Clinical Microbiology: Open Access
ISSN: 2327-5073

Yildirim et al., Clin Microbial 2013, 2:4
DOI: 10.4172/2327-5073.1000116

Review Article Open Access

# Infection Inflammation and Vitamin D

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## Abstract

Vitamin D is essential for the organism and it interacts with a lot of systems in mammalians. Vitamin D deficiency is common in the world. Many studies have shown that chronic vitamin D deficiency may have serious adverse consequences such as increased risk of hypertension, multiple sclerosis, rheumatoid arthritis, infections and malignancy, autoimmune diseases. New ones have been added on these adverse consequences nowadays.

Vitamin D has got both stimulatory and antiproliferative effects on the immune system. This paradoxical effects of 1, 25-$(OH)_2D_3$ leads to discussions about the relationship between the immune systems and vitamin D. Inflammatory markers can be increased with other reasons in patients with vitamin D deficiency. Vitamin D deficiency may occur due to insufficient intake, hepatic disease, renal disease, loss of vitamin D binding protein etc. Many confounding factors will affect this relationship in both cases.

Despite large-scaled studies found a positive relationship between vitamin D deficiency and some markers of inflammation but on the contrary many studies cannot find this relationship. The aim of this brief review is to discuss whether plasma 25 hydroxy vitamin D [25-(OH) D] level is associated with inflammatory markers in general population and in patients with chronic kidney disease. For this purpose, the old and new data related to the immune systems and vitamin D will be examined.

**Keywords:** Vitamin 25-(OH) D; Immune system; Inflammation

## Introduction

Functions of Vitamin D are to provide calcium absorption from gut, regulate bone remodeling, secretion of insulin from pancreas beta cells, and regulate cell cycles, the renin-angiotensin system, and the development of musculoskeletal systems. Most cells in the body express vitamin D receptors (VDRs) and 1α-hydroxylase, thereby permitting local production of 1, 25 dihydroxycholecalciferol [1,25-$(OH)_2$ $D_3$], which has paracrine effects.

All vitamin D metabolites have got different quantities of the effect of active vitamin D. But 1, 25-$(OH)_2$ $D_3$ is the most active one. However, circulating levels of 25-hydroxy vitamin D [25-(OH) D] is higher in 500-100 times. Thereby, 25-(OH) D levels are more valuable in the evaluation of vitamin D stores.

Vitamin D deficiency is commonly seen in the world. Studies have shown that chronic vitamin D deficiency may have serious adverse consequences such as increased risk of hypertension, multiple sclerosis, rheumatoid arthritis. It has been associated with increased risk of development of infections and malignancy such as cancer of the colon, prostate, breast, ovary. Vitamin D deficiency has also been shown to be related to increased tendency for development of several autoimmune diseases such as type-1 diabetes and inflammatory bowel diseases.

Findings of association of some autoimmune-inflammatory disorders with vitamin D deficiency-insufficiency status indicate the clinical importance of vitamin D again. Vitamin D enhances anti-bacterial response in the innate immune system and anti-inflammatory effects in adaptive immune system. The possible clinical use of vitamin D in certain types of autoimmune disorders and prophylaxis and treatment of some cancers is the issue of scientific discussions.

The researches performed during the past twenty-five years revealed that 1, 25-$(OH)_2D_3$ has also a significant immune modulatory effect. Although large-scaled studies have found a positively relationship between vitamin D deficiency and inflammation markers, there are also many studies that cannot find this relationship. It is known that 1, 25-$(OH)_2D_3$ has anti-inflammatory effects. The aim of this brief review is to discuss the relationship between 1, 25-$(OH)_2D_3$ and inflammatory markers in general population without chronic kidney disease (CKD) and in patients with CKD.

## Vitamin D and Inflammatory Markers

Vitamin D homeostasis seems to be critical for many tissues to maintain normal proliferation and differentiation. A regulatory role for vitamin D homeostasis in the immune system has been clearly demonstrated in animal and human studies. One of site of action of Vitamin D in the immune system is T lymphocytes.

$CD4^+$ T cells expressed VDRs [1]. When active, VDR affects transcription of at least 913 genes and impacts processes ranging from calcium metabolism to expression of key antimicrobial peptides in these cells.

