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The Impact of Nutritional and Dietary Factors on Hashimoto's Thyroiditis: A Comprehensive Review

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Abstract
Introduction. Hashimoto's disease (HD) is the main cause of hypothyroidism in countries where there is no iodine deficiency in the diet. Characteristic antibodies for it are anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) and their level positively correlates with the severity of HD. Whereas its occurrence is related to genetic, environmental and existential factors.
Aim of study. The aim of this study was to analyze dietary factors (protein, fat, vitamin D, iodine, selenium, gluten) and intestinal microbiota on the risk of developing Hashimoto's disease and the influence of each of these factors on its course.
Materials and methods. More than 90 articles addressing these issues were analyzed. They were found using the PubMed search engine, and the time frame of these publications covered the last 10 years.
Results. Excess iodine is the most important environmental factor influencing the development of Hashimoto's disease. Also, selenium deficiency contributes to the development of HD. On the other hand, the concentration of vitamin D is lower in patients with Hashimoto's disease than in the general population. Furthermore, Vitamin D supplementation reduces the concentration of anti-Tg antibodies without significantly affecting the reduction of anti-TPO antibodies. In addition, different types of dietary fat affect thyroid hormone levels differently. For example, vaccenic acid and elaidic acid in humans were positively associated with the ratio FT3/FT4, while all TFAs and their sum were negatively associated with the ratio FT4/TT4. However, a deficiency of protein in the diet causes an increase in TSH and a decrease in thyroid hormones. Moreover, changes in the gut microbiome have been observed in people suffering from Hashimoto's disease.
Conclusions. The risk of developing Hashimoto's disease can be increased and decreased by diet and diet allows for the modification of hormone levels in the hypothalamus-pituitary-thyroid axis.

KEY WORDS: Hashimoto’s thyroiditis, vitamin d, diet, selenium, protein, gut microbiome, fat

INTRODUCTION

The thyroid is a small organ located at the base of the neck, adjacent to the trachea, consisting of two lobes connected by an isthmus, and its function is primarily the production of triiodothyronine (T3) and thyroxine (T4), which is regulated mainly by hormones secreted by the hypothalamus - thyrotropin-releasing hormone (TRH) and through the pituitary gland-thyrotropin (TSH) [1, 2, 3, 4, 5]. The production of thyroid hormones requires, among others, amino acids and iodine, and the main task of these hormones is to regulate the body's metabolism [6, 7, 8].

Diseases that may affect the thyroid gland include hypothyroidism and hyperthyroidism (mainly caused by autoimmune diseases - Hashimoto's disease and Graves' disease), thyroiditis (e.g. subacute - de Quervain's disease), goiter, thyroid nodules and thyroid tumors [3, 9, 10, 11, 12, 13, 14, 15, 16].

Hashimoto's disease (also known as Hashimoto's thyroiditis, chronic lymphocytic thyroiditis) is a common cause of primary hypothyroidism and is an autoimmune disease characterized by the production of autoantibodies - against thyroperoxidase (anti-TPO) and against thyroglobulin (anti-Tg) [17, 18]. There are forms of this disease - atrophic, with normal thyroid volume or with goiter, its course may be characterized by euthyroidism or hypothyroidism, and it is diagnosed primarily by laboratory tests (concentration of autoantibodies, hormonal tests and imaging - mainly ultrasound) [19, 20].

High prevalence of autoimmune diseases (such as Hashimoto's disease; systemic connective tissue diseases, such as systemic lupus erythematosus, rheumatoid arthritis and juvenile idiopathic arthritis; inflammatory bowel diseases, which include ulcerative colitis and Crohn's disease; celiac disease; type 1 diabetes and diseases affecting mainly the nervous system, such as myasthenia gravis and multiple sclerosis), as well as their tendency to co-occur, prompted considerations on the impact of diet (especially high-protein, meat and meat-free diet, selenium, iodine and vitamin D supplementation) and other factors (such as intestinal microbiota), on the risk of their occurrence and course [21, 22, 23, 24, 25, 26, 27, 28, 29, 30].

