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DIAGNOSTICS AND ENVIRONMENTAL FACTORS

Vitamin D and thyroid autoimmune diseases: the known and the obscure

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Vitamin D is a secosteroid hormone, obtained from the diet or synthesized in human skin from 7-dehydrocholesterol after UV irradiation exposure. Its importance in calcium homeostasis is well recognized, as well its role in decreasing the risk of rickets, fractures, osteopenia, osteomalacia, and osteoporosis. What is a new developing issue is the involvement of vitamin D deficiency (commonly defined as less than 30 ng/ml) in the boost of many other disorders and especially in autoimmune diseases [1]. In light of these new acquisitions, vitamin D deficiency may represent a global health problem that has been underestimated for many years.

Among all the autoimmune diseases which show an association with vitamin D deficiency and disease progression, we will focus on autoimmune thyroid diseases (AITD). Indeed, vitamin D deficiency modulates both Hashimoto thyroiditis (HT) and Graves' disease (GD). In several studies, the association between vitamin D and AITD was assessed analyzing various serological parameters, such as serum 25(OH)D levels, serum calcium, phosphate, parathyroid hormone (PTH), and antithyroid antibody levels. HT patients had significantly lower 25(OH)D values than healthy controls ($p = 0.001$), and low levels of serum 25(OH)D were also correlated with disease duration, thyroid volume, and antibody levels [2]. The association between vitamin D deficiency and antithyroid antibodies was reported for the first time by Kivity et al. [3], who studied a cohort of 92 patients with thyroid disorders, collected in a Hungarian endocrinology clinic. Antithyroid peroxidase (TPOAb) and antithyroglobulin (TgAb) antibodies were significantly more common in patients with vitamin D deficiency than in those with normal vitamin D levels. Hypovitaminosis D and thyroid autoimmunity were also described in a Chinese female population, where decreased TPOAb levels were associated with higher vitamin D levels. Interestingly, the correlation was found only in premenopausal women, but not in postmenopausal women or in men [4]. This result suggests a likely involvement of estrogens in modulating AITD. Moreover, the relationship between serum vitamin D status and thyroid-stimulating hormone (TSH) levels was investigated. Vitamin D levels were found associated with low circulating TSH levels in middle-aged and elderly males, independently of T3 and T4 levels. Interestingly, serum TSH levels in women were higher than those of same-aged men, indicating that TSH secretion may be regulated by sex hormones [5].

Vitamin D status was also evaluated in female GD patients, showing significant lower levels compared with controls and demonstrating an association between serum 25(OH)D levels and serum calcium and intact parathyroid hormone levels. Recently, Yasuda and coworkers found an

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Table 1 Observational studies on autoimmune thyroid disease patients with low levels of vitamin D

Authors	Number of subjects	Geographical area	Gender % female
Bozkurt et al. [2]	540	Turkey	68
Kivity et al. [3]	92	Hungary	77
Zhang et al. [5]	1,424	China	60
Yasuda et al. [6]	72	Japan	100
Choi et al. [4]	6,685	Korea	42

association between vitamin D levels and thyroid gland volume, a clinical factor related to GD, pointing to a direct role of vitamin D in GD pathogenesis [6] (Table 1).

Notwithstanding all these studies point to an involvement of vitamin D in AITD, the possibility exists that vitamin D deficiency is not the cause but rather a consequence of the disease. As well as in other autoimmune diseases (such as inflammatory bowel disease), vitamin D levels may be affected by malabsorption due to inflamed intestine, which is common in patients with thyroid disorders as well. In addition to reduced circulating vitamin D levels, an association between AITD and vitamin D receptor (VDR) polymorphisms was assessed, suggesting that in AITD the capacity of vitamin D to act on the immune system may be compromised. Through binding to its receptor, vitamin D can exert its immunomodulatory activities on macrophages, T and B lymphocytes, and dendritic cells (DC), which express VDR. Vitamin D enhances the antimicrobial properties of macrophages and skews cells of the adaptive immune system toward a more tolerogenic status, inducing a Th1 to Th2 shift and inhibiting DC differentiation and maturation. Moreover, vitamin D can modulate Ig production and exert direct effects on B-cell homeostasis. Indeed, it has been observed that differentiation into plasma cells and post-switch memory B cells was inhibited in the presence of $1,25(OH)_2D$ [7].

Four polymorphisms were commonly studied in relation to AITD: FokI, BsmI, ApaI, and TaqI. A meta-analysis of eight studies, analyzing mainly females of various ethnicity (European, Asian, African) and including about 1,000 cases and 1,000 controls for each polymorphism studied, indicates that BsmI or TaqI VDR polymorphism was significantly associated with AITD risk, while ApaI or FokI polymorphism was not. Regarding the BsmI polymorphism, b allele was more associated with AITD risk compared to B allele. However, statistically significant heterogeneity was detected for BsmI polymorphism only when all the eligible studies were pooled into a meta-analysis. After a subgroup analysis by ethnicity, Europeans showed a strong decrease in the heterogeneity, indicating that the genetic background might contribute to the observed heterogeneity. Regarding TaqI, no heterogeneity was detected in the subgroup analysis [8]. In addition, a polymorphism of the CYP27B1 gene which encodes the 1-α-hydroxylase enzyme, responsible for converting 25(OH)D in active $1,25(OH)_2D$, was found in association with AITD, supporting the hypothesis of a link between vitamin D status and thyroid autoimmunity [9].

Considering all these promising studies, many researchers and physicians started to recommend vitamin D supplementation to AITD patients. On this issue as well, there are conflicting opinions. Some researchers state that, as vitamin D is a cheap compound, and without known side effects, its administration may be helpful to ameliorate disease symptoms and progression. On the other side, other researchers claim that the association between vitamin D deficiency and autoimmunity is not so clear, with a remarkable discrepancy between observational and interventional studies; moreover, vitamin D supplementation may lead to hypercalcemia in chronic kidney disease patients, and patients may gain false reassurance from vitamin D prescription [10]. Therefore, more research is needed to ponderate the potential risk, before start to consider vitamin D as an effective treatment recommended for AITD.

Take-home messages

- several studies found a correlation between vitamin D deficiency and the incidence of autoimmune thyroid diseases;
- polymorphism of vitamin D receptor may be involved in AITD onset and progression;
- vitamin D supplementation should be considered for AITD patients, although further research is needed.

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