Vitamin D has got important antimicrobial effect via activation of VDRs. This vitamin increases the expression of VDRs in B cells. Furthermore, it suppresses IgE secretion in B cells. In NK cells,1, 25-$(OH)_2D_3$ inhibits interferon (IFN)-γ. Additional studies have been revealed that, the expression of a proinflammatory transcription factor; nuclear factor kappa B (NF-κB) has increased in 25-(OH) D deficient subjects [2]. NF-κB is a protein complex that controls the transcription of DNA and plays a key role in regulating the immune response to infection (kappa light chains are critical components of immunoglobulins). Incorrect regulation of NF-κB has been linked to

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**Received** April 17, 2013; **Accepted** May 16, 2013; **Published** May 20, 2013

**Citation:** Yildirim I, Magden K, Hur E (2013) Infection Inflammation and Vitamin D. Clin Microbial 2: 116. doi:10.4172/2327-5073.1000116

cancer, inflammatory and autoimmune diseases, septic shock, and viral infection [2].

Vitamin D could control inflammation through regulation of NF-κB. In a study using a mouse model of obstructed nephropathy, paricalcitol reduced the infiltration of inflammatory T-cells and renal expression of the RANTES (regulated and normal T-cell expressed and secreted) protein [3]. These authors could demonstrate that induction of the pro-inflammatory RANTES protein, which is dependent on NF-κB signaling, was prevented by repressing the NF-κB-mediated gene transcription through the nuclear VDR.

Vitamin D has got a lot of activity on antigen-presenting cells (monocytes, macrophages, dendritic cells). Major histocompatibility complex (MHC) class 2 expressions and stimulant receptors such as CD-40, CD-80, CD-86 have been decreased in 1, 25-$(OH)_2D_3$ treated monocyte [4]. 1, 25-$(OH)_2D_3$ also inhibits some maturating inducing proteins ($CD1_{a,}$ CD83) [5].

1,25-$(OH)_2D_3$ stimulates the genetic expression of antimicrobial peptides in human monocytes, neutrophils, and epithelial cells [6]. 1, 25-$(OH)_2D_3$ enhances monocyte chemotactic and fagositic functions [7]. Differentiation of monocyte-macrophage series provides by vitamin D. 1, 25-$(OH)_2D_3$ induces a transcription factor (C/EBP-β) that plays a critical role in antiviral, antibacterial, anti-tumoral effect [8]. In addition, vitamin D also increases chemotaxis and cytotoxicity against tumor cells and bacteria [5], inhibits the maturation of dendritic cells, inhibits proinflammatory cytokines produced by monocytes and macrophages.

Helper T 1 (Th1) and Helper T 2 (Th2) cells are direct targets of 1, 25-$(OH)_2D_3$. T helper cells are a sub-group of lymphocytes that play an important role particularly in the adaptive immune system. 1, 25-$(OH)_2D_3$ inhibits the proliferation of purified Th cells, decrease the production of IFN-γ, interleukin (IL)-2, IL-5 [1,9] and IL 17 [5] in the Th1 cells. This information related to IL 5 is controversial because other studies have demonstrated that vitamin D increases the production of IL 5 [5,10]. IFN-γ directly activates other immune cells, such as macrophages and natural killer cells. IL-2 is necessary for the growth, proliferation, and differentiation of T cells to become "effector" T cells. IL-5 is produced by Th2 cells and mast cells. IL-5 stimulates B cell growth and increases immunoglobulin secretion. It is also a key mediator in eosinophil activation. These anti-proliferative activities of 1, 25-$(OH)_2 D_3$ may influence cancer risk [11].

1, 25-$(OH)_2D_3$ increases the production of IL-4 in Th2 cells [1]. IL-4, is a cytokine that induces differentiation of naive helper T (Th0) cells to Th2 cells. IL-4 increases B-cell and T-cell proliferation, decreases the production of Th1 cells, macrophages, IFN-γ, and IL-12 produced by dendritic cell.

Unfortunately some studies failed to show these relationships between circulating cytokines and vitamin Shea et al. showed that plasma 25-(OH) D were not significantly associated with overall inflammation (CD40 ligand, CRP, fibrinogen, intercellular adhesion molecule-1, myeoloperoxidase, osteoprotegerin, monocyte chemoattractant protein, plasma tumor necrosis factor receptor-2, Tumor necrosis factor α, P-selectin (except IL-6), in participants from Framingham Offspring Study (n=1381, mean age 59 years) [12]. Another study by Elanor et al. also did not show that vitamin D supplementation changed circulating cytokine levels included IL-2, 4, 5, 6, 8, 10, 13, GM-CSF, IFN-$\gamma$ and TNF-$\alpha$ among healthy adults [13].

Briefly, the effect of vitamin D in the immune system is an enhancement of innate immunity and regulation of acquired immunity. It has been known that a relationship between vitamin D deficiency and the prevalence of some autoimmune disorders such as Type 1 diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease etc. In other words, vitamin D deficiency is associated with an exacerbation of Th1 immune response.

