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The effect of vitamin D on the development of Hashimoto's disease and the reduction of the inflammatory process in its course - review

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Abstract

Introduction

Hashimoto's disease is an autoimmune chronic lymphocytic thyroiditis. It is a common condition, more frequent in women. Its diagnosis is based on the presence of specific antithyroid antibodies in the patient's blood which lead to the destruction of the thyroid gland. This can result in the development of hypothyroidism, requiring levothyroxine replacement therapy.

Aim of the review

A summary of the information gathered so far on the involvement of vitamin D in the development and course of Hashimoto's disease.

Results

The articles analyzed have mixed results. Most of them show a positive correlation between vitamin D and Hashimoto's disease, paying particular attention to the contribution of vitamin D in moderating the inflammatory process in HT. Other studies show significant differences in vitamin D levels between groups with different HT severity. Others show a negative correlation between vitamin D levels and the development of Hashimoto's disease.

Conclusions

Large well-controlled randomized double blind trials are needed in order to determine the exact role of vitamin D in Hashimoto’s disease.

Keywords: “diet Hashimoto”, ‘vitamin D’, “vitamin D Hashimoto’s thyroditis”, “Hashimoto’s thyroditis”, “diet”, “diet in autoimmune disease”

Introduction

Hashimoto thyroiditis (HT), also known as chronic autoimmune or lymphocytic thyroiditis, is now considered the most common autoimmune disease which is caused by the body's production of antibodies against thyroid antigens (mainly thyroperoxidase - TPO and thyroglobulin - TG) [5] and by the infiltration of hematopoietic mononuclear cells, mainly lymphocytes, in the interstitium among the thyroid follicles. This leads to the damage of the thyroid cells consisting of atrophy and their transformation into so-called Hurthle cells which are rich in mitochondria. Destruction of the thyroid gland leads to the development of hypothyroidism, although some patients remain in euthyroidism or transient hyperthyroidism, also called hashitoxicosis. Hashimoto thyroiditis may present in an atrophic form, with normal thyroid volume or with goiter (painless enlargement and increased cohesion of the thyroid gland). The diagnosis of HT is based on the presence of circulating anti - TPO and anti - TG antibodies in the blood. It may be helpful to perform an ultrasound, revealing heterogeneity and hypoechogenicity of the parenchyma, visible both in the case of goiter and thyroid atrophy. [1] In order to verify thyroid function the concentration of thyroid-stimulating hormone (TSH) and thyroid hormones (fT3, fT4) in the blood is measured. Treatment is based on supplementation with exogenous hormones (mainly levothyroxine sodium administered orally) in patients with developed hypothyroidism. [2] The development of Hashimoto's disease is influenced by many factors, both genetic and environmental. The most common factor determining the prevalence of HT in society is the region of life and socioeconomic conditions. Additionally, we observe gender differences (women suffer from HT approximately 4 times more often than men). [3] [4] The genetic causes include the involvement of histocompatibility genes (HLA class I and II), immunoregulatory genes (e.g. CTLA4, PD1, CD40), thyroid-specific genes (TG) and genes related to the synthesis of thyroid peroxidase antibodies (e.g. TPO, BACH2). Environmental risk factors include iodine excess, infections (viral and bacterial) and medications (e.g. amiodarone). [21 - 24] Furthermore, nutrients such as vitamin D, selenium and gluten are potential contributors to HT. [25 - 27]

