Vitamin D supplementation in patients with Hashimoto’s disease

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ABSTRACT

Introduction: Hashimoto’s thyroiditis (HT) is the most common autoimmune disease and the leading cause of hypothyroidism in the world. The condition results in damage to the thyroid gland, brought about by the infiltration of lymphocytes. For the majority of individuals with Hashimoto's thyroiditis, a lifelong requirement for levothyroxine substitution is required. The potential contribution of diet and supplements to the management of HT is frequently overlooked. Low vitamin D levels are said to play a significant role in occurrence and severity of autoimmune thyroiditis. Currently, there is a continuing discussion regarding the optimal plasma concentration of 25-hydroxyvitamin D necessary for preventing or treating autoimmune diseases.

Aim of the study: The purpose of this literature review is to evaluate the influence of vitamin D supplementation on the course of Hashimoto’s thyroiditis in the light of most up to date research.

Materials and methods. This article is a review of publications obtained from the PubMed database, published between 2017-2023, based on the keywords "Hashimoto thyroiditis" "vitamin D" and "autoimmune thyroid disease".

Conclusions. The correlation of vitamin D supplementation and Hashimoto’s disease still remains unclear due to conflicting results from numerous studies. Further research is necessary to accurately determine the effect of vitamin D supplementation on Hashimoto’s thyroiditis.

Keywords: "Hashimoto’s thyroiditis" "autoimmune thyroid disease" and “vitamin D”.

1. Introduction and purpose
Vitamin D generally refers to two fat-soluble compounds, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). It plays a crucial role in regulating calcium and phosphorus levels in the body, influencing bone homeostasis and immune function [1]. Presently, there is ongoing debate regarding the ideal plasma concentration of 25-hydroxyvitamin D required for the prevention or treatment of autoimmune diseases. Nevertheless, human experimental studies have indicated positive outcomes associated with vitamin D supplementation in
reducing the severity of disease activity. This review will concentrate on the existing literature, examining the correlation between vitamin D levels and Hashimoto's thyroiditis.

2. Vitamin D – structure, metabolism, sources and supplementation

2.1 Structure and metabolism
Both vitamin D2 and D3 undergo two hydroxylation reactions to become biologically active. First occurs in the liver, converting vitamin D2 or D3 to 25-hydroxyvitamin D [25(OH)D - calcidiol], which is the main circulating and storage form of vitamin D in the human body. Serum levels of this form are considered the best marker to measure whole body vitamin D status. Second hydroxylation leads to production of the active form of vitamin D in kidneys - calcitriol (1,25-dihydroxyvitamin D). This form is produced by 1-α-hydroxylase protein encoded by CYP27B1 and inactivated by 24-hydroxylase, high levels of 1,25(OH)2D and fibroblast growth factor 23 (FGF23).

The biologically active form, 1,25(OH)2D, attaches to the nuclear vitamin D receptor (VDR), which then interacts with the vitamin D response element (VDRE) located in target genes, thereby influencing its effects [2].

2.2 Sources
Vitamin D2 is derived from ergosterol, which is present in certain fungi and yeast, therefore dietary intake is the only ergocalciferol source. Vitamin D3 main source is endogenous production in the skin due to its exposure to UVB radiation from the sun. Its synthesis is performed by 7-dehydrocholesterol reductase [2].

However in the contemporary era, characterized by societal shifts in lifestyle patterns, the attainment of optimal sun exposure prerequisites becomes progressively challenging. Modern lifestyles, characterized by indoor occupations, increased screen time, and sun-protective behaviors, can limit the amount of time individuals spend outdoors. Moreover, in some geographical locations higher latitudes, long winters, and overcast weather conditions can contribute to decreased sunlight availability and consequently inadequate vitamin D production [3].

For this reason, dietary intake is also of great importance. Animal foodstuffs (e.g., fish, meat, offal, egg, dairy) are the main sources for naturally occurring cholecalciferol.

