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Metabolic disorders and nutritional status in autoimmune thyroid diseases

Zaburzenia metaboliczne i stan odżywienia w autoimmunologicznych chorobach tarczycy

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Summary

In recent years, the authors of epidemiological studies have documented that autoimmune diseases are a major problem of modern society and are classified as diseases of civilization. Autoimmune thyroid diseases (ATDs) are caused by an abnormal immune response to autoantigens present in the thyroid gland – they often coexist with other autoimmune diseases. The most common dysfunctions of the thyroid gland are hypothyroidism, Graves-Basedow disease and Hashimoto's disease. Hashimoto's thyroiditis can be the main cause of primary hypothyroidism of the thyroid gland.

Anthropometric, biochemical and physicochemical parameters are used to assess the nutritional status during the diagnosis and treatment of thyroid diseases. Patients with hypothyroidism are often obese, whereas patients with hyperthyroidism are often afflicted with rapid weight loss. The consequence of obesity is a change of the thyroid hormones' activity; however, weight reduction leads to their normalization. The activity and metabolic rate of thyroid hormones are modifiable.

ATDs are associated with abnormalities of glucose metabolism and thus increased risk of developing diabetes mellitus type 1 and type 2. Celiac disease (CD) also increases the risk of developing other autoimmune diseases.

Malnutrition or the presence of numerous nutritional deficiencies in a patient's body can be the cause of thyroid disorders. Coexisting deficiencies of such elements as iodine, iron, selenium and zinc may impair the function of the thyroid gland. Other nutrient deficiencies usually observed in patients suffering from ATD are: protein deficiencies, vitamin deficiencies (A, C, B_6, B_5, B_1) and mineral deficiencies (phosphorus, magnesium, potassium, sodium, chromium). Proper diet helps to reduce the symptoms of the disease, maintains a healthy weight and prevents the occurrence of malnutrition. This article presents an overview of selected documented studies and scientific reports on the relationship of metabolic disorders and nutritional status with the occurrence of ATD.

Key words: autoimmune thyroid disease • metabolic disorders • nutritional deficiencies • nutritional status

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Introduction

The risk of autoimmune and autoinflammatory diseases is thought to depend on interactions between environmental factors and specific variants of specific genes, some of which may confer a risk that an individual disease will develop, and others a risk that several different diseases will develop [62]. The pathologies are mainly caused by errors in obtaining cell competence in the lymphoid organs. Numbers of lymphocyte cells pass through the marrow-blood barrier, which does not possess histocompatibility antigens. The main effect of such dysfunction is an attack on the immune system cells recognized by the body as foreign cells [41]. Autoimmune diseases also include thyroid dysfunctions such as lymphocytic thyroiditis (Hashimoto's thyroiditis/ Hashimoto's disease), hypothyroidism and hyperthyroidism (Graves' disease) [62].

Thyroid abnormalities affect a considerable part of the population. However, the prevalence and the pattern of thyroid disorders depend on ethnic and geographical factors. The number of patients in Poland who suffer from clinically overt or subclinical thyroid dysfunction may be as high as 1 000 0000. Children are afflicted with thyroid disorders 10 times less frequently than adults. The highest number of cases is recorded in the elderly population [16,50].

Hashimoto's thyroiditis is the most common cause of primary hypothyroidism. The majority of cases of autoimmune thyroid diseases (ATDs) are diagnosed in patients aged 45-65 years, but they can also affect children. Women are 10-20 times more likely to be affected by Hashimoto's disease than men. Thyroid inflammation is hereditary, and the familial predisposition to the disease may be present in 50% of the patient's family members [37].

In both sexes the prevalence of hypothyroidism increases with age, and it is about 5 times more common in women than in men. Hypothyroidism is divided into either overt or subclinical disease. The overt form of hypothyroidism can be diagnosed in 0.1-2% of the general population, whereas subclinical hypothyroidism (SH) may be present in 15% of the female population [23]. In Poland, hypothyroidism is observed in 1-6% of people up to 60 years of age [50].

Hyperthyroidism occurs in approximately 2-3% of the adult population. The most common form of the pathology is Graves' disease, which accounts for 75% of cases. Each year, an estimated 30 to 100 thousand people are diagnosed with this disease [16]. Hyperthyroidism occurs about ten times more frequently in women. The average age at diagnosis of hyperthyroidism is 48 years [50,81]. The untreated disease can cause cardiovascular disorders and increased bone resorption, leading to osteoporosis.

