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Review

Is vitamin D a player or not in the pathophysiology of autoimmune thyroid diseases?

Federica D'Aurizio [a], Danilo Villalta [b], Paolo Metus [a], Paolo Doretto [a], Renato Tozzoli [a,*]

[a] Clinical Pathology Laboratory, Department of Laboratory Medicine, S. Maria degli Angeli Hospital, Pordenone, Italy
[b] Allergology and Immunology, Department of Laboratory Medicine, S. Maria degli Angeli Hospital, Pordenone, Italy

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ABSTRACT

1,25-Dihydroxyvitamin D is a steroid hormone derived from vitamin D, playing an important role in maintaining an adequate serum level of calcium and phosphorus. It is now clear that vitamin D exerts an endocrine action on the cells of the immune system, generating anti-inflammatory and immunoregulatory effects. The mechanisms underlying the role of vitamin D in autoimmunity are not completely understood. Lower vitamin D levels have been found in several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes mellitus, multiple sclerosis, inflammatory bowel diseases, autoimmune thyroid diseases (i.e. Hashimoto's thyroiditis and Graves' disease) and autoimmune gastritis. Several genetic studies have demonstrated an association between thyroid autoimmunity susceptibility and gene polymorphisms of vitamin D receptor, vitamin D binding protein, 1-alpha-hydroxylase and 25-hydroxylase. Of note, some papers do not confirm this connection. With regard to the role of vitamin D in autoimmune thyroid diseases, available data remain controversial. Only few reports have analyzed the supposed association between autoimmune thyroid diseases and vitamin D concentration with inconclusive results. In our experience, low serum levels of vitamin D do not correlate either with Hashimoto's thyroiditis or with Graves' disease. The inability to achieve an unambiguous conclusion is in part due to the limitations in study design. In fact, most of the studies are cross-sectional surveys with a small number of subjects. In addition, the heterogeneity of the study population, seasonal variation of blood sampling, inter-method analytical variability of vitamin D assays and different definitions of vitamin D deficiency/insufficiency contribute to contradicting results. Therefore, further randomized, controlled, prospective trials are needed in order to demonstrate the causality of vitD in AITD and consequently the role of vitamin D supplementation in prevention or improvement of AITD, providing also information on the best formulation, dose and timing of supplementation.

Contents

1. Introduction

1,25-Dihydroxyvitamin D [1,25$(OH)_2$D, calcitriol] is a steroid hormone derived from vitamin D (vitD), which plays an important role in

* Corresponding author at: Clinical Pathology Laboratory, Department of Laboratory Medicine, S. Maria degli Angeli Hospital, Via Montereale, 24, 33170 Pordenone, Italy. Tel.: +39 0434 399213, +39 329 2106646; fax: +39 0434 399906.
E-mail address: renato.tozzoli@aopn.sanita.fvg.it (R. Tozzoli).

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maintaining an adequate level of serum calcium and phosphorus [1]. The two main precursors of vitD are vitD$_3$ and vitD$_2$; both vitD precursors, resulting from exposure to sunlight (vitD$_3$) and diet (vitD$_2$), are converted to 25-hydroxyvitamin D [25(OH)D, calcidiol] by 25-hydroxylase (CYP2R1), when they enter the liver [2]. More than 95% of 25(OH)D measurable in serum is typically 25(OH)D$_3$, while 25(OH)D$_2$ reaches measurable concentrations only in patients taking vitD supplementation [3,4]. Calcidiol is carried in the blood as a complex with a vitamin D binding protein (DBP) and converted in calcitriol by 1-alpha-hydroxylase (CYP27B1), the key enzyme in the synthesis of active vitD. The recent description that several human tissues and cells express the vitamin D receptor (VDR) and 1-alpha-hydroxylase allows a growing interest in extra-skeletal functions of this vitamin: it is now clear that vitD plays an essential role in a variety of physiological conditions and that their deficiency is associated with acute and chronic illnesses, including disorders of calcium metabolism, cancers, autoimmune diseases, infections and cardiovascular diseases [5].

2. Vitamin D and the immune system

VitD exerts an endocrine action on the cells of the immune system, generating anti-inflammatory and immunoregulatory effects [6,7]. Macrophages, dendritic cells (DCs) and T and B cells possess the enzymatic machinery to produce vitD and 1-alpha-hydroxylase: the enzyme can be induced by several factors, including interferon γ (IFN-γ) and is down-regulated during DC maturation. This suggests that vitD presents a physiological role of endocrine, intracrine and paracrine regulation of both innate and adaptive immunities, by means of the VDR expressed in the nucleus of these cells [8,9].