Several studies have demonstrated a higher prevalence of vitamin D deficiency in SLE patients when compared to individuals with healthy individuals. In a study, Muller et al. [14] observed that the levels of vitamin D were significantly lower in SLE patients (mean 13 ng/mL) when compared to healthy controls (27 ng/mL). Huisman et al. [15] observed that 50% of SLE patients had vitamin D deficiency (cut off <50 nmol/L or 20 ng/mL).

The effectiveness of 1, 25-$(OH)_2D_3$ for suppression of autoimmune diseases in vivo has been shown to depend on IL-2 [16] and IL-4 [17] secretion. A 3-fold increase in the risk of developing diabetes has been determined in children with vitamin D deficiency [18]. In contrast, an inverse relationship has been shown between vitamin D intake and the risk of development of diabetes mellitus (DM) in early childhood [19]. Another study with a 30-year follow-up observed a significant reduction in the prevalence of DM1 in children who received daily vitamin D supplementation (RR=0.12) [20].

Some studies have shown the association of vitamin deficiency and multiple sclerosis (MS). Vitamin D plays role not only in the prevention of its development but in the reduction of relapse rates [21,22]. The risk of MS decreases considerably (up to 40%) with a high ingestion of vitamin D in Caucasian individuals. The same benefit was not observed in individuals of African descent and Hispanics [21].

Low serum levels of 25(OH) D have been found in inflammatory bowel disease (IBD). In a study by Jahnsen et al. [23], the authors observed vitamin D deficiency in 27% of the patients with Crohn's disease and in 15% of those with ulcerative colitis. It seems that a combination of factors, such as low ingestion and malabsorption of vitamin D, and decreased exposure to the sun, are responsible for the higher frequency of vitamin D deficiency in IBD [24]. Van Etten et al. reported that immune response by Th1 cells to self proteins leads to autoimmune diseases (Type 1 DM, inflammatory bowel disease). Cantorna et al. also reported an increased risk of inflammatory bowel disease in vitamin D deficiency [25].

One of immunosuppressive effects of vitamin D increases the level of IL 8. IL 8 is a well-known inflammatory marker. It has been shown that both treatments with paricalcitol and calcifediol produced a significant decrease in levels of IL-8 in many studies [26]. In another study, a vitamin D analog have augmented IL-8 production by human monocytic cells in response to various microbe-related synthetic ligands, especially NOD2 agonistic muramyldipeptide [27].

1, 25-$(OH)_2D_3$ actives Th2 type transcription factor [trans-acting T-cell-specific transcription factor (GATA-3)] expressions [28] GATA-3 regulates luminal epithelial cell differentiation in the mammary gland. GATA-3, related to asthma. Moreover, treatment of vitamin D deficiency leads the prevention of the development of juvenile diabetes in early childhood, but also increases the risk of development of allergic diseases in late childhood [29].

Human cathelicidin antimicrobial peptide (cAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1, 25-dihydroxyvitamin D [30]. Cathelicidin (LL-37) has potent anti-endotoxin effect and it is localized in the skin. Dysfunction of cathelicidins, is directly related in the pathogenesis of several cutaneous diseases, such as atopic dermatitis, rosacea, and psoriasis. Psoriasis is an autoimmune disease with characterized by an increase of Th1 immune response. A topical vitamin D analogue, 22-Oxa-1 alpha, 25-$D_3$ found to be effective in the treatment of psoriasis [31]. The use of vitamin D and its analogues in the treatment of psoriasis has been studied for several years, demonstrating the effects of calcitriol on the improvement of psoriatic lesions. However, long term use of those agents is limited due to hypercalcemia and hypercalciuria.

Furthermore, vitamin D inhibits the activation of TNF alpha converting enzyme (TACE) [32]. TACE activation in renal cells gives rise to subsequent release of TNF-alpha, ICAM-1, and VCAM-1 into the circulation, promoting systemic inflammation. However, activation of TACE can be blocked by active vitamin D preparations [33]. TACE activation is usually secondary to activation of the renal RAS system, which is also directly inhibited by VDR activation [32,34]. Thus, vitamin D suppresses TACE activation and subsequent inflammation on multiple levels.