Protein, in addition to carbohydrates and fats, is a basic component of a balanced diet, and its roles in the body include proper growth and development during adolescence, stimulating tissue regeneration, participation in the synthesis of enzymes and hormones, as well as influencing immunity, so in the case of hypothyroidism caused by disease Hashimoto, it is possible to link the role of protein and its properties in the context of hormone synthesis, generating the body's immunity, as well as its beneficial effect on metabolism, which is slowed down in the course of this disease [31, 32, 33].

A meatless diet is very popular, and its type includes fish in the menu (rich in omega-3 acids, which have a beneficial effect on the cardiovascular system, which may suffer in the course of hypothyroidism, and the immune system, the defect of which leads to Hashimoto's disease), may have a beneficial effect on health due to the limited consumption of saturated fatty acids, lower caloric value (which is very important in the case of excess weight that often accompanies hypothyroidism) and a lower degree of food processing [34, 35, 36]. However, there are concerns that harmful compounds contained in some products (especially in fish, which results from accumulation) may have an adverse effect on human health [37, 38].

An issue worth considering is iodine supplementation in the case of Hashimoto's disease, because on the one hand it is a substrate for the production of thyroid hormones, and on the other hand, there is a risk of induction of Hashimoto's disease, as well as the risk of the Wolff-Chaikoff effect (blockade of the synthesis of thyroid hormones due to excessive supply iodine) [39, 40, 41].

The role of selenium is emphasized in the context of its beneficial effect on the body's immune system and participation in the synthesis of thyroid hormones, which may have a helpful effect in the case of hypothyroidism caused by Hashimoto's disease, in which both the production of thyroid hormones and the immune system are disturbed [42, 44].

The key functions of vitamin D in the body are the regulation of calcium and phosphate metabolism, the impact on bone metabolism and the immune system, and therefore the relationship between vitamin D deficiency and the increased risk of developing autoimmune diseases, including Hashimoto's disease, as well as the impact of supplementation are observed. on the course of existing diseases [43, 44, 45, 46, 47, 48, 49].

Intestinal microbiota is a set of microorganisms inhabiting the lower gastrointestinal tract, the balance of which is of great importance in the context of the functioning of the digestive, immune and hormonal systems, and the effects of dysbiosis (i.e. disruption of this harmony, which may be the result of an incorrect diet, the use of certain medications and stress) may be hormonal disorders or an increase in the risk of developing autoimmune diseases, so it can be assumed that there is a connection between dysbiosis and Hashimoto's disease [50, 51, 52, 53, 54, 55].

This paper will discuss issues regarding the impact of diet and supplementation on Hashimoto's disease and the resulting hypothyroidism [56, 57].

ROLE OF PROTEIN

Thyroid hormone levels are regulated by many feedback mechanisms functioning within the hypothalamus-pituitary-thyroid axis (HPT). The key importance in adaptive changes of the axis is the hypophysiotropic thyrotropin-releasing hormone (TRH). [58] Many factors regulate the synthesis and secretion of TRH - in addition to the negative feedback regulation by thyroid hormone, there are also arcuate nucleus (ARC) neurons. [59] Some of these neurons stimulate TRH secretion, while others inhibit it. Nevertheless, all of them are regulated by metabolic and hormonal signals, including leptin, insulin, peptide YY (PYY), and ghrelin. [60] Therefore, food significantly influences HPT axis activity. [58]

It is not only the amount of food supply that plays a role in regulating thyroid hormone homeostasis but also diet composition, especially protein intake. Protein content varies depending on various factors, such as health conditions or specific targets of dieting of an individual. [58, 61] We would like to review the literature on its influence on the thyroid hormone levels in Hashimoto’s thyroiditis.

