin D enhances absorption of calcium in the small intestine and stimulates osteoclast differentiation and calcium reabsorption of bone. Vitamin D additionally promotes mineralization of the collagen matrix in bone. In humans, vitamin D is obtained from the diet or it is synthesized in the skin (reviewed in [1]). As vitamin D is cutaneously produced after exposure to UV B light, its synthesis is influenced by latitude, season, use of sunblock and skin pigmentation. Melanin absorbs UVB radiation inhibiting the synthesis of vitamin D from 7-dihydrocholesterol. This initial vitamin D compound is inactive and it is next hydroxylated in the liver to form 25 OH vitamin D<sub>3</sub> (25 D). 25 D is also an inactive compound, but is the most reliable measurement of an individual's vitamin D status. It is converted in the kidney to the active compound 1,25 dihydroxy vitamin D (1,25 D) or calcidiol by 1- $\alpha$ -hydroxylase (CYP27B1), an enzyme which is stimulated by PTH. 1,25 D may be further metabolized to the inactive 1,24,25 vitamin D by 24-hydroxylase (CYP24). 1,25 D levels are tightly regulated in a negative feedback loop. 1,25 D both inhibits renal 1- $\alpha$ -hydroxylase and stimulates the 24-hydroxylase enzymes, thus maintaining circulating levels within limited boundaries and preventing excessive vitamin D activity/signaling.

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1,25 D acts on the intestine where it stimulates calcium reabsorption, and upon bone, where it promotes osteoblast differentiation and matrix calcification. The active hormone exerts its effects on these tissues by binding to the vitamin D receptor (VDR). This complex dimerizes with the retinoid X receptor (RXR) and the 1,25D-VDR-RXR heterodimer translocates to the nucleus where it binds vitamin D responsive elements (VDRE) in the promoter regions of vitamin D responsive genes and induces expression of these vitamin D responsive genes.

Many tissues other than the skeletal and intestine express the VDR including cells in the bone marrow, brain, colon, breast and malignant cells and immune cells suggesting that vitamin D may have functions other than calcium and bone homeostasis[2]. Additionally, tissues other than the kidney express 1- $\alpha$ -hydroxylase and are capable of converting 25 D to 1,25 D, in non-renal compartments[1, 3-4]. Therefore, in addition to its endocrine functions, vitamin D may act in a paracrine or autocrine manner. Some of the more recently recognized non-classical actions of vitamin D include effects upon cell proliferation and differentiation as well immunologic effects resulting in 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 necessary machinery to synthesize and respond to 1,25 D, vitamin D may act in a paracrine or autocrine manner in an immune environment. Moreover, local levels of 1,25 D may differ from systemic, circulating levels as local regulation of the enzymes synthesizing and inactivating vitamin D are different from the controls originating in the kidney. The extrarenal 1- $\alpha$ -hydroxylase enzyme in macrophages differs from the renal hydroxylase as it is not regulated by PTH[5]. Instead, it is dependent upon circulating levels of 25 D or it may be induced by cytokines such as IFN- $\gamma$ , IL-1 or TNF- $\alpha$ [6]. Furthermore, the macrophage 24 hydroxylase enzyme is a non-functional splice variant, so there is no negative feedback of local 1,25 D production by 1,25 D.

## Vitamin D and Protective Immunity

Vitamin D has been used (unknowingly) to treat infections such as tuberculosis before the advent of effective antibiotics. Tuberculosis patients were sent to sanatoriums where treatment included exposure to sunlight which was thought to directly kill the tuberculosis. Cod liver oil, a rich source of vitamin D has also been employed as a treatment for tuberculosis as well as for general increased protection from infections[7].

There have been multiple cross-sectional studies associating lower levels of vitamin D with increased infection. One report studied almost 19,000 subjects between 1988 and 1994. Individuals with lower vitamin D levels (<30 ng/ml) were more likely to self-report a recent upper respiratory tract infection than those with sufficient levels, even after adjusting for variables including season, age, gender, body mass and race[8]. Vitamin D levels fluctuate over the year. Although rates of seasonal infections varied, and were lowest in the summer and highest in the winter, the association of lower serum vitamin D levels and infection held during each season. Another cross-sectional study of 800 military recruits in Finland stratified men by serum vitamin D levels[9]. Those recruits with lower vitamin D levels lost significantly more days from active duty secondary to upper respiratory infections than recruits with higher vitamin D levels (above 40nmol). There have been a number of other cross-sectional studies looking at vitamin D levels and rates of influenza [10] as well as other infections including bacterial vaginosis[11] and HIV[12-13]. All have reported an association of lower vitamin D levels and increased rates of infection.

Results of studies looking at potential benefits of administering vitamin D to decrease infection have not been consistent, most likely secondary to a number of methodologic concerns[14]. One recent well-designed prospective, double blind placebo study using an objective outcome, nasopharyngeal swab culture (and not self report), and a therapeutic dose

of vitamin D showed that vitamin D administration resulted in a statistically significant (42%) decrease in the incidence of influenza infection[15].

