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Autoimmune thyroid diseases in patients on the vegan diet

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Abstract
Introduction and purpose: Autoimmune thyroid diseases (AITDs) are the most common thyroid dysfunctions. Among them, we distinguish entities such as Hashimoto's disease and Graves' disease. Diet is one of the environmental factors that may influence the onset and progression of autoimmune diseases. A vegan diet is characterized by the complete elimination of animal products and a greater supply of fiber, vitamins, and unsaturated fats. The study aimed to evaluate the influence of a vegan diet on the course of AITDs.
A brief description of the state of knowledge: Numerous studies have shown significant changes in the severity of symptoms and blood laboratory parameters, as well as in the composition of the microbiota among people using only a vegan diet, which could indicate its protective effect on the body. However, an inadequately balanced vegan diet may predispose to deficiencies of key micronutrients such as vitamin B12 or iodine and selenium, so special attention should be paid to the appropriate balance of consumed products, especially in the case of people suffering from AITDs.
Conclusions: Reports from various studies may be the basis for developing a rational diet, which will be one of the elements of AITDs prevention or treatment. It is essential to remember the proper balancing of meals that will ensure an adequate supply of microelements or vitamins, which is especially important in AITDs.

Keywords: autoimmune diseases; Hashimoto's disease; Graves' disease; vegan diet

Introduction
Autoimmune thyroid diseases (AITD) are the most common autoimmune diseases and also the most common thyroid dysfunctions. The dysregulation of the immune system occurs in them, which leads to the production of antibodies against the thyroid gland and consequently to the destruction of its tissues. (1) The term AITD includes two entities: Hashimoto's disease (HT) and Graves' disease (GD). In HT, autoimmunity occurs mainly with the participation of T lymphocytes and in the presence of antibodies against thyroid peroxidase

(TPOAb) and antibodies against thyroglobulin (TGAb), while the course of Graves' disease is characterized by a humoral response and the presence of antibodies against the thyrotropin (TSH) receptor (TRAb). Interactions between genetic and environmental factors probably lead to the disease's development, which is still not fully understood [1]–[3]. One essential environmental factor is diet. In recent years, more and more people are choosing to go vegan, which is gaining recognition as a healthy eating option [4]. Analyzing the results of the study about consumption preferences of Polish people, it can be concluded that the average consumption of legumes as an alternative to meat in the Polish population is relatively low. However, consumers are optimistic about purchasing and consuming legumes on a broader time horizon [5]. In 2019, over 28% of Polish people declared that they eat plant-based meat alternatives, 6% eat such products regularly, and 8.4%, during the month preceding the survey, were on a vegetarian diet (6.6%) or vegan (1.8%). As a key feature that would convince them to consume a specific plant alternative, as many as 55% of respondents indicated "health benefits of their consumption." [6]

Vegan diet and autoimmune diseases

A vegan diet that excludes all animal products has been linked to health and environmental benefits. Eating a minimum amount of animal products is believed to be optimal for preventing and treating chronic disease and prolonging life [7]. A vegan diet is characterized by a higher content of fiber, folic acid, vitamins C and E, potassium, magnesium, and unsaturated fats. Vegans, compared to omnivores, are characterized mainly by lower blood pressure, triglycerides, and fasting glucose. It has also been shown that the parameters of sedentary vegans are similar to those of endurance athletes. This is a lower body mass index (BMI) and reduced levels of lipids, lipoproteins, glucose, insulin, and C-reactive protein (CRP) compared to people who lead a sedentary lifestyle and eat products from all food groups [4], [8]. A particularly noticeable difference is the level of CRP protein, which is inflammation's primary marker and mediator. A meta-analysis by Menzel et al. showed a relationship between a vegan diet and lower CRP levels compared to omnivores in a group of apparently healthy subjects [9]. In turn, 19 out of 21 studies have shown that vegetarians also have lower CRP levels than omnivores. The decrease in CRP correlated with the duration of the vegan diet and was particularly marked in people who had been on a diet for more than 10 years. Switching to a plant-based diet may be associated with mitigating inflammatory processes and reducing inflammatory markers, lowering the risk of chronic diseases. However, the benefits also depend on the length of the diet itself. Chronic diseases for which a vegan and vegetarian diet can be protective include, for example, type II diabetes, cardiovascular diseases, and cancer. Despite the similarities between vegetarianism and veganism, a review of research has shown that a vegan diet can provide unique protective effects for the body that are not possible with a vegetarian diet alone, but this requires further analysis [8] In the 1950s, it was noticed that the use of a vegan diet might be one of the factors affecting the prevention or mitigation of autoimmune diseases. Trowell, in his analysis, noted the case of Africans from sub-Saharan regions which led a traditional lifestyle and did not follow a Western-type diet. Among this population, the incidence of autoimmune diseases such as rheumatoid arthritis (RA), Addison's disease, or HT was negligible [10]. Downregulation of IGF-1 activity has been suggested as a mechanism to mitigate autoimmune processes. The vegan diet is lower in calories and contains more products with a lower glycemic index, in contrast to the Western diet rich in animal proteins, starches, or sugars with a high glycemic index, which increases IGF-1 activity through increased insulin secretion and direct effect on hepatocytes. It is assumed that there is also a mechanism in which a diet rich in animal proteins increases the assimilability of antigens that can cause autoimmunity or may promote the growth of intestinal flora that will generate such antigens [11]. The influence of intestinal microbiota on other diseases is still valid and has yet to be precisely explained. Host-gene-microbiota interactions may likely be the basis of autoimmune and inflammatory diseases. A better understanding of gut microbiota diversity could improve the accurate identification of diseases and their treatment [8]. An apparent effect of a vegan diet on bacterial flora has been observed in patients suffering from RA. After a month of following a vegan diet, the bacterial flora of the study group changed, and the symptoms of the disease were alleviated [12].