Low-protein intake is frequently observed in patients with autoimmune thyroid diseases. Both low-protein content and starvation downregulate the HPT axis. Protein-calorie malnutrition can cause thyroid gland damage, thus influencing thyroid hormone activities, especially in children. [62, 63, 64]. A significant correlation between TSH activity and body mass index (BMI) was also observed. Patients with protein-energy deficiency tend to have higher activity of TSH than well-nourished individuals. It is probably a result of the body’s natural adaptive response which is stimulation of the pituitary gland by TRH to secrete TSH. [63]

Often protein-calorie malnutrition can play a significant role also in iodine deficiency, which can also influence thyroid gland activity. Not only can low-protein intake be the reason for low-iodine intake, but it can also lower the bioavailability of iodine, resulting in worse iodine absorption. [63]

Hence, one of the nutritional recommendations for Hashimoto patients is a sufficiently high intake of protein, meeting the daily requirement in the state of Hashimoto’s thyroiditis, which is higher than the daily requirement of a healthy person.

Ihnatowicz et al. suggest increasing the supply of protein from the recommended 10-15% total dietary energy intake to 15-20% or even 25%. [56, 64] Proper protein intake improves the nutritional status of patients, which can help to restore the normal function of the thyroid gland. Protein sources suggested for Hashimoto thyroiditis patients are oily fish, chicken eggs from organic farming, and organic cow meat, as they also provide appropriate iodine, iron, zinc, and omega-3 acids intake. [56, 60]

IODIUM AND SELENIUM

Selenium is one of the trace elements present in the human body. The recommended daily intake of selenium ranges from 30 to 75 micrograms, with an optimal amount of 55 micrograms per day [70]. Foods rich in selenium, for example, are tuna, pork, beef, turkey, chicken, unprocessed cereal products, sunflower seeds, and mushrooms [70, 56]. Selenium plays a crucial role in many biological processes, possessing antioxidant and anti-inflammatory properties. It is essential for the proper functioning of selenoenzymes, which have a multifaceted impact on the body. Selenium significantly regulates thyroid function, accumulating in large quantities in this organ, particularly in cases of deficiency throughout the body. Selenium is a component of iodothyronine deiodinases and determines their enzymatic activity, facilitating hormone conversion reactions in peripheral tissues and the thyroid gland. Glutathione peroxidase present in thyrocytes, along with its isoforms, is also selenium-dependent. Isoforms GPX1 and GPX4 participate in intracellular antioxidant defense mechanisms, while GPX3, secreted into the thyroid colloid, reduces hydrogen peroxide levels, crucial for inhibiting oxidation, iodine organification, and coupling of iodotyrosines. Thioredoxin reductase reduces thioredoxin (Trx) and other substrates, regulating key redox reactions in thyroid cells [65, 66, 67, 70].

Studies on animal models suggest that selenium deficiency may contribute to fibrotic processes, thyroid cell damage, and impaired regeneration [66]. Furthermore, it may be associated with impaired functioning of T lymphocytes and B lymphocytes, leading to decreased immunity [66]. Selenium deficiency increases the Th1/Th2 lymphocyte ratio and intensifies the immune response, contributing to the development of autoimmune thyroiditis [67].

Patients with Hashimoto's disease often have significantly lower selenium levels in their blood compared to healthy individuals [65, 56]. Those with Hashimoto's disease and mild thyroid insufficiency, with selenium levels below 80 µg/L, exhibit significantly higher levels of C-reactive protein than patients with higher selenium levels [65].

Researchers worldwide are studying the impact of selenium on thyroid function and its role in thyroid diseases. The majority of studies suggest a beneficial effect of selenium supplementation in Hashimoto's disease, by inhibiting the production of anti-TPO antibodies [65, 66, 67, 69]. Additionally, selenium supplementation has been shown to reduce anti-Tg levels and serum TSH levels [66, 67]. Despite promising research findings, there is insufficient evidence to recommend routine selenium supplementation for treating autoimmune thyroid dysfunction. Further research with larger sample sizes, varying selenium doses, and consideration of other factors influencing anti-Tg antibody levels is necessary [67, 68].

Iodine is a trace element essential for the proper functioning of the human body. It is recommended that adults consume 150 µg of iodine daily, while pregnant and lactating women should intake up to 250 µg [70, 72, 56]. Iodine is primarily obtained from diet. Foods rich in iodine include seafood, animal products, cranberries, and eggs [70, 71 72]. In the 20th century, the WHO and UNICEF recommended the use of iodized salt in many countries to increase iodine intake from food [70, 71].