VDR is a member of a transcription factor family, characterized by a highly conserved DNA-binding domain and a structurally conserved ligand-binding domain, and it acts as modulator of gene transcription [10]. Ligand binding initiates a conformational change that increases the receptor's affinity to the retinoid X receptor (RXR): once the VDR–calcitriol complex is heterodimerized with RXR, the complex will bind to vitamin D response elements and recruit a number of nuclear coactivator and corepressor proteins [11]. In humans, the VDR locus is located at chromosome 12q13.1. The gene encoding VDR spans over 100 kb and contains 9 exons and 8 introns and harbors approximately 200 single nucleotide polymorphisms (SNPs). Four SNPs, including Fok1 (re2228570), ApaI (re7975232), BsmI (rs1544410), and TaqI (rs731236) have been identified in the VDR gene and extensively studied with regard to their association with the risk of autoimmune diseases (AIDs) [11], particularly in patients with multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus, inflammatory bowel diseases and autoimmune thyroid diseases (AITDs).

Several studies confirm that calcitriol 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. Calcitriol causes direct regulatory effects on the functions of T lymphocytes by: (a) inhibiting the proliferation of type 1 T helper cells (Th1), capable of producing IFN-γ and interleukin-2 and activating macrophages; (b) increasing the quantity of type 2 T helper cells (Th2) through a direct effect on native CD4 or acting on the DC/APC facilitating the production of interleukin-4, interleukin-5 and interleukin-10 (IL-10), which move T differentiation in favor of phenotype Th2; and (c) increasing the quantity of $CD4^+/CD25^+$ T-regulator cells which produce IL-10, by means of which they block the development of Th1 and inhibit the secretion of interleukin-17 by the T-effectors [12]. 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 [12].

3. Vitamin D and autoimmunity

VDR regulates 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, it is legitimate to assume that a deficiency of vitD could have consequences on their maturation and function and consequently on the risk and/or progression of AIDs.

Over recent years, it has been demonstrated that vitD 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; (b) serum levels of the hormone may play a role in their pathogenesis [13]; and (c) the administration of high doses of vitD may perform a preventive action [14].

AIDs are characterized by a loss of immune homeostasis, resulting in altered self-antigen recognition and in destruction of body tissues by autoreactive immune cells. AIDs are the result of a combination of genetic predisposition, epidemiological/existential factors and environmental triggers, among which one important factor is the availability of sufficient vitD levels.

The mechanisms underlying the link between vitD with autoimmunity are not completely understood, but probably are associated with its anti-inflammatory and immunomodulatory functions [15]. Studies of vitD levels comparing populations with and without existent AIDs have been conducted around the world and with somewhat conflicting results. Lower vitD levels have been found in several autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, type 1 diabetes mellitus, multiple sclerosis, inflammatory bowel diseases, AITDs and, very recently, autoimmune gastritis [12–14].

4. Vitamin D and autoimmune thyroid diseases

Thyroid diseases are the most frequent endocrine disorders, among which AITDs, i.e. Hashimoto's thyroiditis (HT) and Graves' disease (GD) occupy the primary position concerning approximately 5% of the population [16–18]. AITDs are multifactorial diseases in which autoimmunity plays a fundamental role with infiltration of the gland by T- and B-cells and production of specific autoantibodies, reactive to thyroid antigens [anti-thyroglobulin, anti-thyroid peroxidase (TPOAb), and anti-TSH receptor (TRAb)].

As with other autoimmune diseases, AITDs result from the interactions among genetic susceptibility factors (thyroid-specific genes and immunoregulatory genes), existential factors (sex, parity, X-chromosome inactivation, etc.), and various environmental triggers (e.g. smoking, alcohol, selenium, iodine, vitD, stress, infections, drugs, etc.) [19–21].

Recently, several genetic studies have demonstrated an association between thyroid autoimmunity susceptibility and gene polymorphisms of numerous proteins and enzymes associated with vitD functions, including VDR, DBP, CYP27B1 and CYP2R1 [22–24]. Of note, some papers do not confirm some of these associations (Table 1) [25–37].

With regard to the direct role of serum vitD levels in AITDs, available data remain controversial. In animal models, vitD administration efficiently prevented the induction of experimental autoimmune thyroiditis [38]; moreover, vitD-deficient BALB/c mice developed persistent hyperthyroidism following three immunizations with TSH-receptor as opposed to their counter mates receiving adequate vitD supply [39].

Taking into account human studies, some years ago, Orbach and Shoenfeld found lower vitD levels in patients with AITDs than in healthy volunteers [40]. In contrast, a study from India found a weak connection between low vitD levels and AITDs [41]. More recently, only few reports have analyzed the supposed association between AITD and vitD levels, with inconclusive results (Table 2). In particular, as regards the relationship between HT and vitD, Kivity et al. found a significantly higher vitD deficiency (vitD levels < 10 ng/mL) in patients with HT compared with