Little is known about the effects of vitamin D supplementation in the prevention and treatment of graft rejections; however 1, 25-$(OH)_2D_3$ induces apoptosis, activates IL-10, inhibits IL-12 [35]. So it suppresses the ability of antigen-presenting dendritic cells [36]. This state provides immunosuppressive effect on transplantation immunology. Reduction in rate of renal graft loss has been determined in patients who received 1, 25-$(OH)_2D_3$ [36]. In experimental models, it has been found to be successful in reducing the risk of graft rejection [37]. Eventually, it is believed that its supplementation is adequate for the control of graft rejection and vitamin D has beneficial effects on renal allograft function.

## Vitamin D and Infectious Diseases

Little is known about the role of vitamin D and 1,25-$(OH)_2D_3$ in regulating immune responses to infectious diseases. However the number of studies that found a link between 25-(OH) D and viral, bacterial or other infections, increase every day. Present epidemiologic and experimental data has been demonstrated that vitamin D has a protective effect against some infectious diseases. Vitamin D deficiency also has been correlated with increased rates of infection in several studies.

As mentioned above, AMPs are initiators of innate immune responses against viral, fungal and bacterial attack. The regulation of the cathelicidin antimicrobial peptide (CAMP) gene is a primate-specific adaptation and is not conserved in other mammals. The interaction between 1, 25-$(OH)_2D_3$ and Toll-like receptors (TLRs) signaling and the direct induction by 1, 25-$(OH)_2D_3$ of AMP gene expression provide a strong molecular defense for against infectious diseases. TLRs are usually expressed in macrophages and dendritic cells that recognize structurally conserved molecules derived from foreign microorganisms. Activated macrophages and dendritic cells express extrarenal 1-alfa-hydroxylase (CYP27B1) [38-40], which, is regulated primarily by immune inputs, mainly gamma interferon and agonists of the TLR pattern recognition receptors. In addition, CAMP and some beta-defensins that induced by 1,25-$(OH)_2D_3$ can function as chemoattractants for neutrophils, monocytes, and other cellular components of immune responses [41].

Vitamin D's anti-viral mechanism may be related to its ability to up-regulate the anti-microbial peptides LL-37 and human beta defensin 2 [42]. Defensin expression is induced in response to H. pylori infection in the gastric mucosa [43] and rhinovirus infection in airway epithelia [44]. However, 1, 25-$(OH)_2D_3$ has been shown to have no effect on the susceptibility of mice to infections with herpes simplex virus or Candida albicans [45].

Epidemiological studies provide evidence that vitamin D deficiency may confer increased risk of influenza and respiratory tract infection. A few interventional studies confirm the protective effect of vitamin D against epidemic influenza. For example; Cannell et al. proposed that the lack of vitamin D during the winter may be a "seasonal stimulus" to the infectivity of the influenza virus. These reports provide a rationale for vitamin D supplementation in the prevention of colds and influenza [46].

Vitamin D deficiency is also prevalent among patients with HIV infection. Even though there are conflicting results related to the role of vitamin D signaling in controlling HIV infection, it should be noted that human cathelicidin inhibited the replication of a number of HIV isolates [47] and that the human homologues reduced the infectivity of lentiviral vectors [48], suggesting that vitamin D signaling may indeed induce antiretroviral activity. Cell culture experiments support the thesis that vitamin D has direct anti-viral effects particularly against enveloped viruses.

Vitamin D also has got potent anti bacterial effect. 1, 25-$(OH)_2D_3$ increases CD-14 that acts as a co-receptor for the detection of bacterial lipopolysaccharide (LPS) [49]. Liu et al. found in their studies that signaling through human macrophage TLR1/2 heterodimers stimulated with bacterial lipopeptides induced expression of both CYP27B1 and the VDR [50].

Studies on vitamin D's anti-bacterial effect have been focused on respiratory tract infections and tuberculosis. Chalmers et al. measured 25-(OH) D by immunoassay in 402 stable patients with bronchiectasias. They found that Vitamin-D deficiency is common in bronchiectasias and correlates with markers of disease severity [51].

There is also a link between vitamin D deficiency and cases of tuberculosis. It has been reported that tuberculosis is more common in vitamin D deficient patient [52].

