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Vitamin D and the Immune System

Vikram Singh Chauhan

Abstract

In the past few decades, various novel actions of vitamin D have been discovered. The mechanism of action of calcitriol or vitamin D is mediated by the Vitamin D receptor (VDR), a subfamily of nuclear receptors, which acts as a transcription factor in the target cells after formation of a heterodimer with the retinoid X receptor (RXR). As the VDR has been found in virtually all cell types, vitamin D exerts multiple actions on different tissues. Vitamin D has important immunomodulatory actions, which includes enhancement of the innate immune system and inhibition of the adaptive immune responses. These actions are associated with an increase in production of interleukin (IL)-4 by T helper (Th)-2 lymphocytes and the up-regulation of regulatory T lymphocytes. Vitamin D can regulate the immune responses in secondary lymphoid organs as well as in target organs through a number of mechanisms. Vitamin D inhibits the expression of APC cytokines, such as interleukin-1 (IL-1), IL-6, IL-12, and tissue necrosis factor- α (TNF- α) and decreases the expression of a set of major histocompatibility complex (MHC) class II cell surface proteins in macrophages. Vitamin D also inhibits B cell differentiation and antibody production. These actions reflect an important role of Vitamin D in balancing the immune system.

Keywords: Vitamin D, Immunity, Vitamin D receptor

1. Introduction

Vitamin D is now recognized as a vitamin as well as a pro hormone. It exists in two major forms: vitamin D₂ (ergocalciferol) and vitamin D₃ (cholecalciferol). Vitamin D₃ is formed in the human skin and is obtained in the diet through the intake of animal-based foods such as fish oils, whereas vitamin D₂ is present in plant sources [1]. Vitamin D is traditionally known to be involved in the regulation of calcium and phosphate metabolism. Apart from its role in maintaining bone mineralization, vitamin D also has a well described function as an immunomodulatory hormone [2]. The Vitamin D receptor (VDR) and metabolizing enzymes are expressed by numerous types of immune cells such as lymphocytes, macrophages, monocytes and dendritic cells [3, 4]. Preliminary studies have revealed that vitamin D has noteworthy biologic activities on the innate and adaptive immune systems. Some preclinical studies have demonstrated that administration of vitamin D leads to changes in the occurrence and progression of many immune-related diseases [2, 5]. This is supported by clinical data that explains the possible association of vitamin D with the incidence of many disorders such as type 1 diabetes, psoriasis, rheumatoid arthritis, multiple sclerosis and infectious diseases. The purpose of the present chapter is to provide a summary

of the effects of vitamin D on the immune system and the link between vitamin D and numerous types of immune-related diseases and conditions.

2. Vitamin D and the immune system

A significant role of vitamin D in the regulation of the immune system has been discovered in the last few decades. In 1983, the contribution of macrophages in producing vitamin D was documented by separation of VDR in activated human inflammatory cells [6, 7]. The role of vitamin D in the inhibition of T cell proliferation was discovered by Rigby, *et al* in 1984 [8]. Further evidences were found for elaborating the role of vitamin D in the regulation of the immune system [8].

T cells and B cells respond to $1, 25(\text{OH})_2\text{D}$ in a paracrine or autocrine manner in an immune environment. The action of $1, 25(\text{OH})_2\text{D}$ on the inhibition of T helper cells was documented in preclinical studies. These effects include directly lowering the dendritic cell capability to activate T helper 17, inhibition of T helper 17-related IL-17 and hampering the ability to support T helper 17 polarization of naïve CD4^+ T cells production [9]. In an autoimmune uveitis preclinical model, oral administration of $1, 25(\text{OH})_2\text{D}$ prevented and inhibited immunological responses, as shown by reduction of both ROR- γ -t (Retinoic acid Receptor-related Orphan Receptor γ t) and IL-17 in CD4^+ T cells, which are two indicators of T helper 17 cell function. Moreover, $1, 25(\text{OH})_2\text{D}$ inhibited bone marrow-derived dendritic cell ability to influence T helper 17 polarization of naïve CD4^+ T cells [9].

