Research Article

Immunomodulatory Role of Vitamin D in Infectious and Non-Infectious Diseases

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Abstract | Vitamin D secosteroids are group of liposoluble prohormones consisting of five different vitamins, the most important forms being vitamin D2 and vitamin D3. Previous and current studies revealed the putative immunomodulatory role of $1,25(OH)_2D_3$ besides its classical role of maintaining phosphorus and calcium metabolism inside body. Vitamin D is involved in homeostasis of innate and adaptive immune responses by modulating activity of monocytes, dendritic cells, macrophages and activation of T and B lymphocytes. Vitamin D modulates cytokine response and anti-microbial peptides (AMPs) production which boost innate immune response. Hypovitaminosis D is a significant risk factor for infectious and non-infectious diseases however its exact mechanism is still unknown, but low levels of vitamin D has been detected in different diseased cases. Recent investigations have reported various cells of body exhibiting vitamin D receptors and CYP27B1 which is capable of converting inactive form vitamin D into biologically active form $1,25(OH)_2D_3$, that important for maintaining immune homeostasis. These findings lead to more studies on the non-classical effects of vitamin D especially on immune responses. Vitamin D receptor (VDR) regulated transcription depends on co-modulators, which act in a cell specific manner. Also, increasing the resistance to currently used antibiotics requires cost effective alternatives while vitamin D can serve as inexpensive therapeutic agent in prophylaxis as well as treatment of several infections. This review summarizes current knowledge on complex immune-modulatory role of vitamin D at cellular level as well as different mechanisms through which vitamin D exert protective role against different viral, bacterial, parasitic infections and non-infectious disorders.

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Introduction

From the mid of 17th century, it was known that deficiency of vitamin D resulted in several clinical disorders, but the exact cause remained mysterious until Adolf Windaus identified link of vitamins with sterols (Wolf, 2004). He won noble prize in 1928 in chemistry for detailed work on sterol constitution. Rickets was endemic in different parts of England but no one knows the exact causative agent until beginning

of 20th century, when anti-rachitic properties of UV-radiations and cod liver oil were studied and different biochemical tests revealed insufficiency of vitamin D the cause of disease (Baeke et al., 2010). Vitamin D is categorized as fat-soluble vitamin and first identified as a cure for nutritional Rickets (Huh and Gordon, 2008). Vitamin D exerts various functions in the body which can be divided in to two general forms; classical and non-classical functions. Classical function includes calcium and phosphorus homeostasis while non-classical function includes the regulation of both adaptive and innate immune responses (Yin and Agrawal, 2014), hormone secretion, cell proliferation inhibition, differentiation of various cell types and anti-carcinogenic effects (Adams and Hewison, 2008).

There are two important members of vitamin D family; (i) ergocalciferol (D2) which is synthesized from ergosterol in plants through ultraviolet radiations and (ii) cholecalciferol (D3) which is synthesized in mammalian skin epidermis under sunlight exposure (Hoffmann et al., 2015). Both ergocalciferol and cholecalciferol undergoes same metabolic reactions and have same functions (Hoffmann et al., 2015). Vitamin D has 12-16 hour's half-life and itself biologically inactive compound. 25-hydroxyvitamin D (25(OH)D) is a predominant form in circulation and is stable marker to determine the body status while calcitriol (1,25 dihydroxyvitamin D) is a metabolite of vitamin D which is biologically active form in circulation (Mora et al., 2008). All metabolites of vitamin D are lipophilic like other steroid hormones (Dusso et al., 2011) and more than 99% in blood are bound by vitamin D binding proteins (DBP, also called Gc-globulin) while the remaining 1% unbound portion is carried by lipoprotein or albumin (Dusso et al., 2011). Vitamin D that bound to DBP has a very little effect on target cells while most of its biological activity is related to free hormone levels (Chun et al., 2014). This is universally accepted 'free hormone hypothesis' because of their lipophilic nature and ability to passively diffuse across cell membranes, but this theory is still under-investigation (Chun et al., 2014). DBPs are synthesized in liver as part of albumin protein family, possess pluripotent properties besides vitamin D binding that include macrophage activation, fatty acid transport and actin binding (Yamamoto and Naraparaju, 1996).

Satisfactory vitamin D serum level is 40-60 ng/mL while <25 ng/mL of 25(OH)D indicates hypovitaminosis D (Del Valle et al., 2011). About one billion population of world is estimated to be deficient of vitamin D. In Pakistan, despite of sunshine throughout the year, 53.5% population is estimated to have vitamin D deficiency (Riaz et al., 2016). Vitamin D insufficiency poses a great risk for developing numerous infectious and non-infectious diseases, which is an indicator for the relationship between vitamin D and immunity. Low body level of vitamin D is related to several autoimmune disorders including systemic lupus erythematous (SLE) (Ritterhouse et al., 2011), rheumatoid arthritis (RA) (Rossini et al., 2010), diabetes mellitus type 1 (Anderson et al., 2010) and multiple sclerosis (MS) (Ascherio et al., 2014). Hypovitaminosis D is also associated with cardiovascular diseases, hypertension, multiple malignancies and high infection rates (Nnoaham and Clarke, 2008). Immune-modulating characteristics of vitamin D being highlighted in various cell culture and animal model experiments that might cause these extra-osseous effect of vitamin D (Holick, 2008).

