Immunomodulatory Function of Vitamin D

Subjects: Health Care Sciences & Services

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Hashimoto's thyroiditis (HT), also known as chronic autoimmune thyroiditis, is the most prevalent organ-specific autoimmune disorder. Hashimoto's thyroiditis (HT) is marked by self-tissue destruction as a consequence of an alteration in the adaptive immune response that entails the evasion of immune regulation. Vitamin D carries out an immunomodulatory role that appears to promote immune tolerance.

Keywords: autoimmunity ; autoimmune thyroiditis ; immune cells ; vitamin D ; vitamin D supplementation

1. Introduction

Hashimoto's thyroiditis (HT), also known as chronic autoimmune thyroiditis, is the most prevalent organ-specific autoimmune disorder whose frequency has increased considerably in recent decades. At present, HT constitutes one of the most common thyroid diseases, with an incidence of 0.3–1.5 cases per 1000 persons, especially in the female gender. HT is currently the leading cause of primary hypothyroidism, both in adolescents and adults. The main feature of the disease is the presence of thyroid autoantibodies against thyroid peroxidase (TPOAb) or thyroglobulin (TGAb). Antibody titers show a positive correlation with hypothyroidism. This condition is a T-cell-mediated autoimmune disorder characterized by thyroid lymphocytic infiltration. Even though the concrete etiology has not been fully elucidated, the pathogenesis of HT is thought to be related to the interaction among genetic influences, environmental triggers, and epigenetic effects [1][2].

The classic function of active vitamin D (calcitriol or 1,25-dihydroxyvitamin D3) is the regulation of calcium and phosphate concentrations, but recent evidence has suggested that vitamin D is also associated with non-skeletal roles [3][4]. Most body cells and organs (muscle, heart, blood vessels, pancreas, brain, mammary gland, colon, prostate, gonads, skin, immune cells, malignant cells, etc.) have nuclear vitamin D receptors (VDR) and activating enzymes for calcitriol synthesis that, in these locations, are not regulated by parathyroid hormone. Vitamin D performs most of its biological actions by binding to the VDR and, consequently, modulates the expression/transcription of numerous coding genes responsible for the regulation of cell proliferation, differentiation, and apoptosis (genomic pathway). Thus, vitamin D has pleiotropic effects and can even act in a paracrine or autocrine manner in addition to its endocrine function. This fact would explain the additional non-calciotropic effects of vitamin D, as its involvement in autoimmunity, endocrine, infectious, metabolic and neurological diseases, and mood disorders. Obviously, the expression of VDR in immune cells suggests that vitamin D plays a critical role in regulating both innate and adaptive immune systems. That is, vitamin D deficiency could compromise the integrity of the immune system and lead to inappropriate immune responses such as autoimmune diseases [5][6][7][8].

According to the US Endocrine Society's guidelines, calcidiol levels are considered the best indicator of organic vitamin D content, given its long half-life (two to three weeks). Additionally, calcidiol concentrations below 20 ng/mL (<50 nmol/L) are considered to indicate vitamin D deficiency, whereas levels between 20 and 29 ng/mL (50–75 nmol/L) indicate a relative insufficiency, and levels of 30 ng/mL or greater indicate sufficient vitamin D. That is, optimal vitamin D levels range between 30 and 50 ng/mL (75–125 nmol/L) and maximum safe levels go up to 100 ng/mL (250 nmol/L) [9]. Although these cut-off points are based on observational studies, they are being accepted and used by most authors.

While there is current evidence that low vitamin D levels are a risk factor for autoimmune diseases (diabetes, multiple sclerosis, systemic lupus erythematosus, juvenile idiopathic arthritis, etc.), it remains uncertain if vitamin D deficiency is a significant factor in the pathogenesis or functional consequences of autoimmune hypothyroidism [1][10][11][12].

