

REVIEW

The Role of Vitamin D on Thyroid Antibodies in Patients with Chronic Autoimmune Thyroiditis

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ABSTRACT

Vitamin D deficiency is a global problem, which has taken the form of a pandemic. Existing data indicate that vitamin D is not only a nutrient. It has also a hormone-specific activity. Vitamin D is characterized by anti-inflammatory and immunomodulatory properties. Chronic autoimmune thyroiditis is a disease of autoimmune genesis, in which lymphocytic infiltration gradually destroys thyroid tissue. There are some evidences about vitamin D deficiency and the development of chronic autoimmune thyroiditis. The article has reviewed the current literature about the impact and the benefits of vitamin D on thyroid antibodies levels.

1. Introduction

The active form of vitamin D-1,25 (OH)₂ D, also called calcitriol - is a steroid hormone. Its important function is to regulate the level of calcium and phosphorus in blood [1]. Recent data indicate that in addition to participating in the metabolism of the musculoskeletal system, vitamin D is characterized by immunomodulatory effects. It is especially interesting that vitamin D can reduce the risk of developing various chronic diseases, including cancer, autoimmune diseases, infectious and cardiovascular pathologies [2]. According to various studies, vitamin D can prevent or inhibit some autoimmune diseases. Calcitriol

is associated with disease activity and anti-citrullinated protein antibodies in rheumatoid arthritis patients [3]. The prevalence of vitamin D deficiency is very common in patients with type 1 diabetes [4,5]. Multiple sclerosis has also been shown to be associated significantly with environmental factors such as the lack of vitamin D [6-8].

Chronic autoimmune thyroiditis, also called Hashimoto's thyroiditis (HT) is one of the most widespread endocrine autoimmune diseases. It is characterized by lymphocytic infiltration of the thyroid parenchyma and increased levels of thyroid antibodies (thyroid peroxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-TG)) in

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blood. The basis for the development of chronic autoimmune thyroiditis is the autoimmune destruction of thyroid tissue by T and B lymphocytes^[9-11]. Some studies have suggested a possible link between vitamin D level and the development of chronic autoimmune thyroiditis. The article has reviewed the current literature about the role and benefits of vitamin D on thyroid antibodies levels during chronic autoimmune thyroiditis.

2. Vitamin D and Its Immunomodulatory Effects

Vitamin D was first identified in the early 20th century and was considered as a necessary nutrient for the prevention of rickets, although it is currently considered as a prohormone^[12].

Vitamin D is produced by the human body - in the skin under the influence of sun ultraviolet rays (UVB), although in small quantities it can be obtained from food. There are two main forms of vitamin D: D2 and D3^[13]. Vitamin D (both ergocalciferol or cholecalciferol) is biologically inactive. To achieve its main effects, vitamin D needs hydroxylation first in the liver, to form the basic circulating form with little biological activity - 25-hydroxyvitamin D (25(OH)D2 or 25(OH)D3). 25(OH)D is then converted into a bioactive form 1,25 dihydroxy-vitamin D (1,25(OH)₂D or calcitriol) in the kidney^[14,15]. For further action, calcitriol needs to bind to the vitamin D receptors (VDRs). These receptors are located in all organs and cells. Therefore, vitamin D has a great impact on all organ systems.

Vitamin D has long been considered as an essential vitamin for the musculoskeletal system^[16,17], but newer studies indicate its influences on various organ cells and systems^[18], including the immune system^[19]. The active form of vitamin D has a significant impact on the innate and adaptive immune system. Vitamin D is an important factor for the maturation of macrophages and can promote the differentiation of monocytes into macrophages, as well as enhance phagocytosis and chemotaxis and promote the anti-tumor action of mononuclear macrophages. Vitamin D inhibits the production of inflammatory cytokines (e.g. TNF- α , which plays an important role in the inflammatory process) and inhibits inflammation^[20]. The active form of vitamin D promotes the differentiation of monocytes and inhibits the maturation of dendritic cells. Calcitriol can also inhibit cytokines such as IL-1, IL-2, IL-6^[21].

As mentioned, calcitriol promotes the innate immune system response but inhibits the action of the adaptive immune system. Vitamin D reduces the production of inflammatory cytokines by monocytes, such as tumor necrosis factor (TNF) and interleukin 6 (IL-6). Calcitriol

promotes apoptosis of B cells and thus inhibits their proliferation and differentiation into plasma cells^[22].