Besides that, vitamin D receptors (VDR's) being used by 1,25-dihydroxyvitamin D signaling. VDR's are included within nucleoprotein superfamily (Haussler et al., 2008). Since early 1980, vitamin D immunobiological studies were succeed through molecular cloning of CYP27B1 and VDR by Suda's laboratory. Their experiments showed that maturation of WBC's (white blood cells) induced by $1,25(OH)_2D_3$, when delivered to extracellular culture medium which was a possible indicator for bio-response of vitamin D other than skeletal homeostasis and intestinal calcium (Ca) absorption (Adams et al., 2014). Recently, thousands of VDR's have been recognized in most of cell type along with VDR bindings sites which control thousands of genes, indicating the impact of vitamin D on diverse biological processes within the body other than classical functions of maintaining calcium and phosphorus homeostasis (Bikle, 2014). In human, vitamin D signaling enhances the innate immune responses to infections. Biological effect of vitamin D is dependent upon VDR's which control transcription and trans-repression of approximately 900 genes (Wang et al., 2005). Gene repression or activation occurs equally in response to $1,25(OH)_2D_3$ signaling and gene transcription can be repressed by hormone bound VDR through various mechanisms which implicated directly on the interactions of VDR with other classes of trans-activators (Giovannucci et al., 2008). 1 Activation of VDR being mediated by

$1,25(OH)_2D_3$ which regulates the gene expression in several tissues of the body while the different cells of the immune system expressing VDR as listed in Table 1.

Active form of vitamin D ($1,25(OH)_2D_3$) does not induce differentiation of progenitor cells from bone marrow in VDR knockout mice (Mathieu et al., 2001). In another experimental study, when asthma was induced in VDR knockout mice, no eosinophilia and airway inflammation was observed despite high concentrations of Th2 cytokines and IgE which conclude the potential involvement of vitamin D in response to allergy (Wittke et al., 2004). This review will summarize current knowledge on the immune-modulatory role of vitamin D on immune system at cellular level as well as mechanisms through which vitamin D exert a protective role against autoimmune, infectious and non-infectious diseases. Moreover, interactions between vitamin D and various infectious and non-infectious diseases will be also described.

Vitamin D synthesis and metabolism

Humans and animals can get vitamin D from three main sources; ultraviolet dependent endogenous production at skin epidermis which is the main source, nutritional source and supplements have little importance in providing of vitamin D to the body. Several factors can influence the endogenous production of vitamin D that include season, skin pigmentation, latitude and genetic determinants. Dietary sources have two types of vitamin D; (i) ergocalciferol and (ii) cholecalciferol. Very few natural products contain vitamin D including mushrooms (Shiitake) and fatty fish (cod liver oil). In some countries like United states, they can artificially fortify natural products with vitamin D (Prietl et al., 2013). Ergocalciferol is synthesized from ergosterol (plant sterol) while the endogenous production of cholecalciferol (Vitamin D3) occurs in skin epidermis by proteolytic conversion of 7-dihydrocholesterol under influence of ultraviolet radiations (UVB) (Holick, 2006) which is inactive and undergoes several metabolic conversions. After cholecalciferol production, it immediately binds with albumin or vitamin D binding proteins (DBP) and undergoes hydroxylation in liver leading to the production of 25(OH)D (25-hydroxyvitamin D). The predominant enzyme that catalyze this hydroxylation reaction is still unknown however it is most likely to be CYP2R1, CYP27A1 and P450. 25-hydroxyvitamin D is a predominant vitamin D metabolite in circulation and considered a reliable marker to define vitamin D body status. Vitamin D activating enzyme/CYP27B1 (25(OH)D-1α-hydroxylase) is located in proximal convoluted tubules of kidney and convert inactive 25-hydroxyvitamin D to $1,25(OH)_2D_3$ (calcitriol), which is a biologically active hormonal form. Parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) tightly regulates calcitriol levels in circulation (Ferrari et al., 2005). FGF-23 is involved in phosphate/calcium metabolism in the body (Bergwitz and Jüppner, 2010) while high levels of FGF-23 and calcitriol can inhibit CYP27B1 resulting in stimulation of mitochondrial CYP24A1 (24-hydroxylase) that limits the production of tissue $1,25(OH)_2D_3$ and acts as "feedback" control enzyme and causes metabolic conversion of calcitriol into water-soluble calcitroic acid. After renal secretion, $1,25(OH)_2D_3$ goes to circulation and acts on target tissues present in periphery. VDR (vitamin D receptor) is nuclear receptor and response of target cells depends upon VDR expression (Haussler et al., 2008). VDR acts as transcription factor and have targets specific sites in DNA called VDRE (vitamin D response element). There are thousands VDRE in gene promoter regions which regulates hundreds of cell specific genes. Renal CYP27B1 enzyme activity determines the calcitriol levels in circulation (Krishnan et al., 2013). Initially it was thought that after renal production, 1,25D mostly has is an endocrine hormone (White, 2012), however recent studies revealed that CYP27B1 can be also expressed by several other cell types like immune cells so will be able to convert 25(OH)D to $1,25(OH)_2D_3$ either in paracrine or autocrine manner (Morris and Anderson, 2010). Several immune system cells express both VDR and CYP27B1 (Hewison, 2012). $1,25(OH)_2D_3$ extra-renal synthesis was first identified in patients affected with sarcoidosis where macrophages were producing CYP27B1 instead of kidney tissues (GACAD and Uskokovic). Later studies showed that synthesis of $1,25(OH)_2D_3$ by macrophages was common in most diseased cases with granulomas. In such cases, the extra-renal production of $1,25(OH)_2D_3$ in affected peripheral tissues which called 'barrier sites'(Townsend et al., 2005) is enough to enter to general circulation and dysregulate Ca^{++} homeostasis (Papapoulos et al., 1979). Different cells can co-express VDR and CYP27B1-hydroxylase without any apparent diseases as listed in Table 1. Recently, scientists have now focused on possible impact of VDR and CYP27B1 (non-classical function) on vitamin D responses indicating its potential immunomodulatory role.

