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Biochemical Perspectives of Immune Cell Response to Vitamin D

Sunil Nawaz*

Department of Microbiology, Government College University, Faisalabad, Pakistan

***Corresponding author:** Sunil Nawaz

sunilnawaz@gmail.com; scorleestar@gmail.com

Department of Microbiology, Government College University, Faisalabad, Pakistan.

Tel: 923428889228

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Abstract

Vitamin D use could possibly boost therapeutic response and restrain requirement of antibiotic treatment when used according to recommended dietary allowance (RDA). An increasing role of Vitamin D and its analogues is documented for the controlling of psoriasis, vitiligo, atopic dermatitis, rosacea and acne. Besides this, it also aids in B and T cell activation as well as enhancing the activity of macrophages and monocytes. All these potentially contribute to anti-microbial response of immune system. Evidence supports that vitamin D shows enhanced antimicrobial activity and a deficiency in its RDA dosage may affect general well-being and longevity in an irreparable way. Possible mechanism for these effects is by an increased scrutiny of inbound pathogenic microorganisms. Multiple other mechanisms of Vitamin D may decrease the risk of infection. Vitamin D can boost innate immunity by modifying the cytokine response and production of anti-microbial peptides (AMPs). A reduction to infection susceptibility is documented in patients suffering atopic dermatitis. Ability of Vitamin D to balance inflammatory responses and local immunity offers thrilling prospective to understand and better treat chronic inflammatory dermatitis's. Taking into account the potential antimicrobial benefits and the abundance of broad benefits that an adequate vitamin D level confirms, make it discreet to regularly check vitamin D status and maintain an adequate 25(OH) D levels. Vitamin D establishes itself as an economical prophylactic variant and therapeutic product. It also establishes itself as a synergistic approach to traditional antimicrobial agents. This review outlines the specific responses of immune cells which boosts their antimicrobial responses in combating a wide range of organisms due to vitamin D. These are responses by which vitamin D ensures its therapeutic role in treatment of variety of infections.

Keywords: Vitamin D; Immunology; Biochemistry; Immune system; Immune cells

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Introduction

Vitamin D plays an essential role in immunomodulation [1] as well as in balancing inflammatory response and chemokine production [2]. Vitamin D along with its analogues may pose effects on different cell types, sebocytes, melanocytes and keratinocytes and offer a stimulating opportunity for treating several chronic inflammatory dermatitides [3]. Vitamin D may also boost innate immunity that improves survival in acute illness [4]. Vitamin D shows systemic antimicrobial effects [5] that could be critical in a range of both type of acute and chronic illness. Biggs et al. [6] established that the mast cell's ability to suppress cutaneous inflammation can be boosted vitamin D dependent induction of interleukin-10 by mast cells.

In addition, vitamin D can potentially improve production of antimicrobial peptides in the skin by modulating T cell profiles [7]. Furthermore, the overdose of antibiotics still persists despite many efforts to address this problem and contributes to resistant organisms such as methicillin resistant *Staphylococcus aureus* [8]. These anti-inflammatory and anti-infective roles of Vitamin D are becoming increasingly important in a variety of skin diseases. Vitamin D has a modulating effect on the dermal immune system is obvious from the neonatal period, with the altered regulatory T cell profile persisting to adulthood [9]. Possibly Vitamin D use could potentially reduce inappropriate antibiotic prescription and boost therapeutic response when combined with appropriate antibiotic use. In this review we discuss the possible mechanisms

by which Vitamin D may modulate the Immune System and its antimicrobial effects.

Immunomodulatory Function of Vitamin D

Vitamin D exerts an immunomodular response equally on mononuclear and polynuclear cell lines through its effects on the vitamin D receptor VDR [10]. VDR is present in all types of cells, including T and B lymphocytes (both resting and activated), dendritic cells, innate lymphoid cells and Monocytes [8].

Circulating Vitamin D has a direct influence on macrophages, it increases their potential for oxidative burst that is production and maturation of cytokines, hydrogen peroxide and acid phosphatase, and inhibit disproportionate expression of inflammatory cytokines. Vitamin D also facilitates phagocytic function and neutrophil motility [11].

T-Cell

The basic effects of Vitamin D include modulation of cytokine secretion in T Cells and its differentiation, but VDR is also required for T cell activation by maintaining T Cell Receptors TCR signaling [12]. The CD4+ T cells present themselves as a heterogeneous group of Th1, Th2, Th17, and Treg cells. During a normal immune system response, resistance against intracellular pathogens is presented by Th1 cells, Th2 cells have effect on helminth infections and Th17 type of T cells are responsible for fungi and extracellular pathogens. Alternatively, Tregs reconcile immunological tolerance against harmless foreign antigens and self-antigens [13].