The exact impact of veganism on thyroid disease

The exact impact of a vegan diet on AITD has yet to be explored, but several studies have already been undertaken to elucidate the relationship between the type of food intake and the manifestation of HT and GD, as well as the composition of the gut microbiota of AITD patients.

The Adventist Health Study-2 (AHS-2) was one of the first studies to show that overweight and obesity were associated with hypothyroidism [13]. It also indicated that factors such as white race, female gender, higher BMI, and higher education correlate positively with the occurrence of hyperthyroidism. Compared to a traditional diet containing foods from all food groups, a vegan diet is associated with a reduced risk of hypothyroidism, unlike a lacto-ovo-vegetarian diet. It has been shown that a vegan diet, understood as a diet excluding the consumption of red meat, poultry, fish, eggs, milk, and dairy products, is associated with a lower incidence and morbidity of hypothyroidism, however, this relationship was considered to be statistically

insignificant. At the same time, it was noted that this diet is associated with a lower BMI, which is also associated with a lower risk of hypothyroidism. The exclusion of variables such as demographic factors and BMI in the examined patients did not increase the risk of developing hypothyroidism, so it can be assumed that this diet is protective in this clinical entity [13]. This state of affairs may be indirectly due to other effects of a vegan diet, including lower iodine intake [14]. Again, lower levels of inflammatory markers were shown [15] such as CRP [16], contributing to the occurrence of inflammation, including the thyroid, responsible for the development of its hypothyroidism. The lacto-ovo-vegetarian group had a higher prevalence rate of hypothyroidism than the vegan group, but the incidence of the disease was the same. It is believed that there are several products consumed on a vegetarian diet that have goitrogenic potential - soy products or cruciferous vegetables. It is worth mentioning that clinical data do not provide significant results that could state that soybean consumption disturbs the functioning of the thyroid gland. As part of the observation of the same study group, the effect of individual diets on the morbidity and incidence of hyperthyroidism was also examined [17]. In this case, it was observed that in the group of people using a vegan diet, the occurrence of hyperthyroidism is two times lower than in the group using a traditional diet containing foods of animal origin. In the groups using the intermediate exclusion of animal products, such as lacto-vegetarian and pesco-vegetarian, the protection against hyperthyroidism was lower, but in this group the protection was indirect, prevailing to the effect of the omnivorous diet. Researchers have not been able to directly identify the mechanisms responsible for this state of affairs, however, there have been hypotheses related to the exclusion of pro-inflammatory products of animal origin that provide exogenous estrogen [18], which may intensify autoimmune processes responsible for improper thyroid function. The protective effect of a vegetarian diet may also be due to the effects of plant foods, as well as reduced iodine intake. It was also indicated that important factors affecting the occurrence of hyperthyroidism are: older age, female sex, overweight and obesity. The association between the reduced incidence of hyperthyroidism in the vegan group may be due to the lower average BMI in this group. Previous studies show that overweight and obesity correlate with the occurrence of autoimmune diseases, which may be associated with elevated leptin levels [19] in people with a BMI >25 [20]. Reducing the activity of insulin-like growth factor [11], as a modulator of lymphocyte proliferation and apoptosis may be of importance, as well as the role of polyphenols [21] present in plant foods in preventing autoimmune cellular processes.

