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# VITAMIN D AND IMMUNITY

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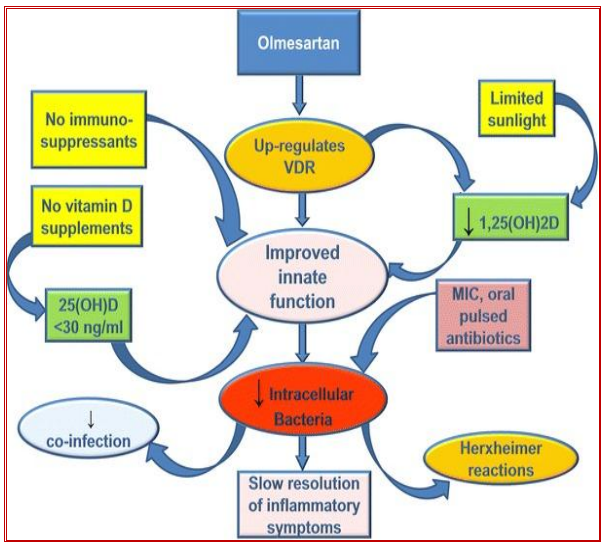
## ABSTRACT

Vitamin D is well known for its classic role in the maintenance of bone mineral density. However, vitamin D also has an important "non-classic" influence on the body's immune system by modulating the innate and adaptive immune system, influencing the production of important endogenous antimicrobial peptides such as cathelicidin, and regulating the inflammatory cascade. Multiple epidemiological studies in adults and children have demonstrated that vitamin D deficiency is associated with increased risk and greater severity of infection, particularly of the respiratory tract. Although the exact mechanisms by which vitamin D may improve immune responses to infection continue to be evaluated, vitamin D supplementation trials of prevention and adjunct therapy for infection are underway. Given its influence on the immune system and inflammatory cascade, vitamin D may have an important future role in the prevention and treatment of infection.