Table 1: *Cells expressing VDR.*

Renal tubular cells	Pancreatic β cells	Parathyroid cells
Macrophages	Dendritic cells (DC's)	Hair follicle
Mammary epithelial cells	Adrenal medulla	Placenta
Fetal trophoblast	Keratinocytes	Vascular epithelial cells

Modulation of innate and adaptive immune responses

The non-classical modulation of immune responses by 1,25-dihydroxyvitamin D has been known three to four decades ago but more intention has been paid recently after discovery of VDR and metabolic enzymes of vitamin D that co-expressed by vast number of immune system cells. Several clinical and epidemiological studies on animal models suggest the possible role of 1,25-dihydroxyvitamin D in maintaining balanced immune system (Kamen and Tangpricha, 2010). VDR's belong to family of nuclear receptors and can be dimerized with retinoid X receptor's isoform.

Innate immune response is non-specific against pathogenic invasion through activation of complement system, macrophages and neutrophils and help in antigen presentation through acquired or adaptive immune system. Different studies reported that involvement of vitamin D in crucial steps of innate immune response at which cells of innate immune system express vitamin D receptors (VDR's) in response to pathogen threat and become responsive to 25(OH)D resulting in VDR-driven innate immune response (Hewison, 2010), then vitamin D responsive cells can bind with this heterodimer (VDR-RXR) molecule (Yasmin et al., 2005) resulting in transcriptional activation of approximately 2000 encoding antimicrobial peptides (AMP's) including cathelicidin antimicrobial peptide (CAMP) along with displacement of nuclear factors of activated T cells causing repression of genes related to cytokines (Gombart et al., 2005). Recent studies on CYP27B1 (vitamin D activating enzyme) provide data about putative role of vitamin D metabolism in modulation of innate immune responses (Quarles, 2008).

Toll like receptors (TLRs) are important component of innate immune responses and their activation exerts antimicrobial activity against intracellular pathogens (Rasmussen et al., 2009). Monocytes can phagocytose pathogens expressing pathogen-associated molecular patterns (PAMPs). Monocytes sensing of pathogen recognition receptors (PRR) including toll like receptors (TLRs) is helpful in phagocytosis. To date, there are approximately 12 functional TLRs have been identified in mice and 10 in humans to date, with each PAMPs specific receptor that respond to different pathogens including virus, fungi, bacteria and parasites (Kawai and Akira, 2010). Extensively studied TLRs which include TLR2, TLR3 and TLR4 can specifically respond to gram-positive and gram-negative bacteria, and double stranded RNA viruses, respectively (Takeda and Akira, 2005). The most important role of TLRs in innate immunity and the effect vitamin D on TRLs suggested possible an immunomodulation for innate immune responses by vitamin D through TLRs (Arababadi et al., 2018). Human macrophages TLRs activation lead to up-regulation of 1-hydroxylase genes and VDR's, inducing CAMP which results in killing of *Mycobacterium tuberculosis*. Another study indicated that lower concentrations of 25-hydroxyvitamin D serum levels in Afro-American population might be ineffectively support the induction of cathelicidin mRNA, and might be there is link between vitamin D dependent innate immunity and TLRs (Liu et al., 2006).