In a study by the University of Split School of Medicine, which compared the diet of healthy people with the diet of people with Hashimoto's disease [22] attention was drawn to the increased consumption of animal fats and processed meat in the diet of the group with HT, while the control group showed increased consumption of red meat, soft drinks, whole grain products and vegetable oil. It was also noted that patients with HT who consumed vegetable oil had higher triiodothyronine (T3) concentrations, and those treated with levothyroxine who consumed olive oil had lower systolic blood pressure. The protective effect of vegetable fats may be due to their anti-inflammatory properties and reduction of oxidative stress associated with the presence of vitamin E [23]. In turn, olive oil has been shown in numerous studies to alleviate the course of autoimmune diseases, associated with the presence of oleocanthal, with the properties of drugs from the group of non-steroidal anti-inflammatory drugs (NSAIDs) [24]. HT has also been found to be associated with a 50% higher consumption of animal fat compared to controls. Animal fats contain mainly saturated and monounsaturated fatty acids, which intensify inflammatory reactions, also have a negative effect on T3 and thyroxine (T4), and raise TSH levels [25]. Cereal products rich in fiber and short-chain fatty acids were consumed in greater amounts by the control group. This group also includes cereals containing gluten, the consumption of which is controversial among people with HT. The observation may be important in overthrowing the popular myth about the healing effect of a gluten-free diet on thyroid diseases. The latest research also shows that a diet rich in products with anti-inflammatory potential, vitamins and minerals is recommended in patients with HT, such products include cereals, including gluten, and fruit. (19) Studies on rats have shown a relationship between the consumption of the above-mentioned lipids with increased concentrations of TPOAb and TgAb in the blood of rats [26]. Processed meat is also rich in animal fats, as well as nitrogen compounds that cause morphological changes in the thyroid gland, resulting in changes in the hormonal profile [26]. At the same time, fats of animal origin, in the form of fish oil or supplementation with DHA, omega-3 PUFA and EPA acids, showed a positive effect in reducing the concentration of antithyroid antibodies, especially during pregnancy, and are a suggested prophylactic effect against thyroiditis in the postpartum period. High content of selenium, zinc and iodine in the above-mentioned fats also has a beneficial effect on the functioning of the thyroid gland.

Significant differences in food intake between the control group and people with HT were also found in a study by Ruggeri et al. [27]. Compared to the control group, people with HT consumed more meat, in particular red/processed meat and refined sugars from processed sweets, and fewer vegetables, fruits, legumes, and nuts. The dietary patterns of people with HT resembled a Western-style diet, high in saturated fat and animal protein, and low in fiber and antioxidants. The control group, on the other hand, followed the Mediterranean diet, which eats more fruits, vegetables, and grains. Thyroid antibodies were not detected in any of the subjects who did not eat meat or did it no more than twice a month. The parameters of oxidative stress were also analyzed and showed their significant dependence on age and consumption of animal foods. People with euthyroid HT had a

higher number of oxidants and a lower number of antioxidants, which confirms the dysregulation of redox reactions in them. Adherence to a Mediterranean diet protected against the risk of developing thyroid autoimmunity, while a higher frequency of meat and dairy consumption was significantly associated with an increased risk of thyroid autoimmunity.

The study by El-Zawawy et al. examined the gut microbiome of Egyptian HT and GD patients [28]. Most of the patients were recently diagnosed and not on treatment, and the patients who received the drugs had not used them for 6 years. All HT patients and 85% of GD patients followed a diet rich in fats, animal proteins, and refined sugars, in contrast to the control group where 90% received a diet rich in fresh fruits and vegetables. Microbiome analysis showed significant differences in gut bacterial composition in AITD patients compared to controls. In subjects with AITD, intestinal dysbiosis was observed with a 41% rate of dissimilarity with the control group. All AITD patients had significantly higher levels of Bacteroidetes and Prevotella and significantly lower levels of Firmicutes, with no significant differences between HT and GD. Bacteria of the genus Prevotella are known to produce anti-inflammatory metabolites that reduce the level of Th17 lymphocytes and promote the differentiation of anti-inflammatory cells in the intestine. However, other studies have noted that the most abundant species of the genus Prevotella, Prevotella copri, is associated with certain inflammatory conditions, as well as some autoimmune diseases such as RA and GB orbital inflammation. The results of this study showed a decrease in the relative abundance of beneficial, anti-inflammatory bacteria associated with the intestinal barrier; A. mucinophilia, Bifidobacterium, Lactobacillus, F. prausnitzii, however, this change was not statistically significant. A correlation was also found between TPOAb antibodies from Bacteroidetes, F. prausnitzii, Firmicutes, and Prevotella, while TRAb showed a significant positive correlation with Bacteroidetes and Firmicutes [28]. Dietary patterns affect the composition of the gut microbiota, hence the gut microbial dysbiosis found in AITD patients may be related to their eating habits. Therefore, patients on a diet high in fat and animal products may be at risk for AITD.

