Autoimmunity Reviews 12 (2012) 127–136

Contents lists available at SciVerse ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature

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ARTICLE INFO

Available online 7 July 2012

Keywords:
Vitamin D level
Hypovitaminosis D
Autoimmunity
Autoimmune diseases
Supplementation
Systematic review
Risk factors

ABSTRACT

Objective: To evaluate whether vitamin D levels are related to the risk of developing autoimmune diseases and whether supplementation with vitamin D can modify the course of the diseases.
Methods: We reviewed the most relevant papers published from January 1973 to October 2011, using Medline and EMBASE and the search terms "vitamin D"; "autoimmune disease"; "autoimmunity"; "rheumatoid arthritis"; "systemic lupus erythematosus"; "scleroderma"; "systemic sclerosis"; "type 1 diabetes"; "multiple sclerosis"; and "undifferentiated connective tissue disease". We selected studies on the environmental, genetic and epidemiologic association of vitamin D with autoimmune diseases.
Using the strategy described, we identified 1268 articles. 331 articles were eliminated on the basis of the title and another 703 on the basis of the abstract, since they were considered irrelevant for the purposes of the study. Full-text examination was performed on the remaining 234 studies, and a further 15 studies were excluded from the review, since the results had been confirmed or superseded by more recent research. Finally, a systematic review was conducted on 219 articles concerning cross-sectional data on: vitamin D levels and autoimmune diseases; interventional data on vitamin D supplementation in autoimmune diseases; prospective data linking vitamin D level or intake to autoimmune disease risk.
Results: Physiopathology studies confirm that hypovitaminosis D, in genetically predisposed subjects, can impair self tolerance by compromising the regulation of dendritic cells, of regulatory T-lymphocytes and of Th1 cells. Cross-sectional studies show that levels of vitamin D <30 ng/mL are present in a significant percentage, not only in patients with autoimmune disease, but also in healthy subjects (30–77%), and link profound deficiency (<10 ng/mL) with aggravation of symptomatology, while genetic studies associate polymorphism of vitamin D receptors to various autoimmune diseases. Among experimental studies on humans, only those on type-1 diabetes prove that the risks are significantly reduced in infants treated with vitamin D after the 7th month (OR 0.71, 95% CI, 0.60 to 0.84) and that a dose–response effect exists.
Conclusions: Basic, genetic, and epidemiological studies indicate a potential role of vitamin D in the prevention of autoimmune diseases, but randomized and controlled trials are necessary to establish the clinical efficacy of vitamin D supplementation in ill or at-risk subjects.

Contents

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doi:10.1016/j.autrev.2012.07.007

1. Introduction

The cause of the loss of immune tolerance towards self antigens that leads to the development of autoimmune diseases (AIDs) is not yet known. It is considered that environmental causes [1–3], genetic polymorphisms [4,5], and epidemiological risk factors [6,7] favor the emergence of autoimmunity in susceptible individuals, but the event that triggers the different pathologies remains unknown. AIDs are widespread throughout the world and their incidence is continually increasing [8]. For reasons that have not yet been clarified, in industrialized countries the incidence is higher among women, for whom these diseases represent the third cause of death [9,10]. There is as yet no general consensus about the possible strategies for prevention and treatment of most autoimmune diseases; treatment frequently involves the use of corticosteroids, immunosuppressive agents and biological drugs aimed at various inflammatory cytokines [11].

Vitamin D (vit D) is a prohormone that also exerts an endocrine action on the cells of the immune system, generating antiinflammatory and immunoregulatory effects [12,13]. Macrophages, dendritic cells (DCs) and T and B cells possess the enzymatic machinery to produce vit D, and an enzyme expressed in these cells (1 alfa hydroxylase) can be induced by several factors, including interferon-γ (IFN-γ) and is down-regulated during DC maturation [14]. This suggests that vit D is capable of physiologically contributing to the autocrine and paracrine regulation of both innate and adaptive immunities, by means of the vit D receptor (VDR) expressed in the nucleus of these cells. Numerous studies confirm that $1,25(OH)_2D_3$ (calcitriol; the active form of vit D) enhances the innate immune response whereas it exercises an inhibitory action on the adaptive immune system, in which it regulates the interaction between lymphocytes and antigen presenting cells (APCs) and modulates the effector mechanisms [15–17].