Most of immune system cells including antigen presenting cells (APC's) and particularly dendritic cells (DC's) are expressing VDR. Vitamin D can influence on T-cells activation, function and phenotype of APC's that modulates the adaptive immune system (Kamen and Tangpricha, 2010). VDR and $1,25(OH)_2D_3$ can regulate the maturation of human dendritic cells (Arima et al., 2010). Exposure of mouse and human differentiating monocytes to $1,25(OH)_2D_3$ lead to inhibition of DC's maturation and increasing the expression of various molecules related to antigen capture which results in impaired functioning of CD8+ T-cells (van Halteren et al., 2004). APC's initiate the adaptive immune response and they are either tolerogenic or immunogenic. Immunogenic APC's can modulate T-cells responses while tolerogenic are characterized by cytokine production favoring Treg (regulatory T) cells induction and also can reduce the expression of co-stimulatory molecule's (Steinman and Banchereau, 2007). Co-stimulatory molecules present at the surface of APC's including CD80, CD86 and CD 40 and can be reduced in presence of $1,25(OH)_2D_3$ (Almerighi et al., 2009). In addition, $1,25(OH)_2D_3$ can also inhibit the production of IL-α, IL-2, IL-6 and tumor necrosis factor (TNF-α) in the presence of pro-inflammatory stimuli (D'ambrosio et al., 1998). Maturation of dendritic cells enhances IL-

10 production and override the production of IL-12, while these physiological alterations might explain the ability of $1,25(OH)_2D_3$ to induce dendritic cells with tolerogenic properties resulting in enhanced Treg development. So, these modulated DC's might be used in development of future strategies to explain immune tolerance in case of autoimmune diseases or in transplantation of organs.

Moreover, $1,25(OH)_2D_3$ can regulate DC's and macrophages, which are crucial in innate immune responses through differentiation of monocytes to macrophages and stimulation the PGE2 (prostaglandin E2) production from macrophages by $1,25(OH)_2D_3$. Expression of chemokines, granulocyte macrophage colony stimulating factor (GM-CSF) and pro-inflammatory cytokines is down-regulated by $1,25(OH)_2D_3$ (Shojadoost et al., 2015). Hypovitaminosis D compromises the maturation of macrophages, production of lysosomal acid phosphatase and H_2O_2 which are required for antimicrobial activity (Helming et al., 2005). In response to interferons (IFN), TLRs and macrophages activation results in the production of $1,25(OH)_2D_3$ which is synthesized from $25(OH)_2D_3$ through activated macrophages in both animals and human's immune systems (Hewison, 2010). In-vitro treatment of human monocytes with $1,25(OH)_2D_3$ results in inhibition of pathogen recognizing receptors expression including TLR2, TLR9 and also alters TLR-9 dependent IL-6 production (Dickie et al., 2010).

Vitamin D can directly modify B and T cells immune responses, so it is an important component of adaptive immune responses. VDR expression from inactive CD4+ T-cells is very low, and these cells are only activated after increase in their VDR expression (Von Essen et al., 2010). $1,25(OH)_2D_3$ affects T cells directly through inhibition of T-cells proliferation and indirectly through dendritic cells (Mahon et al., 2003). $1,25(OH)_2D_3$ along with glucocorticoids can induce the production of IL-10 through Tr1 cells that suppress the immune response (Wittke et al., 2004). These finding may add and explain the role of vitamin D in eosinophilia, mid-airway inflammation, bronchial hyper-reactivity, allergic and autoimmune diseases, despite the presence of Th2 cytokines and IgE (Wittke et al., 2004).

Down-regulation of major histocompatibility complex II (MHC-II) by $1,25(OH)_2D_3$ can induce cathelicidin production. In an experimental study, using VDR knockout mice, CD4+ T cells cause less production of IL-2, IL-5 and increased production of IFN compared to wild type mice (Froicu et al., 2003). In the presence of IL-2 in vitro, $1,25(OH)_2D_3$ up-regulates the transcription of CTLA4 and Fox P3 leading to the induction of Treg cells so, $1,25(OH)_2D_3$ can promote Tr1, Th2 cells immune-modulatory responses, inhibits Th17 and Th1 pro-inflammatory response and down-regulation for the cell mediated immunity (Lacey et al., 1987). Moreover, $1,25(OH)_2D_3$ can inhibits CD8+ T cells mediated cytotoxic response, prevent the production of IL-2 that inhibit Th1 responses and prevents IL-6 and IL-23 production which alters Th17 responses (Daniel et al., 2008). In contrast, $1,25(OH)_2D_3$ either don't affect or reduces IFN-γ concentrations produced by CD4+ T-cells while the inhibitory effect of $1,25(OH)_2D_3$ includes cytokine production from Th1 cells or only differentiation into Th1 cells (Ikeda et al., 2010).