2. Hashimoto's Thyroiditis

Chronic autoimmune thyroiditis is characterized by self-tissue destruction via the adaptive immune responses that evade immune regulation. Under normal conditions, once the human body has obtained the ability of tolerance to certain

antigens, the process of autoimmunity does not take place. However, whenever this process of tolerance is broken, autoimmunity occurs, just as it does in HT. It is characterized by a diffuse goiter, circulating anti-thyroid peroxidase (TPOAb) and/or anti-thyroglobulin (TGAb) antibodies, erratic degree of thyroid hypofunction, and intrathyroidal infiltration of B and T lymphocytes, with CD4+ type 1 T helper (Th1) subtype predominance. The antibody titer levels are positively correlated with the severity of thyroid inflammation and hypothyroidism. In particular, TPOAb is the most important autoantigen involved in the induction of autoimmune thyroid disease. Thyroid peroxidase has an essential role in the production of thyroid hormones (thyroxine and triiodothyronine) while thyroglobulin produces the storage of thyroid hormones in the thyroid follicles. The diagnosis of HT is based on clinical symptoms, anti-thyroid antibodies, and histological features. TPOAb is perceived as the most important feature of HT and is present in about 95% of patients. In contrast, TGAb is present in a lower (60–80%) percentage of cases and, therefore, these antibodies are less reliable for diagnosis. All these facts lead us to consider that TGAb may represent the expression of an initial immune response, whereas TPOAb may be the result of a posterior immune response in a way that simulates an immune escalation. At present, HT remains an incurable disease with an unpredictable evolution, often leading to lymphocytic destruction of the thyroid parenchyma that subsequently originates hypothyroidism and the need for thyroid hormone replacement for life [2].

The etiology of HT is multifactorial, involving (a) genetic predisposition (the role of genetic factors in HT pathogenesis is suggested both by the high concordance rate for HT in monozygotic twins and by the frequent finding of thyroid autoantibodies or other autoimmune diseases in blood relatives of the HT probands; the results of association studies of VDR polymorphisms -ApaI, BsmI TaqI, and Fok1- with autoimmune thyroid diseases are inconclusive), (b) environmental factors (e.g., radiation, infections, iodine, selenium intake, smoking, and dietary habits), and (c) endogenous factors (e.g., body mass index, adipokines, estrogens, microchimerism, glucocorticoids, and potentially the gastrointestinal microbiome). Environmental factors are thought to play an important role, as recent epidemiological changes have demonstrated, and the development of HT may be ascribed not only to innate predisposition but also to environmental factors that have changed rapidly. These factors might finally trigger the development of autoimmunity. Thereby, in those individuals with genetic predisposition, the disruption of these immune-endocrine interactions by environmental factors is the key to switching the physiological balance between the Th1 and Th2 immune response. This maladjustment results in a Th1-cell-mediated autoimmune reaction with thyrocyte destruction and secondary hypothyroidism in HT. Furthermore, a shift in the balance between Th17 and Treg cells in thyroid autoimmunity has been recently observed [13][14][15][16].

3. Autoimmune Mechanism of Autoimmune Hypothyroidism

The core of the autoimmune process in HT is a breakdown in self-tolerance to thyroid autoantigens that results in thyroid destruction by the infiltration of CD4+ Th1 cells, macrophages, and plasma cells. Additionally, these cells produce autoantibodies against thyroid peroxidase (TPOAb) and thyroglobulin (TGAb). Therefore, the detection of elevated titers of these antibodies is generally used for HT diagnosis [17].

First, the presence of environmental/genetic factors originates the activation of antigen-presenting cells (APCs), mainly DCs, which, in turn, present autoantigens to naive CD4+ T cells in lymph nodes. Consequently, these cells differentiate into Th1, Th2, Th17, or Tregs. As a remarkable fact, the follicular thyroid cells of HT patients may express MHC-II, which is crucial for presenting antigens to CD4+ T cells. Therefore, thyroid cells can act as APCs by presenting autoantigens to T cells and activating their differentiation. Second, the cytokines produced and released by Th1, including IL-2 and IFN-γ, induce the expression of MHC-II on the surface of the thyroid cells, and secondarily cause the differentiation of the naive CD4+ T cells into Th1. Finally, Th1 cells, via IL-2 and IFN-γ, induce the activation of CD8+ T cells (cytotoxic T cells). CD8+ T cells induce apoptosis of thyroid cells, which leads to the release of pro-inflammatory cytokines that contribute to the activity and migration of pathological Th17 cells and the suppression of Tregs cells, and consequently amplifies and sustains the immune feedback process. Some authors have suggested that Th1/Th2 cell imbalance and Th1 cell activity enhancement would be the main contributors to the development of HT, but other authors estimate that increased Th17/Treg ratio would play a critical role in the pathogenesis of autoimmune thyroid diseases. This results in positive feedback and the initiation of the autoimmune process and subsequent consolidation. However, in the destruction of the thyroid gland and the mechanism of the autoimmune process, a humoral response also occurs.