**KEYWORDS:** Antimicrobial, cathelicidin, immune system, infection, inflammation, vitamin D.

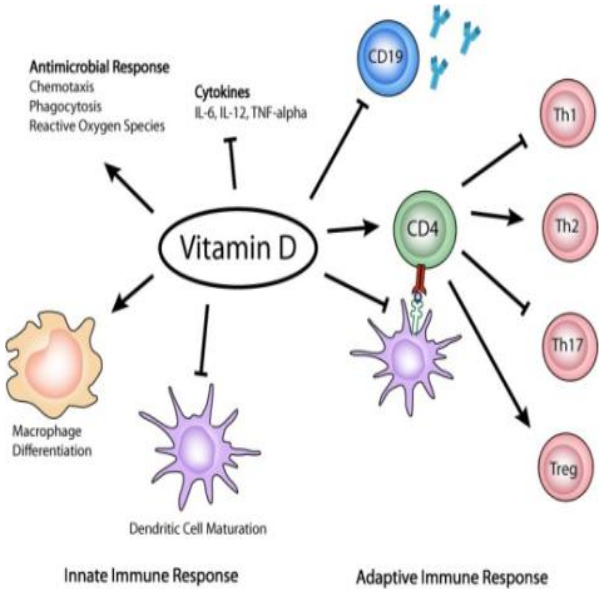



## INTRODUCTION

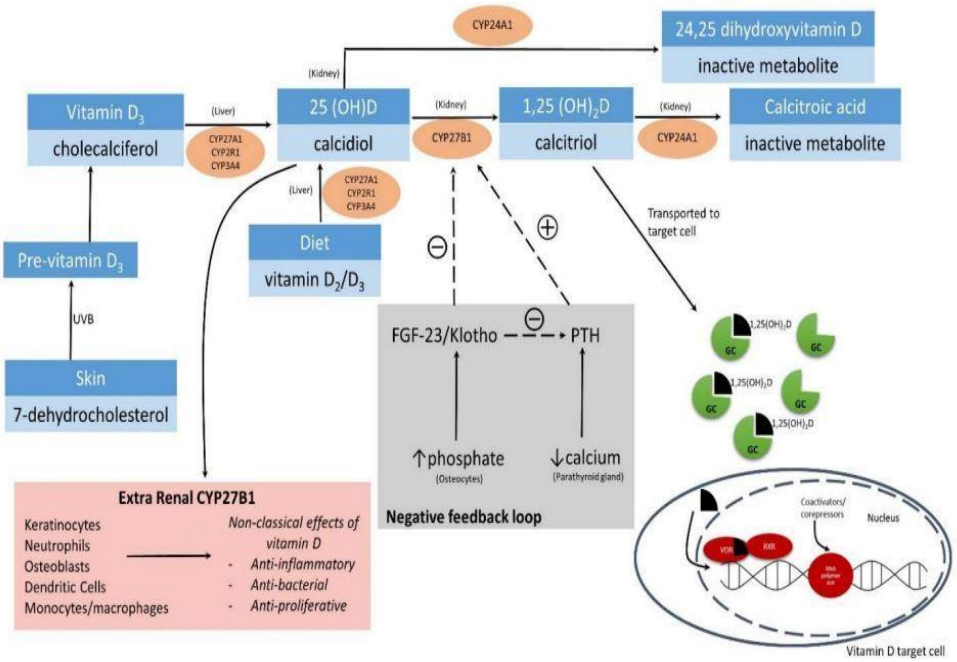
The serum level of Vitamin D was correlated inversely with level of parathyroid hormone and this observation has urged the introduction of a new term called Vitamin D insufficiency.[2,6] The Vitamin D insufficiency is defined by sub-optima level of Vitamin D that is not rachitic.[4] Geographical, social, or economic factors can affect the Vitamin D status in different populations and Vitamin D insufficiency is considered as worldwide epidemic.[2,8] Vitamin D has important function other than calcium and bone homeostasis and epidemiological studies documented the possible link between Vitamin D insufficiency and various human diseases including autoimmune, infectious, cardiovascular, neurologic, immune deficiency and even cancer.[2-3] Vitamin D has a paracrine or autocrine function beside the endocrine function. The active Vitamin D manifests its diverse biological effects by binding to the VDR. In the same time, many tissues beside the kidney express 1-α-hydroxylase and can convert the 25 D to 1, 25 D.[3] VDR is expressed in organs and tissues involved in bone metabolism and in more than thirty-five target tissues that are not involved in bone metabolism and explains the pleiotropic effect of Vitamin D hormone.[3] These tissues include T/B lymphocytes, antigen presenting cells (APCs), monocytes, hematopoietic cells, cardiac and skeletal muscle cells, endothelial cells, islet cells of the pancreas, neurons and placental cells.[3] VDR activation either directly or indirectly regulate about 100-1250 genes that represent about 0.5-5% of the total human genome and include the genes responsible for the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis.[3,5] Because the immune cells express VDR and can synthesize the active Vitamin D metabolite and in the same time, Vitamin D can modulate the innate and adaptive immune responses, it is reasonable that the Vitamin D deficiency will be associated with increased autoimmunity and increased susceptibility to infection.[29] The VDR gene is located on chromosome 12 and is a member of trans-acting transcriptional regulatory factors that include the steroid and thyroid hormone receptors.[3,5] The VDR gene contains 11 exons and spans approximately 75 kb. The exons 1A, 1B, and 1C are present in the noncoding 5-prime end and its translated product is encoded by 8