T lymphocytes are also a major target for the action of vitamin D^[23,24]. Vitamin D receptors are expressed on T cells, therefore vitamin D can have a direct effect on T cells and regulate their response. There are some direct endocrine, intracrine, paracrine and indirect mechanisms by which vitamin D may influence T cell function^[25]. In addition, vitamin D can have an effect on the distribution of Th1, Th2 and Th17 cells. Th1 cells produce proinflammatory cytokines (including IFN- γ and IL-2). Th17 cells can produce another pro-inflammatory cytokines such as IL-17 and IL-22. Calcitriol inhibits the activity of Th-17 and Th1 cells. The activity of these cells leads to the development of various chronic inflammatory processes due to the secretion of several cytokines^[26]. 1,25 (OH)₂ D3 promotes the polarization of CD4 + cells in favor of Th2 cells, which promotes increased cytokine secretion, such as IL-4, IL-5, IL-10^[27]. Calcitriol inhibits maturation of dendritic cells, reduces antigen uptake and promotes activation of naïve T lymphocytic cells, which are an important factor in inhibiting autoimmune processes^[20,28].

3. Chronic Autoimmune Thyroiditis (Hashimoto's Thyroiditis)

Chronic autoimmune thyroiditis (Hashimoto's thyroiditis (HT)) is a widespread autoimmune endocrine disease. It belongs to the group of chronic autoimmune diseases of the thyroid gland and is characterized by increased levels of thyroid auto- antibodies in the blood (thyroperoxidase antibodies (anti-TPO) and thyroglobulin antibodies (anti-TG), and lymphocytic infiltration of the thyroid tissue. All of the above contributes to the gradual decrease of thyroid function and often leads to various degrees of thyroid hypofunction^[29,30].

The development of chronic autoimmune thyroiditis is facilitated by a combination of different genetic factors and environmental conditions^[31,32]. Its prevalence depends on various factors such as age (more common between the ages of 45-55), gender (women are 4-10 times more likely to get this disease than men) and race (more common in whites than blacks, asians and hispanics). Other additional factors such as alcohol consumption, stress, pregnancy and the use of certain medications (e.g. interferon- α , iodine, immunomodulatory agents - pembrolizumab, ipilimumab, nivolumab...) may contribute to the development of chronic autoimmune thyroiditis. Although HLA-DR antigens are not physiologically found on thyrocytes, expression of HLA-DR antigens on the surface of thyrocytes is observed in patients with chronic autoimmune thyroiditis. This factor contributes to the onset of autoimmune

process^[33]. It is currently known that the HLA-DR3 allele is associated with chronic autoimmune thyroid disease^[34].

Although the exact mechanism of progressive thyroid tissue destruction is not clear, HT is regarded as a disorder of T cell-mediated immunity^[30]. Autoimmune thyroid disease is caused by an imbalance between Th1 and Th2 cells. Patients with HT have high levels of Th1 cells secreting the cytokine IFN- γ ^[35]. HT is characterized by low number of CD4+ T cells and increased number of CD8+ T cells. CD8+ T cells have cytotoxic properties in HT^[36]. Th1 cells activate cytotoxic lymphocytes and macrophages, which directly affect thyroid tissue by destroying thyroid follicular cells. In the tissues of the thyroid in patients with HT, Th1 are the predominant cells. In HT, damaged thyroid follicles with apoptotic thyrocytes (pyknotic nuclei, condensed cytoplasm with enlarged mitochondria and endoplasmic reticulum cisterns) were visible in these tissues. Blood and thyroid Th17 cells, which secrete the cytokine IL-17, are increased in HT. In addition to IL-17, Th17 cells secrete IL-22, a cytokine which targets epithelial cells and which is also secreted by Th22 cells. High levels of Th22 cells have now been reported in the blood and thyroid of HT patients^[37]. Whereas vitamin D plays an important role in regulating Th1, Th2, and Th17 cells, as well as the secretion of cytokines, various studies have been conducted to investigate association between vitamin D deficiency and chronic autoimmune thyroiditis.

4. A Possible Link between Vitamin D Deficiency and Anti-thyroid Antibodies Levels

Various studies indicate on a possible association between D hypovitaminosis and HT^[38,39] (Table 1). Data indicate that patients with increased thyroid antibodies have lower 25(OH)D3 compared to thyroid antibodies negative subjects: Unal, Asli Dogruk, et al. found a significant correlation between thyroid autoantibodies and vitamin D: Thyroid autoantibodies were higher in patients with lower 25(OH) D status^[40]. Kivity, Shaye with coauthors indicate that vitamin D deficiency was more common in patients with thyroid disorder compared to healthy subjects^[41]. Sayki Arslan, Muyesser, et al declared that thyroid autoantibody positivity was more frequently in vitamin D deficient patients than in patients with an adequate 25(OH) D level^[42]. Bozkurt, Nujen Colak, et al. showed that very low vitamin D (<10 ng/mL) was inversely correlated with serum anti-TPO - anti-TG levels^[43]. Muscogiuri, Giovanna, et al. evaluated vitamin D deficiency and its link to chronic autoimmune thyroiditis: There was a statistically negative correlation between vitamin D and anti-TPO titers^[44]. In chinese population vitamin D deficiency or/and insufficiency was more common in anti-TG positive