A Randomized Controlled trial found that High Dose of Vitamin D3 reduced CD4+ T-cell activation in comparison to a its low-dosage. This Study provided evidence that vitamin D dosage in humans can alter cell-mediated immunity [14]. T Cells and B cells as antigen presenting cells have the auxiliary machinery for the synthesize and response to Vitmin D, In an immune system vitamin D may act in a paracrine or autocrine manner [15].

There is a documented proof that T cells of patients suffering from Multiple Sclerosis (MS) respond to vitamin D. These stimulated CD4 cells show an increase in production in MS patients; its controls are likewise inhibited subsequently to pre-incubation in increased concentrations of vitamin D [16]. In another random trial of vitamin D supplementation, Five out of six individuals (one healthy and four patient volunteers) showed a surge in circulating Tregs after periods of 3 to 12 months [17].

B cell

Increasing evidence is available in support of Vitamin B that shows its role in multiple sclerosis (MS) while an inflammation primarily T-cell-mediated is present in MS patients. A poor level of vitamin D associated as a key environmental factor with such disease prevalence and severity.

An *in vitro* review by Rolf et al. indicated several effects of vitamin D on B cells; it may be favourable in reduction of T-cell co-stimulation, inhibiting plasma cell generation and boosting Breg cell activity in MS. Available data for the effects of B-cell-depleting drugs, supports the 'innate' B-cell functions while makes it less likely for production of autoantibodies to play a key role in MS pathology [18].

Though a well published record is available in support of Vitamin D, still the impact of 1,25(OH)2D3 on Regulatory B cells is not absolute. There is a hypothesis that 1,25(OH)2D3 revokes the pathogenicity of B cells in autoimmune response by obstructing plasma cell differentiation and by this means auto-antibody production is hindered [19].

B Cells go through various stages of differentiation, class-switch recombination and somatic hypermutation before becoming plasma cells that can secrete high-affinity antibodies. Another study suggests that if VDR binds at promoter region of genes that are involved in activating immune response mechanism of lymphoblastic B cell lines, this lights up the role of vitamin D in B cells regulated autoimmune diseases [13].

Innate lymphoid cells

Relatively a new epitome of immune system response is Innate Lymphoid Cell (ILC). There is a significant part played through ILC in tissue homeostasis, tissue repair and the immune response against pathogenic microorganisms. ILCs can be grouped into three classes as follows:

1. **Group 1 ILCs (ILC1):** Secretes IFNγ and depend on T-bet expression.
2. **Group 2 ILCs (ILC2):** Secretes type 2 cytokines like IL-5 and IL-13 and depend on GATA3.
3. **Group 3 ILCs (ILC3):** Secretes IL-17A and/or IL-22 and depend on RORC [20].

The ILC1s takes in natural killer cells (NK), this NK cells have long been discovered and are known for their attack on viruses. Subsequently, auto immune diseases are considered to be under the influence of viral triggers, there are significant discoveries for NK cells for their role in this perspective. However, a recent review by Poggi and Zocchi proposes that under particular conditions, NK cells behave as defensive, while in some cases they are pathogenic in nature [21]. This data is still contradictory to the concept that 1,25(OH)2D3 induces the cytolytic killing ability of NK cells [22]. However, increase in number of NK cells can be decreased, their cytotoxicity as well as IFNγ production can also be reduced if $1.25(OH)_2D_3$ is supplemented to the *in vitro* differentiation of NK cells through hematopoietic stem cells [23].

Recurrent cases of women with pregnancy losses [24] imposes inhibition of activation, cytotoxic capacity and pro-inflammatory cytokine production regarded to 1,25(OH)2D3 dosage specifically in over activated NK cells. It holds the hypothesis that 1,25(OH)2D3 has no effect on immune response as a general inhibitor, but supports it as a regulator for immune homeostasis. Hence, it builds a case for 1,25(OH)2D3 in which it modulates abnormal NK activation and also plays a role in autoimmune diseases [24].