additional exons. Exons 2 and 3 are involved in DNA binding, and exons[7-9] are involved in binding to Vitamin D.[35-37] Vitamin D binds to VDR and then dimerise with the retinoid X receptor (RXR). This complex of vitamin D-VDR-RXR translocates to the nucleus and binds in the promoter of Vitamin D responsive genes to Vitamin D responsive elements (VDRE) with subsequent expression of this. Vitamin D responsive genes.[2,9] DNA sequence variations "polymorphisms" which occur frequently in the population can have modest and subtle but true biological effects. Their abundance in the human genome as well as their high frequencies in the human population have made them targets to explain variation in risk of common diseases. Recent studies have indicated many polymorphisms to exist in the VDR gene.[3,8] Over 470 VDR single nucleotide polymorphisms (SNPs) are known.[3,9] Their distribution and frequency vary among ethnic groups. Most of the work done on VDR polymorphisms has been conducted in Caucasian populations and has focused on six SNPs: rs10735810 or FokI in exon 2, rs1544410 or BsmI in intron 8, rs731236 or TaqI in exon9, rs7975232 or ApaI in intron 8, rs757343 or Tru91 in intron 8 and the poly (A) mononucleotide repeat in the 3′-untranslated region (UTR).[9] The discovery of the VDR in the cells of the immune system and the fact that activated dendritic cells produce the Vitamin D hormone suggested that Vitamin D could have immunoregulatory properties. The most evident effects of the D-hormone on the immune system seem to be in the down-regulation of the Th1-driven autoimmunity. Low serum levels of Vitamin D might be partially related, among other factors, to prolonged daily darkness (reduced activation of the previtamin D by the ultra violet B sunlight), different genetic background (i.e. VDR polymorphism) and nutritional factors and explain to the latitude-related prevalence of autoimmune diseases such as rheumatoid arthritis by considering the potential immunosuppressive roles of Vitamin D. The Vitamin D plasma levels have been found inversely correlated at least with the RA disease activity showing a circannual rhythm (more severe in winter). Recently, greater intake of Vitamin D was associated with a lower risk of RA as well as a significant clinical improvement was strongly correlated with the immunomodulating potential in Vitamin D-treated RA patients.[4,2] In immune cells, activation of VDR leads to production of downstream gene products. These proteins have potent antiproliferative, pro-differentiative, and immunomodulatory effects.[4,3] Active Vitamin D inhibits several intracellular pathways such as the nuclear factor-κB (NF-κB) signaling pathway, X-box binding protein 1 (XBP1) and endoplasmic reticulum to nucleus signaling 1 (ERN1). This inhibition has been observed in T cells, monocytes or macrophages[4] and subsequently may influence the expression of various essential secreted molecules on the cell surface. On the other hand, the active Vitamin D has no inhibitory effect on the expression of other transcriptional regulators such as Paired box-5 (PAX-5), B-cell lymphoma 6 (BCL-6), activation, and IFN-regulatory factor 4 (IRF4).[4,3]

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 methodological 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.[3]




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 lipopolysacharide 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 bacterialcidal activity such as cathelicidin and beta defensin 4.[6] These peptides colocalize within phagosomes with ingested bacteria where they disrupt bacterial cell membranes and have potent anti-microbacterial activity.[7]




**Vit.D and Immunologic Functions**

Vitamin D has numerous effects on cells within the immune system. It inhibits B cell proliferation and blocks B cell differentiation and immunoglobulin secretion.[3,2] Vitamin D additionally suppresses T cell proliferation[3] and results in a shift from a Th1 to a Th2 phenotype.[3] Furthermore, it affects T cell maturation with a skewing away from the inflammatory Th17 phenotype[3,7] and facilitates the induction of T regulatory cells.[3,4] 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 monocytes production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNFα.[4] 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[4] 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]

**Vit.D and Immunological Functions**

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 methodological concerns.[4] 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.[1,5] 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 lipopolysacharide 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 bacterialcidal activity such as cathelicidin and beta defensin 4.[6] These peptides colocalize within phagosomes with ingested bacteria where they disrupt bacterial cell membranes and have potent anti-microbacterial activity.[7] Vitamin D plays an important part in the innate antimicrobial response. TLR

binding leads to increased expression of both the 1-α-hydroxylase and the VDR.[7,8] 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.[1,7] It is now clear that transcription of beta defensin 4 requires binding of NFkB to appropriate response elements on the beta defensin 4 RNA.[9] TLR 2-1 signaling facilitates IL-1 receptor engagement which results in translocation of NFkB to its binding site.[1,9]

## VIT.D AND IMMUNOLOGICAL FUNCTIONS

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.[3] There is also data linking decreased inutero exposure to vitamin D and islet cell autoimmunity.[2,4] 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.[2,5] 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.[2,6] 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.[2]

## CONCLUSION

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. VDR is expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all are capable of synthesizing and responding to Vitamin D. Vitamin D interaction with immune system is one of the most well-established non-classical effects of Vitamin D. Vitamin D can modulate the innate and adaptive immune responses. The ability of Vitamin D to influence normal human immunity will be highly dependent on the vitamin D status of individuals; therefore, deficiency or insufficiency of Vitamin D is associated with increased autoimmunity and infection. The 25- hydroxyvitamin $D_3$ ($25OHD_3$) is the main circulating metabolite of Vitamin D and is the most reliable measurement of an individual's Vitamin D status. The Vitamin D supplements in deficient individuals will have beneficial immune-modulator effects on the autoimmune status.

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