There are a few studies about the relationship between other infectious status and vitamin D deficiency, however there are many clinical studies related to serum C-reactive protein (CRP) levels and mortality rates in vitamin D deficient patients. Many studies have reported that all cause-morbidity and mortality increase in patients with 25 OH D deficiency [53-55] and it is certain that a link between vitamin D deficiency and high mortality. But too controversial results have been reported on the relationship between vitamin D and serum CRP levels. Michos et al. study failed to detect a cross-sectional association between serum 25-(OH) D levels and CRP in 650 Amish participants [56]. Amer et al. observed a statistically significant inverse relation between 25-(OH) D at levels <21 ng/ml and CRP in asymptomatic adults from the continuous National Health and Nutrition Examination Survey 2001 to 2006. They found that 25-$(OH)_2D_3$ at a level ≥ 21 ng/ml is associated with an increase in serum CRP [57]. Ashraf et al. measured serum hs-CRP and 25-(OH) D in 62 healthy adults. They found that hs-CRP was inversely associated with 25-$(OH)_2D_3$ in subjects with <20 ng/mL 25-(OH) D (n=27) [58]. 25-(OH) D, intact parathormone (iPTH), high-sensitivity C-reactive protein (hsCRP) were evaluated in another study with 133 obese adolescents. The serum iPTH level was a predictor of chronic inflammation and dyslipidemia, independent of 25-(OH) D in that study [59]. Murr et al. measured serum concentrations of 25-(OH) D and 1,25-$(OH)_2D_3$ and the immune activation markers neopterin and hsCRP in 2015 patients derived from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. They showed that there was

| Serum 25-(OH) D | Levels (ng/mL) | Levels (mmol/L) |
|---|---|---|
| Severe deficiency | < 5 | <12 |
| Moderate deficiency | 5-15 | 12-37 |
| Insufficiency | 16-30 | 40-75 |
| Normal | >30 | 75 |

**Definition from KDOQi Guidelines,*

*25-(OH) D: 25-Hydroxy Vitamin D*

**Table 1:** Classification of Vitamin D Status Based on Total 25-Hydroxy Vitamin D Concentrations*.

an inverse correlation between serum 25-(OH) D or 1, 25-$(OH)_2D_3$ concentrations and serum neopterin. Their results indicate increased inflammatory processes in patients with low vitamin D status [60] (Table 1).

The relationship between CRP levels of vitamin D also contains conflicting information in patients with renal failure. Kalkwarf et al. found that 25-hydroxyvitamin D levels were positively associated with 1,25-dihydroxyvitamin D, the relationship being greatest in advanced renal disease (significant interaction), and inversely related to those of inflammatory markers CRP and IL-6 in 182 patients with CKD and 276 healthy children. In this study, the association with C-reactive protein persisted when adjusted for the severity of kidney disease [61]. In the study performed by Eleftheriadis et al. thirty-three hemodialysis patients not under vitamin D receptor agonist treatment were enrolled into the study. Serum levels of 25-(OH) D, CRP, IL-6, receptor activator of nuclear factor-kappa-B ligand (RANKL), and osteoprotegerin, as well as iPTH were assessed by immunoassays. Regarding inflammation, 25-(OH) D inversely correlated with both CRP and IL-6 [62].

An observational study of 135 outpatients with stage 3-5 CKD was undertaken by Echida et al. In this study clinical and biochemical parameters were analyzed in terms of nutritional status, inflammation, and mineral metabolism in relation to serum levels of 25-(OH) D [63]. The inflammatory state according to the CRP levels showed no significant difference between the two groups in serum 25-(OH) D levels.

In a prospective cohort study of more than 3,000 consecutive patients undergoing coronary angiography, the baseline 25-(OH) D and 1,25-(OH) D levels were independently associated with cardiovascular and total mortality during a prospective follow-up of over 7 years [64]. This study also showed that low of 25-(OH) D levels were significantly correlated with markers of inflammation, i.e., C-reactive protein (CRP) and interleukin-6 (IL-6) levels, and with markers of oxidative stress and intercellular adhesion molecules (ICAM-1, VCAM-1), thus suggesting a link between low vitamin D-levels, inflammation, and subsequent mortality.

## Conclusions

Vitamin D has got both stimulatory and antiproliferative effects on the immune system. The paradoxical effects of 1, 25-$(OH)_2D_3$ on the ability of the host to mount an immune response to infectious microorganisms while suppressing autoimmune disease require additional investigation.

Available data indicate that vitamin D deficient patients may enter a vicious cycle of low calcitriol, increased inflammation markers, and renal impairment, which may be difficult to escape by simple vitamin D supplementation.

In clinical studies have been shown that vitamin D deficiency is the propensity to infection. It facilitates the progression of the infection. It is more common in all-cause hospitalized patients and all cause mortality. However there are complexity between vitamin D deficiency and some inflammatory markers such as CRP. Higher CRP levels in Vitamin D deficient patients probably depend on other reasons. Moreover, the cause of vitamin D deficiency and other co-morbid conditions increasing CRP should be known in studies investigating the association between vitamin D and inflammatory markers such as CRP.

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