CD8+ T cells are two types; (i) Tc1 that produce interferon and (ii) Tc2 which involves in the production of IL-4. There is no clear evidence available regarding the effect of VDR's on both cell types. CD8+ T-cells can be stimulated through different methods, so limited data is available regarding the effect of vitamin D on them. In the presence of $1,25(OH)_2D_3$, the proliferation of CD8+ T-cells might be unaffected, enhanced or even inhibited (Thien et al., 2005). Supplementation of vitamin D cause continuous reduction of CD8+ T-cells which are capable of producing IL-2 while the cytotoxicity can also be avoided if pre-treated with $1,25(OH)_2D_3$. Presence of vitamin D cause reduction in IL-17 mRNA levels in CD8+ T-cells (Baeke et al., 2010). According to some scientists, presence of $1,25(OH)_2D_3$ have no influence on IFN-γ and CD4+ T-cells however, some *in-vitro* studies showed that inhibition of IFN-γ might be happened (Willheim et al., 1999). Th2 cells exhibit high VDR expression levels which makes them direct target for $1,25(OH)_2D_3$.

IL-4 is proteotypic cytokine for Th1 cells (Chang et al., 2010). CD4+ T-cell and IL4+ percentage was increased due to $1,25(OH)_2D_3$ mediated stimulation of murine T cells (Nashold et al., 2001) while other studies did not confirm such results. These conflicting results may be due to the difference in the experiments conditions (Nashold et al., 2001). Thus, $1,25(OH)_2D_3$ can enhance IL-4 production from differentiated

Th2 cells but inhibits the differentiation of Th2 cells. Likewise, IL-17 is marker cytokine for Th17 cells and murine Th17 cells that exhibit relatively higher VDR expression. IL-17 VDR expression is deceased with vitamin D. IL-22 is considered either Th17 or Th22 cell's product, while $1,25(OH)_2D_3$ down-regulates IL-22 production in both human and murine experimental studies (Collin et al., 2010).

Natural killer (NK) cells regulate the adaptive immune response through chemokine and cytokine production which rapidly destroy the affected cells (Vivier et al., 2011). NK cells are involved in pathogenesis of autoimmune diseases and their role is extensively studied (Popko and GórsKa, 2015). Supplementation with vitamin D or 1-α-(OH)D in case of autoimmune diseases can normalize or improve the activity of NK cells. Vitamin D along with dexamethasone can lead to up-regulation of IL-10 mRNA of IL-10 in freshly enriched and purified NK cells (Deniz et al., 2008). $1,25(OH)_2D_3$ can inhibit B-cell's proliferation, production of immunoglobulins and differentiation to plasma cells so, patients of autoimmune diseases have low serum levels of 25(OH)D compared to healthy people (Chen et al., 2007). Vitamin D supplementation can decrease the severity of autoimmune diseases that indicates the possible therapeutic role of vitamin D in case of MS, diabetes type 1 and rheumatoid arthritis. Also, vitamin D supplementation can play a promising role in prevention of different disease conditions including inflammation like autoimmune diseases, cardiovascular disease, and malignancies (Boissier et al., 2009).

Infectious diseases and vitamin D

During 19th century, patients of tuberculosis (TB) were treated with cod liver oil, which naturally contains vitamin D. After this, sunlight was used in sanatoriums as a treatment tool (Battersby et al., 2012). In 1903, Niels Finsen was awarded Nobel Prize for his discovery of treating tuberculosis using phototherapy. After more than a century, now we are trying to understand how phototherapy is helpful for treating tuberculosis and many other infections. Recently, Liu et al. (2006) postulated that sunlight stimulate vitamin D synthesis which in turn up-regulate the expression of various microbe fighting peptides. Production of AMP's can be produced within white blood cells (WBCs) in circulation and on the surface of epithelial cells which either expressed continuously or in response to stimuli like cell injury. The commonly studied AMP's includes LL-37 (Cathelicidin) which is involved in angiogenesis and β-defensin 2 (Gallo, 2005). Recent studies have identified that the presence of VDR specific sites within LL-37 encoding genes (Zasloff, 2006).