Hypothyroidism or underactivity of the thyroid gland may cause a variety of symptoms and may affect many body functions. Thyroid hormones are important for the regulation of body energy, for the use of other hormones and vitamins in the body, and for the growth and maturation of body tissues. Patients with thyroid dysfunctions have a greater risk of cardiovascular disease (CVD), osteoporosis, overweight, celiac disease (CD) and diabetes. Many nutritional factors play a role in optimizing thyroid function. Both nutrient deficiencies and their excess may trigger or exacerbate the symptoms. In order to determine nutritional status for optimal thyroid health it is advised for a patient to work with a physician and dietician.

Body composition analysis in thyroid diseases

The study of body composition (BC) is a necessary diagnostic step in the states of improper nutrition such as obesity, starvation or cachexia. It is also applied in case of hormonal imbalance [11]. Patients with hypothyroidism are often obese, whereas patients with hyperthyroidism are often afflicted with rapid weight loss [50]. The nutritional status can be assessed during the diagnosis and treatment of thyroid disease by anthropometric methods, such as body mass index (BMI), skinfold thickness measurements, waist circumference and also by physicochemical and biochemical analysis. In order to analyze BC, the following measurements can be used: quantitative digital radiography (QDR) and bioelectrical impedance analysis (BIA) [71].

Miyakawa et al. [52] used BIA to analyze BC in patients with Graves' disease and hypothyroidism. Total body fat (TBF) content in men with hyperthyroidism was significantly lower than in the control group matched for age and sex (11.4 ± 6.4% *vs* 19.9 ± 9.2%). In females with hypothyroidism the TBF content was significantly higher than in the control group. Other parameters of BC such as water content and fat-free mass (FFM) were significantly lower in patients with hypothyroidism. In order to determine the relationship between the volume of the thyroid gland, BC and body structure, a study in a Bulgarian school was conducted. Students aged 11-15 years were the main subject of the study [13]. The authors observed a relationship between thyroid volume and weight, and found no relationship between thyroid volume and TBF content in the body. However, in a study carried out in Italy that involved men with diagnosed hyperthyroidism, lower TBF content was obse-

rved in comparison to the control group. Inversely, the increase of TBF content was reported in womewn with hypothyroidism [67].

During the assessment of the effects of thyroxine on serum insulin-like growth factor the analysis of BC with the use of BIA showed no significant changes in the percentage of TBF and FFM and no significant changes in the body anthropometry in 28 patients with thyroid cancer [85]. Skinfold thickness increased from 21.8 ± 6.5 mm to 23.7 ± 6.4 mm ($p < 0.001$) in patients who discontinued the use of thyroxin and decreased after the resumption of therapy. Similar changes occurred during measurements of waist and hips; minor changes were observed in the arm muscle circumference measurements.

Direct analysis of resting energy expenditure (REE) is a sensitive parameter for determining thyroid hormone activity at the tissue level. REE deficit may be one of the factors leading to obesity. Tagliaferri et al. [79] showed that obese patients with impaired activity of thyroid-stimulating hormone (TSH) require direct assessment of REE. Significantly higher activity of TSH was observed in patients with SH in comparison to patients with TSH values at normal levels. Furthermore, there were no significant differences between the analyzed diet energy intake, the content of FFM and fat mass (FM), or between the thyroxin concentrations and lipid profile. The authors noted that SH has a significant influence on REE in obese patients only when TSH activity exceeds the reference value. Evaluation of the activity of TSH in obese patients with SH may be useful to exclude disorders of REE.

Obesity and metabolic syndrome in thyroid dysfunction

Obesity may be caused by the presence of a genetic factor or environmental influences, as well as by endocrine disorders in the body [72]. The thyroid gland is responsible for the 30% of daily energy expenditure at rest. Thyroid hormones regulate many metabolic pathways affecting the process of thermogenesis, lipolysis and BMR. Furthermore, hormones can modulate a number of cellular processes that are essential for REE [46]. Consequences of obesity include changes in thyroid hormone activity, whereas weight loss leads to their normalization. The increased concentration of thyroid hormones leads to increased REE and results in decrease of the availability of energy, which is accumulated in the form of fat cells. Chronic imbalance between REE, energy supply and its availability can lead to the loss or growth of fat cells [74].