Macrophages

1,25(OH) 2D3 has distinct role in both macrophage activation and differentiation. This differentiation of monocytes into macrophages is stimulated by 1,25(OH)2D3 during early stages of an infection. Moreover, the conversion of 25(OH)D3 into 1,25(OH)2D3 is initiated by one of two ways IFNγ-induced activation that activates Cyp27B1 or toll-like receptor triggering [25]. 1,25(OH)2D3 converted via this pathway is then required for the antimicrobial activity of human monocytes, macrophages and producing cathelicidin [5]. In addition, induces IL-1β by up regulation of C/EBPβ or Erk1/2, is also controlled by 1,25(OH)2D3 [26]. So primarily, for an effective pathogen clearance in body 1,25(OH)2D3 is essential.

A randomized control study on mice describes the hyper responsiveness of Lupus Prone Strain stimulation that specifies the role of 1, 25(OH)2D3 in later stages of infection, as it induces the contraction of the immune response [27]. The characterization of anti-inflammatory effect of 1,25(OH)2D3 on macrophages as a result of decrease in production of pro-inflammatory factors such as IL-6, IL-1β, TNFα, COX-2, RANKL, nitric oxide and increased anti-inflammatory IL-10 [28].

These changes suggest an increase in M2 phenotype while inhibition of M1 phenotype that results in restoration of balance between subsets of M2 and M1 Phenotype, this phenomenon occurs in abundance of 1, 25(OH)2D3. In addition, 1,25(OH)2D3-treated macrophages possess reduction in T cell stimulatory aptitude [29].

Latest studies show some developments in understanding the mechanism for an anti-inflammatory effect of Vitamin D3 on macrophages. Such findings suggest that thioesterase superfamily member 4 (THEM4) which is an inhibitor of the NFκB signalling pathway is important target of 1,25(OH)2D3. THEM4 prevents COX-2 transcription by inhibiting the targeted binding of NFκB to the COX-2 Chromosome locus [30].

Studies to understand the treatment of autoimmune disease, focus on the balancing effect of 1,25(OH)2D3 on both the anti and pro-inflammatory status of macrophages. At present, M1 macrophages secrete many inflammatory mediators, like IL-1β, COX-2, IL-6, and especially TNFα that play important role in various autoimmune diseases as successful therapeutic targets [28]. However, patients may become prone to infections due to systemic reduction of these therapeutic mediators. Consequently, this raises interest for understanding the process by which 1, 25(OH) 2D3 maintains a balance between both anti- and pro-inflammatory actions [13]. This could deliver comprehensive understanding in how to suppress the hyper activation of pro-inflammatory cytokines, without triggering disturbance in the standard immune response.

Discussion

One thing is clear from above data that there is irrefutable effect of vitamin D on the immune system. The *in vitro* data explains the overwhelming physiological role of vitamin D in immune system modulation. Its regulatory effect on immune system can be detected by exposing immunocytes to nutritional and medicinal doses according to RDA [31] of vitamin D metabolites. Moreover, the periodic use of vitamin D, in daily or weekly comparable cumulative RDA doses [31] instead of every 6–12 months, may pose long-term compatibility of immune system subject to the standard of living of the target individuals. For better effect, the timing of intake of vitamin D medication is crucial.

As described by Grant and Holick [32] In humans, an association occurs between hostile autoimmune diseases or infections and vitamin D deficiency. When designing clinical trials the important reason might be the miss interpretation of dose, frequency of administration and the choice of the vitamin D metabolite. As many isolated immune cells show *in vitro* effects if induced by concentrations of 1,25-(OH)D_2D_3, which are exceeding to RDA [33].

These concentrations risk hyper-calcemia and soft tissue calcifications, it is probably because normal daily dosage could be interrupted with dietary habits for regular vitamin D supplementation [34]. Consequently, prospective both random and controlled trials will make it obligatory to investigate whether supplementation with consistent vitamin D can indeed inhibit or adjust the prevalence of autoimmune diseases or inflammatory infections in at-risk subjects.

We are in accordance with Martens et al. [35] that the regular dose of vitamin D may avoid any severe autoimmune disease which may occur due to vitamin D deficiency and decreases susceptibility to autoimmune diseases as well as improves immune cells health. Another type of immune cells has gained light in recent years, innate lymphoid cells (ILC), with relatively lower number of clinical trials the effects of vitamin D on ILC is not yet probed broadly [20]. Existing data after characterization of ILC propose that Vitamin D correspondingly have anti-inflammatory effects on these cells. Still more studies are required to distinguish the effects on the different subsets and its role in the protective effect of vitamin D in autoimmunity [36].

Conclusion

Pharmaceutical and clinical trials should raise the critical analysis if vitamin D is really efficient in modern life to prevent or fight metabolic, inflammatory, and degenerative disorders. Thus further research is therefore needed.

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