Vitamin D - basic information

Vitamin D is considered a steroid hormone, which in the human body is mainly involved in the regulation of calcium and phosphate metabolism. The term “vitamin D” includes vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Both forms of vitamin D are hydroxylated in the liver, leading to the formation of 25-hydroxyvitamin D (calcidiol) - the main circulating form of vitamin D, whose blood concentration is measured. A second hydroxylation step then takes place in the kidneys and 1,25-dihydroxyvitamin D (calcitriol) is formed. Calcitriol is the biologically active form of vitamin D. Humans obtain vitamin D from three different sources: skin production, diet and supplementation. It was once thought that vitamin D receptors were only found in the kidneys, bones and intestines. Today we know that they are found in almost all cells in the human body, including thyroid cells and immune cells. [5, 19] It has long been known that normal vitamin D levels are important for the proper functioning of the human body. A 25(OH)vitamin D concentration greater than or equal to 30 ng/mL (up to a maximum of 100 ng/mL) is considered sufficient. Vitamin D levels between 20 and 29.9 ng/mL are considered insufficient and a drop in concentration below 20 ng/mL is already considered a deficiency. [28] To date, the role of vitamin D has been demonstrated in a number of endocrine and autoimmune diseases such as type 1 and 2 diabetes, polycystic ovary syndrome, adrenal disease, multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis. [29,30] In this paper, however, we will focus on its role in the development of Hashimoto's disease.

Meta-Analyses and Systematic Reviews

In 2021 the Journal of International Medical Research published a meta-analysis [6] covering eight eligible randomized controlled trials published between 2015 and 2020. [7 - 14] These eight studies included 652 HT patients, their number being 332 in the intervention groups and 320 in the control groups. The meta-analysis showed that vitamin D supplementation in patients diagnosed with Hashimoto's disease can lead to a reduction in anti-TPO and anti-TG antibodies in the blood. This effect of supplementation may be due to the involvement of vitamin D in the regulation of immune system function. [6] As we mentioned earlier, Hashimoto's disease is characterized by the infiltration of lymphocytes - helper T cells (Th),

cytotoxic T cells (Tc) and B cells. [16] When the balance between Th type 1 and Th type 2 cells is disrupted and Th1 lymphocytes become more numerous, a cellular immune response is initiated, which is the main pathogenetic mechanism of HT. [17] There are studies showing that vitamin D inhibits the cellular response conditioned by Th1 lymphocytes [15] and also inhibits the production of plasma cells, the formation of memory cells and the subsequent secretion of immunoglobulins IgG and IgM by activated B cells [18] which contributes to a reduction in thyroid inflammation observed as a decreased levels of antithyroid antibodies in blood. This effect is more pronounced when patients supplement calcitriol instead of cholecalciferol or ergocalciferol (although this finding seems to need confirmation in more randomized controlled trials) and the duration of treatment is longer than 3 months. [6]

A meta-analysis of six randomized controlled trials published a couple of years earlier, in 2018, also showed that vitamin D supplementation can lead to a reduction in antithyroid autoantibodies in HT patients. The period of supplementation required to achieve such an effect was about 6 months. [32]

In addition, in 2023 a prospective study showed similar conclusions. At the time 100 patients with diagnosed Hashimoto's disease and coexisting vitamin D deficiency were studied. Patients were divided into two groups, one of which was supplemented with vitamin D and the other received placebo. Serum levels of anti-TPO antibodies at the beginning of the study and after 8 weeks of the study were then compared. A decrease in the average antibody titer was observed in both groups - by 30.5% in the vitamin D supplementation group and by 16.5% in the placebo group. Based on the results it was concluded that vitamin D supplementation reduces thyroid autoimmunity. [20]

Controversies

However, there are studies that question the link between vitamin D and Hashimoto's disease. In 2021, an interesting article was published about a retrospective observational study conducted in a large group of clinically diagnosed HT patients and control subjects from the Croatian HT Patients Biobank (CROHT). There were 461 patients diagnosed with Hashimoto's disease (92.41% of whom were female) and 176 control patients (93.75% of whom were female). What is more, HT patients were divided into 2 groups according to the severity of their disease course. The first group, called MILD, included 240 patients in euthyroid or subclinical hypothyroidism, while the second group, called OVERT, included 219 patients with clinical hypothyroidism (TSH > 10mIU/L or patients treated with

