VitD and Autoimmune Thyroid Disease

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Contributor: Inês Vieira

Vitamin D is a steroid hormone traditionally connected to phosphocalcium metabolism. The discovery of pleiotropic expression of its receptor and of the enzymes involved in its metabolism have led to exploration of the other roles of this vitamin, namely on autoimmune thyroid disease. Most of the existing data support a relationship between vitamin D deficiency and a greater tendency for development and/or higher titers of antibodies linked to Hashimoto's thyroiditis, Graves' disease, and/or postpartum thyroiditis. The nature of this relationship is yet unknown, it may be due to vitamin D's immunoregulatory role, emerge as a consequence of the autoimmune disease, or be a result physiopathological process underlying the autoimmune disease.

Our thesis is that, due to its immunoregulatory role, vitamin D plays a minor role in conjunction with myriad other factors. In some cases, a vicious cycle is generated, thus contributing to the deficiency and aggravating the autoimmune process.

Keywords: Vitamin D ; Autoimmune thyroid disease ; Vitamin D receptor ; Graves' disease ; Hashimoto thyroiditis

1. Introduction

Vitamin D is a steroid hormone traditionally connected to phosphocalcium metabolism. The discovery of pleiotropic expression of its receptor and of the enzymes involved in its metabolism have led to exploration of the other roles of this vitamin. The influence of vitamin D on autoimmune disease—namely, on autoimmune thyroid disease—has been widely studied.

The term vitamin D (VitD) encompasses a group of steroid compounds, namely VitD2 (ergocalciferol) and VitD3 (cholecalciferol) [1].

Its main functions are the regulation of phosphocalcium metabolism and the promotion of bone homeostasis. However, the discovery of the widespread expression of the VitD receptor (VDR) and the enzymes responsible for its metabolism suggests the pleiotropic role of this vitamin and its influence in several diseases[2][3]. An immunomodulatory role is evident and its influence on the development of autoimmune diseases (AID) has been proposed. Autoimmune thyroid disease (AITD) is the most common organ-specific AID[3] and several studies have been carried out to explore the role of VitD in its development and course, as well as the possible impact of supplementation.

2. What is the Nature of the Relationship between Vitamin D levels and Autoimmune Thyroid Disease?

Although there exists some inconsistency in the results of the studies carried out so far, most of the data are consistent with the presence of an association between vitamin D and AITD. However, there are several possible interpretations for this association.

The most commonly cited explanation is the decrease in the immunomodulatory role of $1,25(OH)_2D$, in patients with deficiency, contributing to the development of AID. However, the data obtained to date are mostly resultant from cross-sectional studies, which do not allow for the establishment of causal effects. It is, therefore, essential to evaluate alternative explanatory models.

Some authors have raised the possibility that the various data favoring the involvement of VitD in AITD reflect a consequence, rather than a cause, of the disease. AID may lead to VitD deficiency by causing incapacitation and lower sunlight exposure, malabsorption, and use of corticosteroids[4][5]. In hyperthyroidism, there may be accelerated bone turnover. Kozai et al. found marked decreases in $1,25(OH)_2D$ and CYP27B1 expression in rats with T3-induced hyperthyroidism[6]. In HT, the increase in fat mass caused by hypothyroidism could contribute to the deficiency[7]. Botello et al. studied 88 patients with long-term HT and found a positive correlation between 25(OH)D levels, fT4, and (contrary to expectations) Th17 and TNFα. The authors hypothesized that low levels of fT4 are predictors of a deficiency of 25(OH)D and that the long evolution of the disease and treatment of hypothyroidism are related to a decrease in cytotoxic immune response, regardless of the levels of 25(OH)D[8]. The coexistence of AITD with other AID, such as celiac disease, also deserves consideration. Celiac disease leads to malabsorption with deficiency of several nutrients[9], including VitD[10]and