Iodine plays a critical role in the synthesis of thyroid hormones. It is taken up by thyrocytes and subsequently combines with selected residues of thyroglobulin in the lumen of thyroid follicles [72].

The impact of iodine on thyroid function and its influence on autoimmune diseases, including Hashimoto's thyroiditis, is the subject of extensive scientific research. Excessive iodine intake has been shown to increase the risk of autoimmune diseases and can contribute to both hypothyroidism and hyperthyroidism [72, 74]. This is associated with the generation of reactive oxygen species, which likely enhance the expression of ICAM-1, playing a role in the early stages of the inflammatory response occurring in thyroid follicular cells. Excessive iodine also increases the immunogenicity of thyroglobulin and contributes to elevated levels of H_2O_2, which can damage thyrocytes [73, 56]. Excess iodine inhibits enzymes containing selenocysteine residues, such as glutathione peroxidase and thyroid peroxidases, leading to reduced enzymatic activity and subsequent inhibition of antioxidant enzyme activity. Studies conducted in rats have shown that selenium supplementation alongside excess iodine limits thyroid pathology and reverses changes induced by excessive iodine intake [75].

VITAMIN D

Vitamin D is a group of steroid compounds whose main function is to regulate calcium-phosphate metabolism. Through this, it conditions bone health [76]. A growing number of research indicates that vitamin D also plays a role in modulating the immune system. It turns out that vitamin D receptors – VDRs are expressed in many immune cells. First, in vitro studies show that vitamin D inhibits the differentiation and production of antibodies by B lymphocytes [77]. Additionally, it modulates the activity of T lymphocytes, reducing their ability to induce autoimmune responses [78, 79]. Besides, vitamin D decreases the production of pro-inflammatory cytokines (e.g., IL-17, IL-21) [80] and increases the production of anti-inflammatory cytokines (e.g., IL-10).

Promising in vitro studies on the immunomodulatory role of vitamin D have led to an increasing number of studies examining whether a similar effect can be induced in the human body and, consequently, whether vitamin D can influence autoimmune diseases, including autoimmune thyroid diseases (ATD).

Vitamin D levels in patients with Hashimoto's disease (HD) are lower than in the general population. G. Tamer et al. observed that the study group of 161 patients with HD had lower vitamin D levels compared to a control group of 162 matched for age and sex [81]. However, it is not clear whether the lower vitamin D levels in HD patients are a consequence of the disease or one of its causes.

The level of antibodies against thyroperoxidase (anti-TPO Ab) and antibodies against thyroglobulin (anti-Tg Ab) is positively correlated with the severity of HD [82].

Interesting results were shown in a study by R. Chahardoli et al., which aimed to determine whether vitamin D supplementation affects the concentration of anti-TPO Ab and anti-Tg Ab and thyroid hormone profile (TSH, T3, T4) in patients with HD [83]. The results showed a significant reduction in anti-Tg Ab and TSH hormone levels in the group receiving vitamin D supplementation compared to the beginning of the study, while the placebo group did not show a similar decrease. However, no significant decrease in anti-TPO Ab concentration was found in the vitamin D group compared to the placebo group. No significant changes were observed in the serum levels of T3 and T4 hormones.

Similar conclusions can be observed in a meta-analysis conducted by J. Zhang et al. [84]. It was concluded that vitamin D supplementation in HD patients leads to a decrease in anti-TPO Ab and anti-Tg Ab concentrations. Additionally, it was suggested that to achieve a beneficial effect, supplementation should last at least 3 months. However, the meta-analysis had several limitations. Firstly, no conclusions were drawn about the dose to be supplemented. Secondly, there was significant heterogeneity among the included studies, and thirdly, the power of the analysis might be limited due to the limited number of studies and population size.