levothyroxine). Two patients were not included in either of the two groups due to lack of information about their disease. HT patients were recruited between 2015 and 2017, covering all seasons, while control patients were recruited between December 2018 and June 2019 (covering winter and spring only). The study had several objectives. One of them was to see if vitamin D levels differed between patients diagnosed with Hashimoto's disease and control patients - there were no significant differences in vitamin D levels between either the MILD group and controls, or the OVERT group and controls. The second objective was to see whether vitamin D levels differed in HT patients according to disease severity - a significant difference in vitamin D levels was observed between the MILD and OVERT groups. [19] Although the results of this study are not the same as the results of most meta-analyses conducted to date, it should be acknowledged that this study has many features that increase its credibility. First and foremost, the authors pointed out that multiple factors may contribute to vitamin D deficiency in HT patients - age [33], sex [34], BMI [35], seasonality of blood withdrawal [36-38], smoking and severity of illness. [31] For this reason, the study used adjustments for age, gender, BMI, smoking and seasonality of blood draw to minimize the impact of these variables on vitamin D levels in the patients studied. Another important advantage of this study is the large population of study subjects from the same geographic region.

A study published in 2020 observed lower levels of 25-hydroxyvitamin D in patients with Hashimoto's disease compared to a healthy population. However, the same study ruled out the possibility that vitamin D is an independent risk factor for the development of Hashimoto's disease. Furthermore, there was no correlation between vitamin D and the levels of anti-TPO and anti-TG antibodies in patients' blood. Interestingly, however, it has been shown that patients with deficient or insufficient levels of vitamin D present higher levels of TSH with concomitant lower levels of fT4 and fT3 in the blood. This finding, coupled with the information that TSH is a potential stimulator of IL - 6, IL-12 and tumor necrosis factor among HT patients [44], suggests that it is elevated TSH levels, rather than reduced vitamin D levels, that are an independent risk factor for the development of Hashimoto's disease. [43]

Additionally, the lack of correlation between vitamin D and the development of Hashimoto's disease has been demonstrated in several smaller studies. [39-42] One of them, published in 2018, confirmed the lack of association between vitamin D deficiency and the development of Hashimoto's disease, but low fT4 levels were found to be a risk factor for vitamin D

deficiency in HT patients. This effect was particularly noticeable in patients with fT4 levels below 1.18 ng/dL. [39]

Discussion

The results of most studies to date suggest that there is a positive correlation between the levels of vitamin D and Hashimoto's disease. Particular attention is paid to the role of vitamin D in reducing thyroid inflammation which is observed as a reduction in the concentration of antithyroid antibodies (anti-TPO and anti-TG) in the patient's blood. One of the biggest limitations of the meta-analyses conducted, including the 2021 meta-analysis we cited, is the limited number of studies taken into consideration, their significant heterogeneity and the limited size of the patient populations studied. [6] There are also papers that contradict the claim that vitamin D levels affect the development of Hashimoto's disease. One example is a retrospective observational study from the Croatian HT Patients Biobank (CROHT) conducted on a much larger number of patients, who were additionally recruited from the same geographical region, in which adjustments were made for various factors affecting vitamin D levels to minimize the impact of these variables on vitamin D levels in the studied patient population. [19] Summarizing all the information, it should be recognized that the authors of the various papers are still disagreeing on whether low vitamin D levels are an effect of Hashimoto's disease or part of its pathogenesis. Therefore, it would be worthwhile to conduct additional studies on this topic.

Authors' contribution

All authors contributed to the article. Conceptualization – Jagoda Elias; methodology – Karol Womperski; check - Justyna Woźniak; formal analysis – Julia Szymonik; resources – Sebastian Szopa; data curation - Karol Womperski; writing - rough preparation – Jagoda Elias; writing - review and editing - Jagoda Elias, Justyna Woźniak; visualization – Julia Szymonik; supervision – Karol Womperski; project administration – Sebastian Szopa. All authors have read and agreed with the published version of the manuscript.

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