it is associated with an increased risk of developing other AIDs[9][10]. The presence of biopsy-proven celiac disease in patients with AITD is small, around 1.6% according to a recent meta-analysis (although there may be some underdiagnosis)[11]; therefore, it cannot fully explain the reported lower values of VitD in all AITD patients. However, it is likely to contribute to this association in patients in which both diseases coexist. A group of HT patients with positive transglutaminase antibodies and no symptoms of celiac disease were divided, receiving gluten-free vs. gluten-containing diets. The former group, but not the second one, experienced a reduction in antibody titers and an increase in VitD levels [12]. However, the possibility of VitD deficiency being exclusively a consequence of AIDseems unlikely, given that this relationship has been found in several studies, independently of factors such as age, body mass index, thyroid function tests (i.e., presence of hyper-, hypo-, or euthyroidism) and presence or absence of other AIDs. Furthermore, in a study that evaluated patients with GD and 25(OH)D insufficiency, no statistically significant difference was found in the values of 25(OH)D at baseline and 1 to 2 years after hyperthyroidism therapy (with achievement of euthyroidism)[13]. Therefore, contrary to what would be expected if low levels of VitD were a consequence of the autoimmune disease, treating the autoimmune disease does not improve VitD status.

Another possibility is that the lower levels of 25(OH)D in AID are the result of a pathophysiological mechanism involved in the development of the disease; that is, VDR dysfunction caused by chronic infection by intra-phagocytic microorganisms[7]. This dysfunction could lead to lower production of the antimicrobial peptides that would usually result from activation of VDR. VDR dysfunction could also lead to lesser expression of 24-hydroxylase, with a consequent increase in $1,25(OH)_2D$ levels. Excess $1,25(OH)_2D$ has the ability to displace ligands of nuclear receptors such as α-thyroid, glucocorticoids, and androgens, which can lead to glandular dysfunction [14]. Elevated levels of $1,25(OH)_2D$ further bind to the pregnane X receptor and inhibit the synthesis of 25(OH)D in the liver. In this context, the various data pointing towards a relationship between AID and VitD deficiency may be explained by the fact that the metabolite usually measured is 25(OH)D[15]. This is a counterintuitive hypothesis, with some theoretical background but with little data to support or contradict it directly, as $1,25(OH)_2D$ is rarely quantified. However, some of the above-mentioned studies on VitD supplementation reported elevated PTH and unchanged or slightly lower calcium values, associated with a deficiency of 25(OH)D at baseline with a tendency towards normalization after VitD supplementation[16][17][18]. This does not support the possibility that there is an increase in $1,25(OH)_2D$ in AITD concealed by the quantification of 25(OH)D. Although it may be argued that PTH level elevation and lowering of calcium levels may be explained by VDR dysfunction, it is unlikely that such alterations were susceptible to correction by VitD supplementation, as it would not correct the primary mechanism. The fact that VitD supplementation has shown some beneficial effects on AI parameters is also against this hypothesis.

Analyzing the current evidence, we conclude that, despite that a direct and marked contribution of VitD levels alone in the pathogenesis of AITD is unlikely, given the marked inconsistency of the data, a minor contribution is probable, as the existence of an association has been supported by the majority of the studies cited above (refer to Section 5.2. Data on vitamin D levels and autoimmune thyroid disease). Therefore, it is plausible that the levels of VitD, the polymorphisms of its receptor[19][20][21][22], and the enzymes that govern its metabolism[23] influence its regulatory capacity and, thus, it likely plays a small, yet significant, role in the development and course of AITD. It is likely that this contribution depends upon a multiplicity of other factors, such as age and gender, sex hormones [24][25], and micronutrients[26]. Genetic, epigenetic, and other endogenous and environmental factors which contribute to the predisposition to AITD may also influence this correlation, explaining some of the inconsistency in the results obtained in different populations. The above-mentioned consequences of AITD (e.g., incapacitation, lower sunlight exposure, obesity in hypothyroidism, and increased bone turnover in hyperthyroidism) and, in some cases, the coexistence of other AID may generate a vicious cycle and contribute to the observed relationship.

3. What is the role of vitamin D supplementation in autoimmune thyroid disease?

Given the paucity of data in this regard, a logical approach is to aim for VitD levels within the reference ranges suggested by international guidelines. The Institute of Medicine considers 20 ng/mL to be sufficient for most of the general population[27]. The Endocrine Society Guidelines, focused on individuals with risk of VitD deficiency, identify an optimal level of 25(OH)D > 30 ng/mL and that values up to 100 ng/mL (250 nmol/L) are safe (as they do not cause hypercalcemia) [28].

In the future, more data from investigations with a larger number of individuals, a more global scope, and involving year-round evaluations of VitD levels are necessary, in order to provide more uniform and consistent answers to this question.

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