$1, 25(\text{OH})_2\text{D}$ has also been involved in the inhibition of immunoglobulin production and B cell proliferation and differentiation [10]. Low $1, 25(\text{OH})_2\text{D}$ level had been found in patients with systemic lupus erythematosus (SLE), suggesting that vitamin D could be involved in the regulation of autoantibody expression. Chen, *et al* showed that $1, 25(\text{OH})_2\text{D}$ has a direct effect on B cells, including inhibition of proliferation, on generation of class-switched memory B cells and on immunoglobulin production in patients with SLE [10].

Vitamin D is also involved macrophage regulation and affects their cytokine expression. It increases prostaglandin E2 production from macrophages, which has a role in the inflammatory process and inhibits the expression of granulocyte-macrophage colony-stimulating factor. Moreover, $1, 25(\text{OH})_2\text{D}$ induces macrophages and epithelial cells to produce cathelicidin, a peptide involved in antimicrobial action [11, 12]. Cathelicidin is responsible for activating the innate immune response by binding to its transmembrane receptor and is correlated to higher levels of the enzyme 1- α -hydroxylase in macrophages and keratinocytes [13]. The enzyme 1- α -hydroxylase further increases the production of cathelicidin through the production of $1, 25(\text{OH})_2\text{D}$.

Vitamin D is also involved in the activation of dendritic cells which enhance expression of $\text{CD4}^+/\text{CD25}^+$ regulatory T cells (T reg). In preclinical study by Gregori *et al*, $1, 25(\text{OH})_2\text{D}$ activated dendritic cells with a tolerogenic phenotype and caused an increased percentage of $\text{CD4}^+/\text{CD25}^+$ T reg in the spleen and lymph nodes. These regulatory T cells have a role in the transfer of transplantation tolerance [14].

3. Vitamin D and the innate immune system

Innate antigen presenting cells (APC), specifically dendritic cells (DC) are principal targets for the immune modulatory effects of vitamin D. APCs have a crucial role in the initiation of the adaptive immune response as they present antigens to B cells and T cells and are able to modulate them by immunogenic signals such as the

expression of cytokines. Vitamin D and its analogs modify the function of DCs to induce a more tolerogenic and immature state. Immature DCs result in decreased levels of MHC class II and co-stimulatory molecule expression (CD40, CD80, CD86), which negatively affects antigen presentation accompanied by a lower IL-12 secretion, but an increased production of the tolerogenic interleukin IL-10. High-dose vitamin D supplementation in healthy humans (1 µg twice daily for 7 days) results in significant reduction in the proinflammatory cytokine IL-6 produced by peripheral mononuclear cells. A combination of all these effects results in the induction of potential regulatory T cells which are crucial for controlling immune responses and the development of autoreactivity [15]. A clinical study in 95 patients treated with adjunctive vitamin D therapy, added on to standard tuberculosis therapy demonstrated augmented resolution of inflammatory responses [16].

4. Vitamin D and the adaptive immune system

The expression of the nuclear VDR and vitamin D-activating enzymes in both T- and B types of human adaptive immune cells have been reported in studies. The activation and proliferation of T and B cells results in up-regulation of VDR expression, which ultimately regulates more than 500 vitamin D responsive genes [15].

Following are the proposed mechanisms for influence of vitamin D on T cell function [15]:

1. Direct, endocrine effects on T cells mediated via systemic vitamin D.
2. Direct, intracrine conversion of 25(OH) D to calcitriol by T cells.
3. Direct, paracrine effects of calcitriol on T cells following monocytes or dendritic cells induced conversion of 25(OH) D to calcitriol.
4. Indirect effects on antigen presentation to T cells mediated via localized APCs by calcitriol.