2.3 Dietary supplementation
The global prevalence of vitamin D deficiency has emerged as a pervasive concern in contemporary times, manifesting in conditions such as rickets, osteomalacia and osteoporosis,
therefore the use of vitamin D supplements has increased significantly in recent years. Vitamin D supplements are commonly used to ensure adequate intake, especially in individuals with limited sunlight exposure or those at risk of deficiency. Both vitamin D2 and D3 elevate the levels of serum 25(OH)D, demonstrating comparable efficacy in treating rickets [1]. Furthermore, the majority of processes involved in the metabolism and functions of vitamins D2 and D3 are indistinguishable. Nevertheless, prevailing evidence suggests that vitamin D3 leads to a more significant increase in serum 25(OH)D levels and sustains these elevated levels for a longer duration compared to vitamin D2, despite both forms being efficiently absorbed in the gastrointestinal tract [4][5][6]. The role of vitamin D supplementation and the optimal dose is the subject of many ongoing studies and is yet to be better defined.

3. Vitamin D – impact on Hashimoto’s thyroiditis

3.1 Hashimoto’s thyroiditis
Hashimoto’s thyroiditis (HT) is a chronic autoimmune disorder, characterized by inflammation of the thyroid, leading to gradual destruction of the gland and disruption of its normal functioning. Levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), and thyroid peroxidase antibodies (TPO antibodies) or anti-thyroglobulin (anti-Tg antibodies) are commonly used to confirm the diagnosis of HT. Hashimoto's thyroiditis manifests clinically in three forms: (A) thyrotoxicosis, where stored thyroid hormones are released into circulation due to the destruction of thyroid follicles; (B) euthyroidism, characterized by preserved thyroid tissue compensating for the loss of thyrocytes; and (C) hypothyroidism, arising from insufficient production of thyroid hormones by the affected thyroid gland [7].

The identification of HT relies on clinical manifestations of hypothyroidism and the detection of TPOAbs, though approximately 5%–10% of cases may exhibit seronegative HT. Ultrasound imaging of the thyroid gland can aid in the differential diagnosis, especially for patients with TPOAbs-negative HT. The ultrasound characteristics of HT encompass reduced echogenicity, heterogeneity, heightened vascularity, and the existence of small cysts.[8]. Slowing down the inflammatory process of Hashimoto’s thyroiditis with properly balanced diet that provides all necessary nutrients and covers the demand for not only vitamin D but also vitamin B12, selenium, iodine, zinc and other antioxidants is of great importance [9][10].
3.2 Vitamin D impact on immune system
Vitamin D plays a significant role in modulation of the immune system, enhancing the innate immune response. Various genetic studies have demonstrated that an individual’s susceptibility to autoimmune disorders is linked with polymorphisms in numerous proteins and enzymes associated with vitamin D, such as VDR, DBP, CYP27B1, CYP2R1, and CYP24A1 [11]. Specifically, immune system cells such as B cells, T cells, and antigen presenting cells, due to the expression of 1α-hydroxylase (CYP27B1), possess the capability to synthesize calcitriol, which exhibits immunomodulatory properties [12].

Vitamin D plays a crucial role in immune function by generating anti-inflammatory and immune-regulatory markers through the expression of the Vitamin D Receptor (VDR) within cell nuclei. The VDR actively participates in cellular immunity functions, stimulating both innate and adaptive immune responses. The presence of VDR polymorphisms is associated with an increased susceptibility to thyroid disorders, including hypothyroidism [13]. A meta-analysis conducted by Wang et al. revealed a significant correlation between VDR gene polymorphisms and autoimmune thyroid disorders across diverse ethnic groups. These findings are also supported by the correlation between the polymorphisms of the VDR or the CYP27B1 gene and the pathogenesis of several autoimmune diseases [14].

3.3 Vitamin D and Hashimoto’s thyroiditis – current state of knowledge
In recent years, there has been a considerable volume of research exploring the potential utilization of vitamin D's properties to enhance immune tolerance in the management of autoimmune thyroid diseases (AITD). The majority of clinical studies generally affirm the presence of a correlation between a deficiency in calcitriol and thyroid autoimmunity.