Therefore, it is worth considering what supplementation dose of vitamin D could affect the reduction of the severity of HD. Simsek Y et al. observed a decrease in anti-TPO Ab and anti-Tg Ab concentrations after administering 1000 IU/day of vitamin D for a month in patients with ATD and concomitant vitamin D deficiency. They concluded that vitamin D supplementation could be recommended as adjunctive therapy, especially in patients with vitamin D deficiency [85]. On the other hand, in a study by Chaudhary S et al., a group of patients with newly diagnosed ATD received vitamin D supplementation, cholecalciferol 60,000 U once a week for 8 weeks along with calcium 500 mg/day. After 3 months of observation, a significant decrease in serum TPO-Ab titers was noted in the treated group compared to the control group. However, they showed that the decrease in anti-TPO Ab titers was significant only in patients with baseline serum TSH concentrations $\leq$ 10 mIU. Therefore, the benefits of adjunctive vitamin D therapy may be most effective in patients with low disease activity [86].

There is still a lack of large, multicenter studies that could unequivocally confirm the thesis that vitamin D supplementation can beneficially affect disease activity in HD patients, considering the immunomodulatory potential of vitamin D. Moreover, there is a need for evidence and guidelines to establish the specific supplementation dose and minimum duration of therapy. However, taking into consideration the population-wide vitamin D deficiency and the fact that vitamin D supplementation therapy is low-cost and has minimal side effects, it may be recommended for patients with HD.

THE ROLE OF FAT CONSUMPTION

Evidence suggests that a diet rich in fat, especially animal and saturated fats may have detrimental effects on thyroid function. In a study involving rats, it was observed that a high-fat lard diet resulted in elevated levels of triglycerides in the bloodstream and thyroid, as well as decreased levels of TT4 and FT4 hormones, and increased levels of TSH hormone. The rats on the high-fat diet also exhibited enlarged thyroid glands with altered characteristics [87]. Another study on female rats found that a high-fat diet led to thyroid inflammation and decreased thyroid function, resembling Hashimoto's thyroiditis in humans.

These effects were associated with changes in the PD-1 pathway, increased immune cell activity in the thyroid, as well as thyroid fibrosis and cell death [88]. A study involving male rats fed a high-fat diet rich in saturated and monounsaturated fatty acids showed decreased thyroid iodine uptake, hypothyroxinemia, and elevated TSH levels [89].

Researchers discovered various links between specific trans fatty acids (TFAs) and thyroid hormones in humans. They observed that palmitelaidic acid and elaidic acid were positively linked with TT4, while palmitelaidic acid showed a positive association with TT3. Linolelaidic acid was associated with higher levels of TSH but negatively associated with FT4. Furthermore, all four TFAs and the total sum of TFAs were positively associated with FT3. In addition, vaccenic acid, elaidic acid, linoelaidic acid, and the total sum of TFAs were positively associated with the ratio FT3/FT4, while all TFAs and their sum were negatively associated with the ratio FT4/TT4. These associations were still significant when the data was analyzed separately for women. In men, linolelaidic acid negatively affected FT4 levels, while elaidic acid and the total sum of TFAs were positively associated with FT3. The relationships between TFAs and the ratio FT3/FT4 also remained significant in men [95].

There is evidence suggesting that the ketogenic diet (KD) may lead to thyroid dysfunction and women with obesity who undergo Very Low-Calorie Ketogenic Diet may experience reductions in T3 levels [92, 93]. Randomized study on humans showed that a KD resulted in a decreased level of T3, an increased level of T4, and no effect on TSH [90]. Randomized controlled trial on breast cancer patients showed no impact of KD on thyroid hormones [91]. Men who adhered to a ketogenic diet exhibited a substantial reduction in TSH levels compared to those who adhered to a carbohydrate-based diet. Moreover, there was a notable decrease in both T4 and T3 levels among individuals on the ketogenic diet compared to those on the carbohydrate-based diet [94].