All these effects of vitamin D result in shifting from a proinflammatory status to a more tolerogenic immune status, including very diverse effects on T cell subtypes: Vitamin D suppresses T helper cell proliferation, differentiation and modulates synthesis of cytokines [15].

5. Vitamin D and autoimmune diseases

Clinical studies investigated the association of vitamin D levels with the risk of developing autoimmunity and effect of vitamin D administration on autoimmune diseases. A systematic review of 219 studies demonstrated that vitamin D levels of <30 ng/mL are significantly associated with autoimmune disease. In patients with type-1 diabetes, the risks are significantly reduced in infants treated with vitamin D after the seventh month [17].

6. Vitamin D and Type 1 Diabetes Mellitus

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease with T cell mediated destruction of pancreatic β-cells. It is hypothesized that Vitamin D supplementation

early in life could be protective therapy against the development of T1DM [18]. Vitamin D supplementation in the first year of life in children produced a 33% risk reduction of developing T1D in a subgroup analysis of the EURODIAB study [19]. A meta-analysis of four clinical studies also revealed a significantly reduced risk of development of T1D among infants receiving vitamin D supplementation [20]. Many trials on vitamin D and T1D are currently ongoing which will hopefully expand our understanding of this topic.

7. Vitamin D and multiple sclerosis

Hypovitaminosis D is one of the important risk factors for the increased risk of development of multiple sclerosis (MS). In a cohort of the Nurses' Health Study (92953 women) and Nurses' Health Study II (95310 women), the intake of Vitamin D ≥ 400 IU/day was associated with the reduced risk of developing MS. [21] In a study by Merja et al., vitamin D3 add on treatment to interferon β -1b reduces MRI disease activity in MS [22]. Currently ongoing studies such as *SOLAR* and the *EVIDIMS* study will explore many aspects of the role of vitamin D in the management of MS in the coming years.

8. Vitamin D and psoriasis

Vitamin D is involved in the proliferation and maturation of keratinocytes. This action of vitamin D created interest as a topical therapeutic option in the treatment of psoriasis. A significant association between low vitamin D levels and psoriasis has been reported. Although the exact role of vitamin D in the pathogenesis of psoriasis is unclear, possible mechanisms include the regulation of the cutaneous immune system (inhibition of T cell proliferation, T reg induction) and down-regulation of pro-inflammatory cytokines. However robust clinical data regarding a role of vitamin D in psoriasis is still awaited [23].

9. Vitamin D and rheumatoid arthritis

In addition to inhibiting inflammatory cytokines such as IL-6, TNF α , IL-17 in synovial fluid, vitamin D also reduces fibroblast erosion [24]. Vitamin D supplementation was found to be associated with lower risk of RA in a prospective cohort of 29,368 women over a follow up period of 11 years [25]. A randomized controlled trial (RCT) by Buondonno et al. [26] evaluated the effect of administration of cholecalciferol on T helper cell sub-types and osteoclast precursors. Single dose of cholecalciferol (300,000 IU) along with standard treatment showed improvements in inflammatory cytokines in this study [26]. Further studies are required to estimate the dose of Vitamin D in the treatment of RA.

10. Conclusion and future perspectives

The role of Vitamin D in autoimmune disease is a major area of research. Addressing questions as to whether vitamin D levels are related to the risk of developing autoimmunity and whether vitamin D supplementation can modify the course of autoimmune diseases, several studies performed over the last four decades support

the role of vitamin D in the prevention of autoimmune diseases. However there is still a need of randomized controlled clinical trials in this field. Upcoming clinical trials will find out the optimal mode and dosage of supplementation of vitamin D. However, with available data, vitamin D emerges as a promising nutrient in the prevention and adjunctive treatment of diseases caused by impaired immune-homeostasis.

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Author details

Vikram Singh Chauhan
Dr. Chauhan's Clinic and Jabalpur Hospital and Research Center, Jabalpur, India

*Address all correspondence to: vikramsinghchauhan@gmail.com

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