Vitamin D has emerged as an important immune-modulator due to its critical role in adaptive immune responses and regulation of chemokine production and inflammation, where majority of. of immune system cells expresses VDR (Table 1). Serum levels of vitamin D can directly influence cytokines production, rate of macrophage maturation and increase H_2O_2 levels which help in "oxidative burst" through decreasing the outcome severity of infection by preventing the excessive release of inflammatory cytokines (Thompson et al., 2004). Genes regulated by VDR are depending on $1,25(OH)_2D_3$ serum concentrations. $1,25(OH)_2D_3$ is produced from $25(OH)D_3$ in renal tubules and catalyzed by 1-α-hydroxylase (Horst et al., 2005). Regulation of 1-α-OHase expression maintains the concentration of $1,25(OH)_2D_3$ in circulation which is related to calcium homeostasis via parathyroid hormone (Engstrom et al., 1987). In the last two decades, several studies have reported that macrophages are producing $1,25(OH)_2D_3$. The risk of tuberculosis was increased fivefold in case of hypovitaminosis D (Talat et al., 2010). Some researchers reported that activated macrophages could kill intracellular *Mycobacterium tuberculosis* while activated dendritic cells lack this capability which was proven through comparison of gene expression in both cell types that revealed that expression of VDR and CYP27B1 in activated macrophages while was not seen in dendritic cells (Zasloff, 2006). AMP's can be generated against *Mycobacterium tuberculosis* which are dependent on vitamin D. Also, activation of TLR2/1 by *M. tuberculosis* might lead to increasing VDR expression and enhance the production of $1,25\text{-}D_3$ with subsequent monocytes releasing cathelicidin which is important for antimicrobial activity against *M. tuberculosis* (Liu et al., 2009). Vitamin D can suppress matrix metalloproteinases (MMPs) which are important in tuberculosis pathogenesis (Anand and Selvaraj, 2009). Increased the susceptibility towards tuberculosis might be associated with VDR polymorphism and hypovitaminosis D and could increase the disease severity. Previous studies showed that increased the susceptibility to tuberculoid leprosy could be associated with *t*-allele (part of Th1

immunity) (Roy et al., 1999). Lower vitamin D levels decrease LL-37 (cathelicidin) which has a potent antimicrobial activity against intracellular bacteria (Siddiqui and Rai, 2005). Antibacterial activity of vitamin D might be due to LL-37's associated electrostatic interactions which cause disruption of bacterial membranes (Wilson and Bals, 2003). A case study in United Kingdom reported accumulation of $1,25(OH)_2D_3$ in granulomatous tissue in case of of bovine tuberculosis infections (Rhodes et al., 2003). Only, one study reported that absence of VDR results in delayed kinetics of *Listeria monocytogenes* clearance (Bruce et al., 2009). Also, Vitamin D can inhibit different strains of *Klebsiella pneumonia, Escherichia coli*, *streptococcus pyogenes* and *Staphylococcus aureus* that might be killed or marked growth inhibition when 50,000-90,000 IU/mL of vitamin D was administered. In contrast, hypovitaminosis D poses a great risk for developing methicillin resistant *Staphylococcus aureus* (MRSA) nasal carriage. β-defensin-3 showed activity against gram positive and gram negative bacteria (Zanger et al., 2010).

Previous studies have shown that severity and occurrence of acute viral infections in upper and lower respiratory tract (e.g. influenza) can be reduced with serum concentration of vitamin D >38 ng/mL (Liu et al., 2006). Epithelial cells of lungs show low CYP24A1 and high CYP27B1 levels which helps conversion of vitamin D to its active metabolite. Vitamin D supplementation can increase cathelicidin and CD14 (TLR co-receptor) levels. So, usage of vitamin D during viral infections leads to *induction of* IκBα in *airway epithelium*, *leading* to less *induction* of *NF-kB* driven *genes* resulting in decreased production of virus induced inflammatory genes (Hansdottir et al., 2010). Different studies were carried out to study the relationship of hypovitaminosis D with viral respiratory infections and showed different results. Vitamin D can reduce the severity of infection by minimizing the release of pro inflammatory cytokines which induced in response to infection with influenza H1N1. Some studies also indicated a possible relationship between occurrence of influenza infection and seasonal variation in serum concentrations of vitamin D (Cannell et al., 2008). Mild reduction in influenza A infection in children supplemented with vitamin D during winter and spring season was observed in a Japanese research trial however, only outdoor patients were included in this study without any determination of serum 25(OH)D concentrations so patients exhibiting extreme or milder signs of illness were possibly excluded for data collection (Urashima et al., 2010).

Incidence of respiratory syncytial virus (RSV) infection is increased in case of hypovitaminosis D. Recent data revealed an association between vitamin D in decreasing inflammatory response in airway epithelium in RSV infection. In another study, there were 55% more chances of upper respiratory tract infection with vitamin D levels <10 ng/mL compared to individuals have >30 ng/mL (Hansdottir et al., 2010). Bitetto and co-workers investigated the association between low levels of 25(OH)D in immuno-compromised patients with ineffective antiviral therapy against hepatitis-C virus (HCV) (Bitetto et al., 2011). Findings from another study showed that inability to clear HCV during treatment was mainly associated with low levels of vitamin D and liver fibrosis might be related to hypovitaminosis D (Petta et al., 2010). The antiviral ability of vitamin D may be associated with reactive oxygen species release, human beta defensin-2 and cathelicidin (LL-37) (Beard et al., 2011). LL-37 might induce antiviral activity by disrupting the envelope of viruses. Induction of AMP's by vitamin D may also have anti-viral activity (Beard et al., 2011).