The beneficial effects of vitamin D on protective immunity are due in part to its effects on the innate immune system. It is known that macrophages recognize lipopolysaccharide LPS, a surrogate for bacterial infection, through toll like receptors (TLR). Engagement of TLRs leads to a cascade of events that produce peptides with potent bactericidal activity such as cathelicidin and beta defensin 4[16]. These peptides colocalize within phagosomes with injected bacteria where they disrupt bacterial cell membranes and have potent antimicrobial activity [17].

Vitamin D plays an important part in the innate antimicrobial response. TLR binding leads to increased expression of both the 1- $\alpha$ -hydroxylase and the VDR[17-18]. This results in binding of the 1,25 D-VDR-RXR heterodimer to the VDREs of the genes for cathelicidin and beta defensin 4 and subsequent transcription of these proteins. Transcription of cathelicidin is absolutely dependent on sufficient 25 D[17]. It is now clear that transcription of beta defensin 4 requires binding of NFkB to appropriate response elements on the beta defensin 4 RNA[19]. TLR 2-1 signaling facilitates IL-1 receptor engagement which results in translocation of NFkB to its binding site[19].

## Vitamin D and Autoimmune Disease

There is increasing epidemiologic evidence linking vitamin D deficiency and autoimmune diseases including multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus (DM), inflammatory bowel disease and systemic lupus erythematosus (SLE) (reviewed in reference[20]). Reports of low serum vitamin D predicting development of autoimmune disease in the future have been published for MS, autoimmune DM and RA[21-23]. There is also data linking decreased in utero exposure to vitamin D and islet cell autoimmunity[24]. Lower in utero exposure assessed by a lower maternal intake of vitamin D during pregnancy in women whose prospective child was at risk of developing autoimmune DM is associated with a statistically increased risk of the child developing pancreatic autoimmunity.

Vitamin D has also been shown to facilitate progression of existing autoimmune disease. In one study, 161 patients with an early undifferentiated connective tissue disease were followed for a mean of over 2 years[25]. Most patients did not progress and remained in an undifferentiated state. Thirty-five (21%) patients went on to develop a defined rheumatologic diagnosis including RA, SLE, Mixed Connective Tissue Disease, and Sjogren's Disease while 126 did not progress. Baseline characteristics of the two groups were similar. Importantly, the mean vitamin D level was significantly lower in the group that progressed to a definitive disease.

There have been many studies of vitamin D status in lupus patients from across the globe (reviewed in [26]). Vitamin D levels are typically lower in patients than in disease or normal controls. Deficiency of vitamin D is extremely common, often with more than 50% of lupus patients with deficient levels and severe deficiency (vitamin D levels less than 10ng/ml) is not uncommon. Disease activity has been shown to correlate inversely with vitamin D in many but not all studies. Similar correlations between low levels of vitamin D and disease activity and severity have been observed in other autoimmune diseases such as MS and RA[27-30].

## Vitamin D and Immunologic Function

Vitamin D has numerous effects on cells within the immune system. It inhibits B cell proliferation and blocks B cell differentiation and immunoglobulin secretion[31-32].

Vitamin D additionally suppresses T cell proliferation[33] and results in a shift from a Th1 to a Th2 phenotype[34-35]. Furthermore, it affects T cell maturation with a skewing away from the inflammatory Th17 phenotype[36-37] and facilitates the induction of T regulatory cells[38-41]. These effects result in decreased 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 inhibits monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNF $\alpha$ [42]. It additionally inhibits DC differentiation and maturation with preservation of an immature phenotype as evidenced by a decreased expression of MHC class II molecules, co-stimulatory molecules and IL12[43-45] (Figure 1B).

Inhibition of DC differentiation and maturation is particularly important in the context of autoimmunity and the abrogation of self tolerance. Antigen presentation to a T cell by a mature DC facilitates an immune response against that antigen while antigen presentation by an immature DC facilitates tolerance. Self-antigens are abundant in the normal state from physiologic cell death and turnover. However, presentation of these self-antigens is usually by immature DCs so that tolerance to self is maintained.

