

VITAMIN D AND THE IMMUNE SYSTEM**Shkiryak A.***CEO and chief medical officer "Shkiryak Clinic"*

Ukraine

Neurosurgeon

MD, MsSc

ORCID: <https://orcid.org/0000-0002-2282-8285>**Khanenko S.***"Shkiryak Clinic"*

Ukraine

Family doctor

MD, MBA

ORCID: <https://orcid.org/0009-0000-4237-1158><https://doi.org/10.5281/zenodo.15024979>**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 are 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.

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 D₃ (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 calcitriol by 1- α -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- α -hydroxylase and stimulates the 24-hydroxylase enzymes, thus maintaining circulating levels within limited boundaries and preventing excessive vitamin D activity/signaling.

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- α -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- α -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- γ , IL-1 or TNF- α (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.

Keywords: vitamin D, immunity, infections

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- α -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).

CONCLUSIONS

Vitamin D has important functions beyond those of calcium and bone homeostasis which include modulation of the innate and adaptive immune responses.

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