Chapter

Vitamin D and the Immune System

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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 immuno-modulatory actions, which includes enhancement of the innate immune system and inhibition of the adaptative 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 (MCH) 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$(OH)_2$D in a paracrine or autocrine manner in an immune environment. The action of 1,25$(OH)_2$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$(OH)_2$D prevented and inhibited immunological responses, as shown by reduction of both ROR-gamma-t (Retinoic acid Receptor-related Orphan Receptor gamma t) and IL-17 in CD4+ T cells, which are two indicators of T helper 17 cell function. Moreover, 1, 25$(OH)_2$D inhibited bone marrow-derived dendritic cell ability to influence T helper 17 polarization of naive CD4+ T cells [9].

1, 25$(OH)_2$D has also been involved in the inhibition of immunoglobulin production and B cell proliferation and differentiation [10]. Low 1, 25(OH) [2] 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$(OH)_2$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$(OH)_2$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-alpha-hydroxylase in macrophages and keratinocytes [13]. The enzyme 1-alpha-hydroxylase further increases the production of cathelicidin through the production of 1,25$(OH)_2$D.

Vitamin D is also involved in the activation of dendritic cells which enhance expression of CD4+/CD25+ regulatory T cells (T reg). In preclinical study by Gregori *et al*, 1, 25$(OH)_2$D activated dendritic cells with a tolerogenic phenotype and caused an increased percentage of CD4+/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, TNFα, 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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