$1,25(OH)_2D_3$ causes direct regulatory effects on the functions of T lymphocytes by: inhibiting the proliferation of Th1, capable of producing IFN-γ and interleukin 2 (IL-2), and activating macrophages [18]; increasing the quantity of Th2 through a direct effect on native CD4s [19] or acting on the DCs/APCs facilitating the production of IL-4, IL-5 and IL-10, which move the T differentiation in favor of phenotype Th2 [20]; increasing the quantity of $CD4^+/CD25^+$ T-regulators cells (Tregs) which produce IL10, by means of which they block the development of Th1 and inhibit the secretion of IL-17 by the T-effectors [21].

Calcitriol has powerful and direct effects also on the B cell response, causing induction of apoptosis, inhibition of B cell proliferation, generation of B memory cells, plasma cell differentiation and immunoglobulin production [22].

Moreover it influences the phenotype and function of APCs and mainly of DCs, a highly specialized system of APC critical for the initiation of the $CD4^+$ T-cell response, promoting tolerogenic properties that facilitate the induction of Treg instead of T-effectors [23].

The administration of VDR agonists facilitates the proliferation of DCs with tolerance properties: (a) inhibiting the differentiation and maturation of DCs [24]; (b) decreasing the expression of CD40, CD80 and CD86 co-stimulatory molecules [25]; (c) significantly reducing the production of IL-12 while increasing the production of IL-10 [26], and finally, (d) inducing the expression of immunoglobulin-like transcript 3 (ILT3), an inhibitory molecule associated with tolerance induction [27]. Immature DCs differentiated in monocytes in the presence of calcitriol respond poorly to inflammatory chemokines that regulate their maturation and migration to lymph nodes [18]. This explains the inhibitory effect of the active hormone on the maturation of DCs and on their production of proinflammatory mediators [28]. Consequently, the active synthesis of calcitriol within DCs not only inhibits their differentiation in monocytes but also blocks their ability to undergo a final differentiation in response to maturation stimuli [29]. In addition, vit D regulates monocyte differentiation in macrophages, prevents them from releasing inflammatory cytokines and chemokines, and reduces their capacity to present antigens to lymphocytes by decreasing MHC-II molecule cell surface expression [30]. During inflammatory processes calcitriol negatively regulates the expression of the kB nuclear factor, fundamental both for the differentiation and maturation of DCs and to trigger the inflammatory response [31]. DCs with tolerance properties induced by VDR agonists are capable of inducing differentiation of $CD4^+CD25^+$ Tregs capable of stopping the development of autoimmune diabetes (T1DM) [24]. DCs inducing tolerance, produced after a short treatment with calcitriol, lead to the development of $CD4^+CD25^+$ Tregs able to mediate the tolerance to transplants and to block the development of T1DM [32]. Therefore DCs can be immunogenic, but can also induce tolerance both in the thymus and in the periphery through the vit D action.

Taken together, these data suggest that VDR agonists regulate the activation and differentiation of T-cells, either by acting directly or by modulating DC function. Since DCs are central to the maintenance of both protective immunity and self-tolerance [33,34], it is legitimate to assume that a deficiency of vit D could have consequences on their maturation and function and consequently on the risk and/or progression of autoimmune disease. In experimental animal models the supplementation with $1.25(OH)_2D_3$ forestalls the development of inflammatory arthritis, autoimmune encephalomyelitis (a model for multiple sclerosis), T1DM, and autoimmune thyroiditis [35–38]. Treatment with a low calcemic vit D analog had a prophylactic and therapeutic effect on a murine model of Th1-like colitis [39] and administration of $1.25(OH)_2D_3$ or its analogs to non-obese diabetic mice modulates the expression of chemokines and cytokines and prevents diabetes [40]. Following these experimental indications, the hypothesis was formulated that the dosage and/or administration of this hormone can be effective in the clinical management and treatment of the patient suffering from an autoimmune disease.

Over recent years it has been demonstrated that vit D plays an important role in the immune system and it has been hypothesized that: (a) vitamin D deficiency can act as an environmental trigger that increases the prevalence of AIDs, especially in populations featuring geographical, climatic and ethnic particularities [41]; (b) serum levels of the hormone may play a role in their pathogenesis [42]; and (c) the administration of high doses of vitamin D may perform a preventive action [16]. For these reasons, we performed a systematic review of the literature published over the last 38 years, with the aim of evaluating whether low levels of vit D in humans can be correlated with the risk of developing AIDs and whether the administration of the hormone can modify the incidence of the disease or modify the course of autoimmune pathologies.

2. Methods

2.1. Data sources

The research was carried out in the PubMed and EMBASE databases in October 2011 using the key words “vitamin D”; “autoimmune disease”; “autoimmunity”; “rheumatoid arthritis”; “systemic