The recruitment of Th1 lymphocytes is associated with the stimulation of B lymphocytes, which are located in lymph nodes within the tissue of the thyroid gland. Infiltrating B cells release autoantibodies, mainly TPOAb and TGAb, which are thyroid self-antigens. These antibodies contribute to the apoptosis of thyroid follicular cells in the mechanism of antibody-dependent cell-mediated cytotoxicity [2][8][17][18][19][20]. In the course of HT, self-reactive CD4+ T lymphocytes recruit B cells and CD8+ T cells that gather into the thyroid gland. Finally, the progression of the disease leads to the death of thyroid cells and hypothyroidism.

4. Immunomodulatory Role of Vitamin D in Hashimoto's Thyroiditis

As described above, vitamin D exerts an immunomodulatory role both in the innate and adaptive immune systems that appears to promote immune tolerance, and, in this case, it could contribute to the inhibition of the immunopathological process in HT. On one hand, active vitamin D promotes the differentiation of monocytes into macrophages and stimulates antimicrobial activity via a series of mechanisms that increase the transcription of antimicrobial peptide genes, such as beta-defensin and cathelicidin antimicrobial peptide. That is, vitamin D improves chemotaxis and phagocytic capabilities and antimicrobial properties of innate immune cells. On the other hand, vitamin D also plays a role in the regulation of adaptive immunity, as it modulates the activation and differentiation of naïve CD4+ lymphocytes after antigen presentation by DCs in lymph nodes. In other words, Vitamin D carries out an immunomodulatory role both in the innate and adaptive immune systems that appears to promote immune tolerance, and, in this case, it could contribute to the inhibition of the immunopathological process in HT.

The potential mechanisms by which vitamin D could contribute to inhibiting the autoimmune process in HT would be varied and complementary and could be summarized as follows:

(a)Vitamin D inhibits the expression of various proinflammatory cytokines from DCs (IL-2, IL-6, and IL-12) that activate T cells while enhancing the expression of IL-10 (anti-inflammatory or tolerogenic cytokine); this results in a stage of insufficient immune responsiveness and, in this way, it helps avoid excessive innate responses and consequent tissue damage (systemic inflammation and/or septic shock). Additionally, vitamin D impairs DCs differentiation and maturation as evidenced by a decreased expression of MHC-II and co-stimulatory molecules (CD40, CD80, and CD86); this preservation of the immature phenotype of DCs results in a reduction in the number of antigen-presenting cells and activation of naïve T cells, thus contributing to an induction of a tolerogenic state. Vitamin D also modulates the activation and differentiation of naïve CD4+ lymphocytes after the presentation of the antigen by the DCs in the lymph nodes, resulting in a shift from a T-helper (Th)1 to a Th2 phenotype, which is an inhibition of inflammatory cytokine production (IL-2, IFN-γ, and TFN-α), and an increased production of anti-inflammatory cytokines (IL-4, IL-5, and IL-10).

(b)Vitamin D may reduce MHC-II expression in the follicular thyroid cells, thus preventing T cell activation and proinflammatory cytokine response.