patients and low 25(OH)D was associated with anti-TG titers only in women^[45]. The association of vitamin D deficiency with autoimmune thyroid disease (AITD) has been found in premenopausal, but not in postmenopausal women in Korean studies^[46,47]. However, there are some studies with different outcomes: Goswami, Ravinder, et al. indicate that vitamin D levels had only weak negative correlation with anti-TPO levels^[48]. They think that the narrow range of vitamin D level in their study could have an impact and reduce the protective effect of higher titer of vitamin D on thyroid antibodies. Ma, Jie, et al observed that low vitamin D level is a risk factor for AITD, but any association with the anti-TPO- anti-TG was not found^[49]. Authors indicate that patients in their study had very high titer of thyroid antibodies (anti-TPO, anti-TG). Therefore the correlation of thyroid antibodies with vitamin D was inadequately expressed.

Thus, most studies confirm that patients with D vitamin deficiency have higher titer of thyroid antibodies compared to individuals with adequate vitamin D concentration in blood. This may be explained by the immunomodulatory abilities of vitamin D and its impacts on the immune system: D vitamin suppress production of several proinflammatory cytokines and maintains immune tolerance. The statistically significant association of decreased vitamin D levels with higher levels of anti-TPO or / and anti-TG is mostly found in premenopausal women. The reason of this connection may be the fact that chronic autoimmune thyroiditis is mostly noted in women. It should be also noted that there is a possible connection between vitamin D and estrogen in the development of chronic autoimmune thyroiditis: 17- β estradiol could induce greater binding to D vitamin binding protein to T cells and macrophages, after that calcitriol accumulates in immune cells^[46]. So, low levels of vitamin D may contribute to the development of chronic autoimmune thyroiditis, predominantly in premenopausal women.

However, the optimal levels of vitamin D to prevent the onset of chronic autoimmune thyroiditis or decrease thyroidal antibodies are still controversial. According to the endocrine society, 25(OH) D less than 20 ng/mL indicates on deficiency, 20-29 ng/mL and 30 ng/mL –on insufficient and sufficient levels of vitamin D respectively^[50].

It is not still clear how vitamin D supplementation will reduce anti-TPO and anti-TG concentrations. Various studies have been conducted in autoimmune thyroiditis patients to evaluate the effectiveness of vitamin D supplements (Table 2). Krysiak, R., K. Kowalcze, and B. Okopien. indicate that vitamin D supplementation reduces thyroid antibodies (anti-TPO more than anti-TG). The effect of vitamin D supplementation on anti-TPO

Table 1. Studies on vitamin D and anti-thyroid antibodies levels

Authors	Number of enrolled patients	Country	Definition of vitamin D deficiency	Main findings
Unal, Asli Dogruk, et al. ^[40]	405	Turkey	< 20 ng/mL	25(OH)D was negatively correlated with anti-TG (P=0.025) and anti-TPO (P = 0.003) levels.
Kivity, Shaye, et al. ^[41]	190	Hungary	<10 ng/mL	25(OH) D deficiency was higher in patients with AITDs compared with control group (P <0.001); Vitamin D deficiency correlated to anti-thyroid antibodies titer (P=0,01)
Sayki Arslan, Muyesser, et al. ^[42]	155	Turkey	< 20 ng/mL	A negative correlation was found between anti-TPO, anti-TG and the 25(OH)D3 level (P = 0.017 ; P= 0.05,)
Bozkurt, Nujen Colak, et al. ^[43]	540	Turkey	<20 ng/mL	Vitamin D negatively correlated to anti-TPO (P< 0.001) and anti-TG levels (P< 0.001). Vitamin D deficiency severity (<10 ng/mL) correlated with thyroid antibody levels.
Muscogiuri, Giovanna, et al. ^[44]	168	Italy	<20 ng/mL	A correlation between 25(OH) D and anti-TPO (P = 0.03) was found. Any correlation between vitamin D status and anti-TG was not detected (p = 0.25).
Wang, Xinling, et al. ^[45]	1714	China	<20 ng/mL	A negative correlation (P = 0.014) was found between vitamin D and anti-TG titers only in women.
Kim,Choon-Young, et al. ^[46]	4356	S.Korea	<10 ng/mL	Vitamin D insufficiency /deficiency were associated with anti-TPO(+) in premenopausal female (P<0.001)
Choi, Yun Mi, et al. ^[47]	6685	S.Korea	<10 ng/mL	Decreased 25(OH) D3 status was significantly associated with autoimmune thyroid disease, especially in premenopausal female (In TPO-Ab(+) group- P= 0.003. In anti-TPO(+)/US(+) groups- P < 0.001).