GUT MICROBIOME

According to numerous studies, alterations in gut microbiota are significant factors contributing to the development of inflammatory and autoimmune diseases, including Hashimoto's Thyroiditis (HT). Characterization of the gut microbiota in patients with this condition has confirmed that it is altered compared to that found in healthy individuals [96]. Based on substantial evidence, it is known that gut dysbiosis, bacterial overgrowth, and increased intestinal permeability promote the development of HT [98, 99]. Commensal bacteria inhabiting the gut directly affect innate, cellular, and humoral immunity by interacting with epithelial and mucosal immune cells through receptors located on them. Depending on the metabolites produced, the microbiota can activate either pro-inflammatory or anti-inflammatory pathways [100]. Gut bacteria can influence thyroid hormone levels by regulating iodine uptake, degradation, enterohepatic circulation of these hormones, and the bioavailability of L-thyroxine. The microbiota can affect the hypothalamic-pituitary axis and dopamine production via neurotransmitters, consequently modulating TSH secretion [98].

A study conducted on a cohort of 93 Brazilians, including 40 individuals with HT and 53 healthy controls, demonstrated that the gut microbiota of participants in the study group exhibited an increased number of Bacteroidetes and a decreased number of Bifidobacterium. The study also showed that the intestines of the patients were more permeable, and that dysbiosis in these patients led to the creation of an inflammatory environment. These changes

were also influenced by dietary intake [98]. Similar conclusions were reached by the authors of four studies conducted on a Chinese population, comparing the gut microbiota of patients in euthyroidism with those suffering from HT hypothyroidism [101, 102, 103, 104].

As evidenced by the aforementioned studies, dysbiosis is a common feature in thyroid disorders. The composition of the microbiota can modulate the immune response, promoting inflammation, reducing immune tolerance, damaging the intestinal barrier, and consequently increasing intestinal permeability. This leads to higher exposure to antigens and local inflammation. Altered gut microbiota can directly affect thyroid hormone levels through its enzymatic activity and inhibition of TSH. There is a clear connection between thyroid dysfunction and altered levels of essential minerals required for its function, which are absorbed by gut commensals. Probiotic use has been shown to be beneficial in thyroid diseases and can positively impact the absorption of trace elements such as selenium, zinc, and copper. Gut bacteria can act as a reservoir for T3 and may prevent fluctuations in thyroid hormone levels, thereby potentially reducing the need for T4 supplementation [105].

GLUTEN

Gluten is a protein found mainly in wheat, barley, rye and oats which is sometimes processed in a contaminated environment by other products that contain gluten. Gluten is not fully digested by human gastrointestinal tract, because nondigestible protein may cause autoimmune response that is called celiac disease. Typically, undigested gluten does not cause any damage to the intestines in patients that are not genetically predisposed (without HLA-DQ2 or HLA-DQ8 antigens) [106, 107]. This Autoimmune disease affects 1% of the population and results in symptoms such as diarrhea, constipation, bloating, nausea, and vomiting [108].

Celiac disease involves production of specific antibodies (anti-gliadin [AGA], anti-tissue transglutaminase type 2 [anti-TG2], anti-endomysial [EMA], anti-deamidated gliadin peptides [anti-DGP]) and an autoimmune inflammatory reaction leading to villous atrophy of the small intestinal mucosa [109]. Therefore, absorption surface of small bowel is decreased, for this reason smaller amounts of selenium are ingested from consumed food.

Selenium is a component of selenoproteins (for e.g glutathione peroxidases (GPx), thioredoxin reductases and iodothyronine deiodinase families), its deficiency may lead to incorrect thyroid hormone metabolism [110].

Celiac disease and Hashimoto's thyroiditis have common characteristics because in each of these diseases there is an enhancement of immune sensitivity [70]. They are often noticed in combination with each other [108].

CONCLUSIONS

Hashimoto's disease is one of the most common autoimmune diseases in developed countries. In addition to substitution treatment, patients should also lead an appropriate lifestyle. The above review shows that proper diet and supplementation support thyroid hormone homeostasis. Unless they have any contraindications, patients should follow a high-protein diet, with particular emphasis on foods rich in selenium and iodine. In case of deficiency of these microelements, their supplementation should be considered. In these patients, a ketogenic diet (high in fat) should be avoided.

Safe vitamin D supplementation and the supply of good-quality probiotics may also have a beneficial effect on the course of Hashimoto's disease. Due to the possible co-occurrence of celiac disease, patients should be made aware of the symptoms characteristic of this disease in order to speed up its possible diagnosis and implementation of treatment.

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