(c)Vitamin D affects the differentiation of naïve T cells towards the Th17 phenotype, leading to a decrease in the production of inflammatory cytokines such as IL-17 (linked to organ-specific autoimmunity, inflammation, and tissue damage), and facilitates the induction of T regulatory cells (Tregs) with increased production of anti-inflammatory cytokines such as IL-10 and TGF-β. Treg cells are able to suppress the proliferation and production of inflammatory cytokines by CD4+ T cells as well as the proliferation of CD8+ (cytotoxic lymphocytes) and APCs. Therefore, vitamin D contributes to the restoration of the Th17/Treg ratio (Th17 cells mainly express proinflammatory activity, which secondarily causes the development of autoimmune disorders; Tregs modulate the immune system and maintain tolerance to self-antigens, which in turn prevents autoimmunity). In this way, vitamin D would modulate cell-mediated immune responses and regulate the inflammatory activity of T cells and, consequently, have a significant role in preventing exaggerated or autoimmune responses.

(d)Finally, with regard to B-lymphocyte regulation, vitamin D has an impact on B cell homeostasis in several ways. For example, it reduces naïve B cell activation and proliferation, induces apoptosis of activated B cells as well as suppresses the differentiation of B cells into plasma cells. In addition, vitamin D also inhibits memory B cell generation and reduces immunoglobulin synthesis (IgG and IgM). This control on B cell activation and proliferation may be clinically important in HT, as B cells producing autoreactive antibodies play a major role in the pathophysiology of autoimmunity.

Thereby, vitamin D induces a shift from a pro-inflammatory to a more tolerogenic immune status, resulting in a limitation in the development of self-reactive T cells preventing inflammation and autoimmunity [6][7][10][17][20][21]. Thus, vitamin D appears to play an important immunomodulatory role, and its relationship with autoimmune thyroid disease has been widely studied in recent years.

In addition, a high Th22 cell count has been reported in the blood and thyroid of HT patients, considered decisive in the inflammatory effects of IL-22 on thyroid cells [14].

5. Relationship between Vitamin D Status and Hashimoto's Thyroiditis

Many observational studies (case–control or cross-sectional studies) have unveiled a potential link between hypovitaminosis D and an increased risk of HT onset [21][22][23][24][25][26][27][28][29][30][31][32][33]. In fact, considering the adult population, a low vitamin D status has been reported in patients with autoimmune thyroid diseases or HT, suggesting an association between vitamin D deficiency and thyroid autoimmunity. Furthermore, several authors reported that the prevalence of vitamin D deficiency in patients with HT was significantly higher compared with healthy individuals, and that serum calcidiol levels were inversely correlated with anti-thyroid antibodies (TGAb and TPOAb), suggesting the involvement of vitamin D in its pathogenesis. In addition, considering all the HT cases, patients with hypothyroidism showed a higher prevalence of vitamin D deficiency and lower calcidiol levels in comparison to patients with euthyroidism or healthy individuals.

On the other hand, few studies have focused on investigating the potential correlation between low vitamin D levels and HT in children, whose reported results are similar to those of adults. That is, these authors conclude that low serum vitamin D levels are significantly associated with autoimmune thyroid diseases or HT, also observed in children, although they also indicate that it is not an independent risk factor for the progression to overt hypothyroidism [34][35][36][37][38].

However, the results of other observational studies have not found a relationship between vitamin D levels and antithyroid antibodies or thyroid function [15][39][40][41][42]. Different factors could contribute to this discordance between the studies. These include the application of different commercially available kits for serum vitamin D assay or the consensus on a definition of vitamin D deficiency between the studies, as well as potential confounding factors such as BMI and ethnic, seasonal, or geographical differences [14].

Nevertheless, recent systematic reviews, meta-analyses, and meta-regression of observational studies [42][43][44][45][46][47] have confirmed that vitamin D levels were significantly lower in autoimmune hypothyroidism disease or HT patients compared to healthy people. Accordingly, it seems that there is proven evidence supporting a relationship between low vitamin D status and HT.

Further, several authors have reported an inverse correlation between thyrotrophin (TSH) and Vitamin D status in healthy young people as well as in middle-aged and older men [48][49]. In addition to its association with autoimmune thyroid diseases, vitamin D deficiency has also been detected in other autoimmune diseases, such as multiple sclerosis, diabetes mellitus, systemic lupus erythematosus, and others [11][12]

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