Matana et al showed that a diet group consuming plenty of vegetables, legumes, dried fruits, nuts, and muesli was negatively associated with TPOAb and/or TgAb. In contrast, the dietary group consuming animal butter and fats was positively associated with plasma TPOAb/or TgAb [29]. The mechanism of this correlation is probably related to the separate effect of saturated fatty acids present in butter and animal fats and polyunsaturated fatty acids (PUFA) in which vegetables and nuts are rich. *N*-6 and n-3 PUFAs play the role of precursors in the synthesis of eicosanoids in the cell. N-6 PUFAs serve as precursors to inflammatory eicosanoids, while N-3 PUFAs generate anti-inflammatory eicosanoids. Previous animal studies have shown that a diet enriched with n-3 PUFAs suppresses the inflammation that accompanies autoimmune reactions [30], [31]. This is due to a reduction in the differentiation of Th17 cells from native CD4+ T cells. Th17 lymphocytes are known to positively correlate with TPOAb and TgAb. The level of anti-inflammatory eicosanoids is almost exclusively dependent on the amount of omega-3 PUFA consumed. On the other hand, frequent consumption of saturated fatty acids may cause a low ratio of n-3 PUFAs (anti-inflammatory) to n-6 PUFAs (pro-inflammatory) in the diet, which results in the lack of suppression of Th17 differentiation and the resulting stimulation of TPOAb and TgAb. Phytosterols and polyphenols are also present in vegetables and fruits. They have anti-inflammatory and immunomodulatory properties and may reduce the level of Il-6, and as Il-6 is the main stimulator of Th17 differentiation, reducing their level may be the reason for the protective effect in the pathogenesis of AITD [32].

People following a vegan diet are characterized by significantly lower levels of vitamin B12, vitamin D, as well as iodine and selenium, microelements necessary to maintain proper thyroid homeostasis [33]. Low selenium intake is associated with the risk of developing AITD due to the reduced immune function of the body. Unfortunately, evidence that selenium supplementation can lower TPOAb antibodies and prevent subclinical hypothyroidism remains insufficient [2]. However, research by Socha et. al showed that dietary habits affect the level of selenium in the serum of the examined patients with Hashimoto's disease only in 10%, and the deficiency of this element can initiate or cause the progression of AITD in people with a genetic predisposition to autoimmune diseases [34].

Conclusions

According to the World Health Organization, a properly balanced vegan diet is appropriate at every stage of life [35], however, when using it, one should remember the need to supplement with vitamin B12, whose supply resulting from a vegan diet is insufficient. A review of studies examining the effect of a plant-based diet on autoimmune thyroid diseases shows that there are several benefits from its use. Studies have confirmed positive correlations between reduced levels of inflammation markers, lower BMI, and an increased share of products with antioxidant and anti-inflammatory potential (unsaturated oils, fresh vegetables, and fruits, exclusion from the diet of processed meat and animal fats, lower supply of iodine) in people following a vegan diet. The impact of a vegan diet on the occurrence of hypothyroidism is less than in the case of hyperthyroidism. The research failed to provide a clear answer as to whether the positive effect of the diet is the exclusion of food of animal origin, processed food, or increased consumption of healthy fresh products. Undoubtedly, increasing

the share of plant products in the diet has a positive effect on reducing inflammatory processes in the body. It also has a positive effect on reducing body weight and the level of body fat. Also, it allows for a significant reduction of the parameters affecting specific symptoms of autoimmune thyroid diseases, such as the level of antithyroid antibodies or markers of inflammation. The nutrition of each person is a very individual matter. Still, it is essential to remember the proper balancing of meals that will ensure an adequate supply of microelements or vitamins, which is especially important in autoimmune thyroid diseases.

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