In many systematic reviews and meta-analysis, vitamin D levels were significantly lower in patients with HT compared to healthy subjects [15,16]. In a Chinese study, female patients with newly diagnosed HT were administered VitD for 6 months and a significant decrease in Thyroid Peroxidase Antibody (TPOAb) level was observed in this group compared to the control group [17].

Similarly, vitamin D supplementation in AITD led to significant reductions in TPO-Ab titers in another study by Chaudhary et al., which proves the beneficial effect on autoimmunity [18].
Furthermore, a retrospective study with HT euthyroid subjects with hypovitaminosis D showed TSH levels significantly decreased after therapy with cholecalciferol 100,000 IU/month [19].

Another study indicated, that vitamin D administration (2000 IU daily) led to a reduction in thyroid antibody titers among women with Hashimoto's thyroiditis (HT) who were receiving levothyroxine (LT4) and had serum 25(OH)D levels exceeding 30 ng/mL. However, it did not influence the serum levels of thyroid-stimulating hormone (TSH) and free thyroid hormones [20].

Bhakat and co-authors found that treatment with 60,000 IU cholecalciferol weekly for 8 weeks, is associated with significant decrease in antithyroid antibody titers. It also improved serum TSH level compared with the placebo, i.e. supplementary treatment with cholecalciferol seems to have beneficial effects on AITD [21].

Chahardoli et al. observed a significant reduction of anti-Tg Ab and TSH hormone in the group that received 50,000 IU vitamin D weekly for three months, compared to the start of the study; however, there was no significant reduction of anti-TPO Ab in the Vitamin D group compared to the placebo group. Also, there were no notable alterations detected in the serum concentrations of T3 and T4 hormones [22].

Zhang and and coworkers performed a meta-analysis which indicates that supplementation with vitamin D leads to a decrease in the titre of thyroglobulin antibodies (TGAb) and thyroid peroxidase antibodies (TPOAb) in individuals with Hashimoto's thyroiditis (HT). The impact was more pronounced when patients received vitamin D3, and the duration of treatment exceeded three months [23].

According to Jamka et al. a negative correlation between serum 25(OH)D concentrations and the level of antithyroid antibodies was observed, but vitamin D supplementation reduced the levels of thyroid peroxidase (TPO) antibodies both in patients with deficiency and with normal levels of vitamin D [24].
Ke et al. observed no association between the level of vitamin D and the presence or absence of Hashimoto's thyroiditis. Study revealed that serum 25(OH)D level was not associated with FT3, FT4, TSH, TPOAb, and TGAb [25].

In a randomized, double-blind study involving individuals with backgrounds from South Asia, the Middle East, and Africa, who initially had low vitamin D levels, the supplementation of either 1000UI or 400UI of Vitamin D3 for 16 weeks did not result in any changes in the levels of thyroid peroxidase antibodies (TPOAb) when compared to a placebo [26].

Vahabi Anaraki et al. examined the impact of Vitamin D treatment on autoimmune thyroid markers (TPO-Ab) and thyroid function (TSH) in adult patients with Vitamin D deficiency who were either hypothyroid or euthyroid and had positive TPO-Ab. They suggested that Vitamin D did not exert a noteworthy effect on the thyroid function and autoimmunity within the studied population [27].

Summary
In conclusion, despite new data and numerous papers studying the connections between vitamin D and Hashimoto’s thyroiditis, the results are still inconclusive. While there are indications proposing an association between vitamin D deficiency and an elevated risk of autoimmune thyroid diseases development, it remains unclear whether deficiency has a specific role in the pathogenesis or is a consequence of the disease. Additionally, it has not been established whether vitamin D supplementation could potentially influence the progression or treatment outcomes of AITD. Ongoing and future long-term, randomized controlled trials are required to determine whether vitamin D deficiency poses a risk of developing AITD such as Hashimoto’s thyroiditis.

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