Statistical studies have reported a positive correlation between CD4+ cell count and $1,25(OH)_2D_3$ (Villamor, 2006). Vitamin D can exert anti-HIV activity directly through release of cathelicidin and β-defensin-2 (Wang et al., 2004). VDR haplotype G-A-T-G-L can prevent HIV type-1 transmission (Sánchez de la Torre et al., 2008) while VDR FokI and BsmI BB in HIV patients can cause fast progression of disease and accelerated drop in CD4+ count (Nieto et al., 2004). CCR5 (chemokine receptor) is very important for HIV entry into monocytes and infectious pathway, while vitamin D can block this step through induction of IL-13 cytokines by promoting Th2 response which will downregulate CCR5 expression (Fukuoka et al., 1998). Binding of RANTES (CCR5 ligand) can block the virus entry of virus and its production can be regulated by vitamin D (Fukuoka et al., 1998) so, chances of HIV infection are increased with decreased CCR5 production in body (Fukuoka et al., 1998). These findings suggest a possible link role hypovitaminosis D in favoring disease progression through influence of Th2 on CCR5 (Coenen and Nattermann, 2010).

The anti-parasitic effects of Vitamin D are not extensively studied. Diet lacking of vitamin A, D3 and E increase *Hymenolepis diminuta* due to worm migration caused by paralysis of host intestine (Addis and Chandler, 1946). *Toxoplasma gondii* is an obligate intracellular protozoan and often causes a disease in immune-compromised patients. It is one of most successful parasite on earth regarding host range so it is always challenging to develop its controlling strategies (Tenter et al., 2000). In a murine model study, *T. gondii* infected BALB/c mice which was supplemented with $1,25(OH)_2D_3$ revealed that less parasitic burden along with mild histopathological lesions that suggests the beneficial role of vitamin D against parasitism. Inducing the expression of diacylglycerol acyltransferase, *Plasmodium falciparum* can produce triacylglycerols, which is important for maintaining intra-erythrocytic proliferation of parasite. Schizont and trophozoite stages showed enhanced biosynthetic activity, at these stages high serum levels of $1,25(OH)_2D_3$ can hinder the growth of *P. falciparum* (Rajapakse et al., 2007).

The beneficial role of vitamin D against fungal infections has been known since 1954, when three patients have history of refractory chromoblastomycosis were given 600,000 IU of calciferol the skin lesions of all three patients showed rapid recovery. In case of candidiasis, all patients having end-organ resistance to vitamin D showed slight decrease in neutrophil fungicidal activity (Etzioni et al., 1989). Studies on animal models have reported remarkable reduction in opportunistic infections including candidiasis when vitamin D was administered (Cantorna et al., 2008). Murray and coworkers described a case report at which a patient had a history of disseminated histoplasmosis along with renal insufficiency was treated with supplementation of vitamin D and calcium (Murray and Heim, 1985). Due to granulomas presence, patients hypercalcemic, therefore supplementation of vitamin D to patients with hypercalcemic, therefore the disease condition would be worth Findings of this study suggest that supplementation of vitamin D in granulomas forming fungal infections should be used wisely otherwise it may induce hypercalcemia resulted in impaired neutrophil and monocyte activity.

Vitamin D insufficiency poses a great risk for developing cardiovascular diseases, increased prevalence of coronary artery calcification, stroke, myocardial infarction and peripheral arterial disease associated with hypovitaminosis D (Lee et al., 2008). Likewise, obesity, diabetes mellitus, hypertension and hypertriglyceridemia, are considered important risk factors for developing cardiovascular diseases which are negatively correlated with body status of vitamin D (Martins et al., 2007).

Non-infectious diseases and vitamin d

Interaction of different environmental factors with genetic susceptibility results in autoimmune diseases (Smyk et al., 2013). Various infectious and non-infectious mediators are included in a list of environmental factors, which involved in autoimmune disorders. Hypovitaminosis D and low VDR levels are detected in autoimmune diseases (Smyk et al., 2013). VDR's are abundant in neurons and mostly expressed in substantia nigra, hippocampus, thalamus and hypothalamus (Eyles et al., 2005). Vitamin D is involved in differentiation and maturation of neurons by interacting with synthesis of various neuromodulators (dopamine and acetylcholine) and septohippocampal pathway trafficking (Moretti et al., 2018). These findings could correlate the hypovitaminosis D with neurological pathologies (Moretti et al., 2018). Multiple sclerosis (MS) is a chronic disease of CNS with unknown etiology, mostly affects people living at higher altitudes. Several studies have been conducted to identify possible links between vitamin D and MS which revealed that hypovitaminosis D is a significant risk factor in development of MS especially patients with MS have low serum levels of vitamin D however long term administration of high doses of vitamin D worsen the condition (Alharbi, 2015) which might be due to vitamin D induced secondary hypercalcemia causing T-cells stimulation (Häusler and Weber, 2019).