and 25(OH)D levels was greater in vitamin D deficiency patients compared to vitamin D insufficiency or normal vitamin D status group ^[51]. Simsek, Yasin, et al. also indicated that supplementation of the vitamin D reduced anti-TPO, anti-TG titers in vitamin D deficient subjects ^[52]. Mazokopakis, Elias E., et al. suggested that vitamin D deficiency may have some link to pathogenesis of HT and supplementation with cholecalciferol (CF) may reduce anti-TPO levels and promote of the treatment of chronic autoimmune thyroiditis ^[53]. Chaudhary, Sandeep, with coworkers showed that vitamin D supplementation with high doses (CF 60000 IU/weekly) in patients with HT was associated with a significant decreasing of anti-TPO levels ^[54]. Chahardoli, Reza, et al. administered also a high

dose of vitamin D3 ^[55], because supplementation with low doses (vitamin D3 1000 IU/d or 400 IU/d) during 16 weeks did not reveal significant benefits on the thyroid autoimmunity ^[56]. Most studies indicate that vitamin D could reduce thyroid antibodies parameters, but this effect may be dose-dependent. Data suggested that vitamin D supplementation with doses of ≤1000 IU and durations of ≤2 months did not reach to effects ^[57]. In contrast to the above studies, Anaraki, Parichehr Vahabi, et al reported that 50000 IU cholecalciferol weekly, for 12 weeks in vitamin D deficient patients with HT could not have significant benefits on the function and autoimmunity of thyroid gland ^[58]. However, one of the important limitations of their study was small number of participants.

Table 2. The effects of vitamin D supplements on thyroid antibody levels

Authors	Number of enrolled patients	Country	Vitamin D deficiency criterion	Dose and duration of supplementation	Main findings
Chahardoli, Reza, et al. [55]	42 women	Iran	< 20 ng/mL	50 000 IU vitamin D, once a week (for 3 months)	Vitamin D administration decreased anti-TG (P= 0.009) level.
Krysiak, R., K. Kowalcze, and B. Okopien [51]	53 women	Poland	< 20 ng/mL	4000 IU/daily (in vitamin D deficiency group), 2000 IU/ daily (in vitamin D insufficiency group)-for 3 months	Vitamin D reduced levels of anti-TPO. This association was more found in women with vitamin D deficiency (P = 0.065)
Mazokopakis, Elias E., et al. [53]	218 (180 women, 38 men)	Greece	< 30 ng/mL	Cholecalciferol, 1200-4000 IU, daily, for 4 months, (to maintain 25(OH)D ≥ 40 ng/mL)	Supplementation of CF in vitamin D deficient HT patients reduces anti-TPO
Simsek, Yasin, et al. [52]	82	Turkey	<20 ng/mL	Vitamin D 1000 IU/day (for 1 month)	Vitamin D supplementation decreased TPOAb and TG-Ab levels (P = 0.02 and P = 0.03)
Chaudhary, Sandeep, et al. [54]	102	India	<50 nmol/L	CF 60,000 IU /weekly and - for 8 weeks;	A significant reduction of anti-TPO was detected (P = 0.028)
Knutsen, Kirsten V., et al. [56]	251	Norway	Mean serum 25(OH)D3 26 nmol/L	Vitamin D3 supplementation 1000 IU or 400 IU/daily, for 16 weeks	No effects on anti-TPO level.
Anaraki, Parichehr Vahabi, et al. [58]	56	Iran	<20 ng/mL	Vitamin D 50000 IU weekly (for 12 weeks)	TPOAb did not significantly changed (P = 0.14)

Thus, part of the studies indicate that vitamin D supplements (at least 1000 IU daily) in vitamin D deficient patients help reduction of thyroid antibodies levels. However, according to some studies, this effect has not been revealed.

5. Conclusions

Most studies support the negative association between vitamin D and thyroid antibodies levels: Vitamin D deficiency is associated with higher levels of thyroid antibodies compared to individuals with normal vitamin D status. This association is mostly found in premenopausal women. So, vitamin D deficiency may promote to the development of chronic autoimmune thyroiditis, especially in premenopausal women. Some data also indicate the benefit of vitamin D supplements to reduce thyroid antibodies levels. However, additional studies are needed to confirm the effect and usefulness of vitamin D preparations on thyroid antibodies.

Conflict of Interest

The authors declare no conflict of interest.

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