Given the importance of vitamin D for a functional immune system and the profound deficiency observed in autoimmune disease, as well as the correlation of deficiency with more active disease, an important issue is whether or not the immune components in autoimmune disease are capable of responding appropriately to vitamin D. Immune cells (B cells, T cells, monocytes, DCs) from multiple autoimmune diseases appear to respond to the immunomodulatory effects of vitamin D. Examples of vitamin D responsiveness by immunologic components in different autoimmune disease follow: B cells: Abnormalities of B cells from lupus patients may be partially reversed by vitamin D. Both spontaneous and stimulated immunoglobulin production from B cells from active lupus patients are significantly decreased by pre-incubating cells with 1,25 vitamin D[46]. Additionally, preincubation with vitamin D significantly decreases spontaneous production of anti-DNA antibodies by approximately 60%[46]. T cells: T cells from patients with MS respond to vitamin D. The proliferation of stimulated CD4 cells from MS patients and controls are similarly inhibited after preincubation in increasing concentrations of vitamin D[27]. Moreover, Th17 polarized T cells from both controls and MS patients respond when incubated with vitamin D; both are downregulated with diminished production of IL-17 and gamma interferon[27]. Monocytes: Vitamin D inhibits the production of inflammatory cytokines (IL-1, TNF $\alpha$ ) by monocytes. Cytokine production by monocytes from both normal controls and from patients with autoimmune diabetes (type 1 or latent autoimmune diabetics) is significantly diminished by vitamin D[47]. TLR 4 stimulation by LPS or LTA (leipoteichoic acid) is similarly inhibited by exposure to vitamin D[47]. DCs: Lupus DCs are susceptible to the effects of vitamin D. LPS induced DC maturation is inhibited by preincubation with vitamin D resulting in suppressed expression of HLA class II and co-stimulatory molecules. The response of lupus cells to LPS stimulation is similarly suppressed by vitamin D[48]. Furthermore, vitamin D affects the expression of the interferon (IFN) signature in SLE. Interferon is produced by plasmacytoid DCs; the IFN signature refers to the overexpression of IFN  $\alpha$  inducible genes in peripheral blood mononuclear cells (PBMC s) of lupus patients[49]. The signature occurs in approximately 50% of patients and correlates with disease activity[50-52]. We have observed that interferon inducible genes are overexpressed in lupus patients with low serum vitamin D compared to normal serum vitamin D (Figure 2A). Expression of these interferon inducible genes may be diminished in lupus patients after receiving vitamin D supplementation (Figure 2B). In fact, we have observed that an IFN signature response, the decrease in expression of IFN inducible genes is 2.1 times more likely to occur in vitamin D supplemented lupus patients (unpublished data Ben-Zvi, I). There is currently a double-blind

placebo controlled NIH sponsored trial (ClinicalTrials.gov identifier: NCT00710021) assessing the potential ability of vitamin D to suppress the interferon signature in patients with SLE.

## Conclusions

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 is prevalent in autoimmune disease. Cells of the immune system are capable of synthesizing and responding to vitamin D. Immune cells in autoimmune diseases are responsive to the ameliorative effects of vitamin D suggesting that the beneficial effects of supplementing vitamin D deficient individuals with autoimmune disease may extend beyond effects on bone and calcium homeostasis.

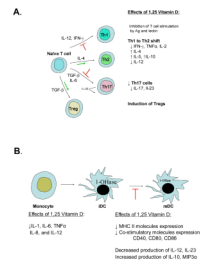
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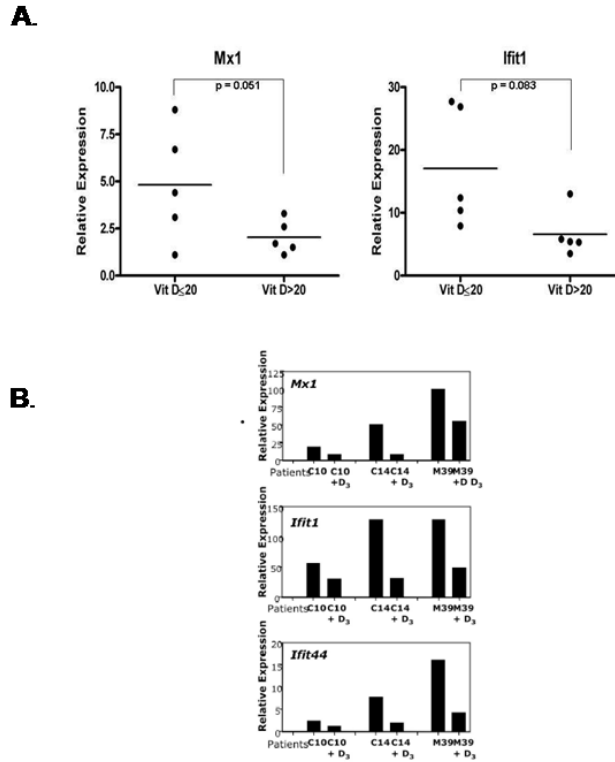
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**Figure 1.**

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 dendritic cells include inhibition of inflammatory cytokine production by monocytes and inhibition of dendritic cell differentiation and maturation.





**Figure 2.**

A. Relative expression of 2 IFN $\alpha$  inducible genes, Mx1 and Ifit1 in SLE patients with vitamin D deficiency ( $\leq 20$ ng/ml) and sufficiency ( $>20$ ng/ml). Relative expression of these genes was determined by RTPCR on PBMCs from clinically stable SLE patients. Expression of interferon inducible genes is higher in patients with SLE with low serum vitamin D (unpublished data Ben-Zvi, I). B. Relative expression of 3 IFN $\alpha$  inducible genes (Mx1, Ifi1 and Ifit44) before and after (+D<sub>3</sub>) supplementation with vitamin D<sub>3</sub> in 3 SLE patients. Vitamin D supplementation reduces expression of IFN $\alpha$  inducible genes (unpublished data Ben-Zvi, I).