In 2030, it has been estimated that 366 million population of the world will be affected with diabetes (Whiting et al., 2011). Increasing cases type 2 diabetes mellitus (T2DM) highlights the importance for developing managemental strategies. Systemic inflammation, insulin resistance and impaired function of pancreatic β-cells cause type 2 diabetes mellitus. HbA1c levels and body mass index (BMI) have inverse relationship with serum concentration of vitamin D. Some studies indicated that incidental T2DM might be related with seasonal variations of HbA1c levels which are lower in summer compare to winter season that suggest better glucose control during summer. Vitamin D can improve the endothelial function by increasing IL-10 production, decreasing

vascular resistance and blood pressure (Lindqvist et al., 2010). Activation of peroxisome proliferator-activated receptor (PPAR-δ) or induction of insulin receptor's expression may increase the sensitivity of insulin. Vitamin D can also involve in extracellular calcium homeostasis that can directly alter insulin production (Sun et al., 2005). Interaction between vitamin D and T cells is leading to development of type 1 diabetes mellitus (Pittas and Dawson-Hughes, 2010), although the exact mechanism is still unknown, some reports suggest that hypovitaminosis D can increase the incidence of cancer while cancer patients supplied with vitamin D, the prognosis being improved. Active form of vitamin D ($1,25(OH)_2D_3$) can interfer with signaling pathways of several growth factors including MAPK5 (MAP kinase 5), Wnt/β-catenin and IGF-1 (insulin like growth factor 1) (Fleet et al., 2012). Vitamin D is also involved in many signaling pathways related to apoptosis, angiogenesis, inflammation, metastasis and proliferation; therefore, it can be involved in carcinogenesis (Krishnan and Feldman, 2010). Defective apoptosis may involve in cancer development as different chemotherapeutic methods which induce death of cancerous cells through apoptotic pathway (Johnstone et al., 2002). Vitamin D_3 synthesis and degradation pathways and single nucleotide polymorphisms (SNPs) in VDR had been studied for their role in cancer development (Feldman et al., 2014). Different studies listed hypovitaminosis D as a main cause of pediatric rheumatic diseases (juvenile arthritis) in children (Vojinovic and Cimaz, 2015). Recently, vitamin D therapy is applied for treatment of Psoriasis which is a proliferative inflammatory skin disorder (Brzezińska-Wcisło and Wcisło-Dziadecka, 2016). Likewise, chances of development of non-infectious ocular inflammatory disorders can be increased with low vitamin D levels (Llop et al., 2018).

Conclusions and Recommendations

The active form of vitamin D ($1,25(OH)_2D_3$), is produced by the immune cells, modify immune responses by modulating of leukocytes gene expression through VDR. Previous studies were conducted based on human and animal models proved the potent immunomodulatory effect of vitamin D on adaptive and innate immune responses. Observational evidence suggests that supplementation of vitamin D may result in prevention and or treatment of various disorders. Studying the role of vitamin D in pathogenesis of several diseases may be helpful to use vitamin D body level as an important health marker for assessing the general body health. So, vitamin D could be a promising candidate to be used as diagnostic marker for rapid and accurate diagnosis of diseases at early stages. Moreover, increasing the resistance to currently used antimicrobials emphasizes the need for identifying new therapeutic agents to be used in routine treatment at which vitamin D may serve as cost-effective solution. But several mysteries have to be solved yet. For example, anti-bacterial activity is limited to primates only which raise several questions about role of vitamin D in innate immunity in murine models. We don't know about different targets of vitamin D for primate's innate immune responses. Scientists suggest conducting experimental trials using animal models to further explore the body status of vitamin D and its interaction with diseases severity. Information about VDR expression on the immune cells in case of viral, bacterial, fungal and parasitic diseases may be beneficial to concoct novel strategies to overcome the severity of infections through the immunomodulatory role of vitamin D. Role of vitamin D therapy in diseased and immune compromised animals may be beneficial, but it is not understood yet. Vitamin D can directly influence APC's activity which reflects on blood levels of vitamin D which raise several questions for the role of vitamin D in response to vaccination. Studying VDR expression at the cellular level and the role of vitamin D in relation to the pathogenesis of different disease may be beneficial to devise strategies for controlling of infections by manipulating nutritional sources. Increasing the resistance to currently used antibiotics demands new antimicrobials while their developing are much expensive. Indeed, vitamin D could serve as cost effective solution. Moreover, body status of vitamin D may be used as diagnostic marker for identifying several diseases. Finally, additional work is required to determine the exact level of vitamin D that necessary for the optimal function of immune system so we will be able to conclude whether vitamin D has therapeutic usage or only limited to prophylaxis of some infectious and non-infectious diseases.

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Author's Contribution

All authors contribute equally in preparation of manuscript.

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