Hypothyroidism is usually associated with weight gain and reduction of thermogenesis and metabolism. Gastrointestinal symptoms of hypothyroidism also include chronic constipation and disturbances in bowel movements [61]. SH can also be related to obesity, altered lipid metabolism and ischemic heart disease (IHD) [65]. However, hyperthyroidism manifests as weight loss despite both increased appetite and increased metabolic rate. In more severe cases a patient may suffer from diarrhea and swelling of legs [64]. Hashimoto's disease, known also as chronic lymphocytic inflammation of the thyroid gland, can occur in patients with rheumatoid arthritis or diabetes, in patients who exhibit reduced resistance to stress or suffer from mental illness. Symptoms of the disease include problems with maintaining a proper weight, constipation, dry skin, constant sense of fatigue and depression [6,63,80]. Pietrych and Philip [61] evaluated the effect of a weight reduction diet on body weight and the occurrence of constipation in patients with Hashimoto's thyroiditis. The total diet energy value was reduced by about 500 kcal. The diet fulfilled the recommendations for all nutrients. Products that are a source of sugar and fat were eliminated. Body weight was measured once a week over a period of 11 weeks. The authors concluded that increasing intake of fiber to 30 g/day in the diet of women with Hashimoto's disease resulted in an increased rate of weight loss and reduction of constipation.

Low levels of thyroid hormones lead to a higher blood lipid profile, increased blood pressure, and elevated levels of the amino acid homocysteine and the inflammatory marker C-reactive protein (CRP). Overt and subclinical hypothyroidism have an adverse effect on the serum lipid profile that may predispose to the development of atherosclerotic disease [60]. The majority of obese patients display increased activity of TSH in comparison to patients of normal weight. Ruhla et al. [66] studied the relationship between the activity of TSH and the prevalence of metabolic syndrome (MS) in 1333 patients whose TSH activity was within 0.3-4.5 mU/L. It was found that persons whose TSH activity was maintained at the upper limit of normal were more obese and had higher concentrations of triglycerides in serum. A favorable serum lipid profile was observed in patients who had TSH activity below 2.5 mU/l. Dunats and Wartofsky [27] observed changed metabolism of cholesterol and lipoprotein serum levels in SH when the activity of TSH was above 10 mU/l. Observed abnormalities included increased total cholesterol, lipoproteins and LDL (low-density lipoprotein) cholesterol. Improper values of these indicators may raise the risk of coronary heart disease (CHD) in patients with SH.

BMI may be a marker of TSH activity in obese patients, given the fact that this hormone seems to be positively linked to presence of obesity. During overfeeding, the activity of thyroid hormones and their rate of changes are modified. Increased energy intake with the diet from 2000 to 4000 kcal/day may cause increased activity of the triiodothyronine hormone (T3) by about 50% without any significant change in the activity of thyroxin (T4) regardless of the type of macronutrient consumed, such as proteins, fats or carbohydrates [21,22]. The activity of the thyroid gland and the synthesis of TSH can also be partially driven by adipocytes which produce leptin. Leptin is a mediator of long-term regulation of energy

balance, suppressing food intake and thereby inducing weight loss. In obese patients with hypothyroidism, leptin concentration may be even 30% higher than in obese patients with euthyroidism. Excessive secretion of leptin leads to leptin resistance and also to a greater feeling of fullness [64,79].

The study conducted by Iacobellis et al. [35] indicated the presence of a link between the activity of thyroid hormones and adipose tissue metabolism. Evaluated thyroid function and its potential impact on BMI, leptin concentration, adiponectin and insulin sensitivity in obese women (BMI=40.1±7 kg/m^2) showed proper function of the thyroid gland – euthyroidism. In examined women with BMI > 40 kg/m^2, higher levels of TSH were observed. The authors demonstrated that, in spite of euthyroidism, the activity of TSH and BMI were significantly related. The increased activity of the TSH hormone may be the cause of impaired body energy imbalance in obese patients.

The decrease by 1 U/l of TSH concentration in serum, within the normal range limits, is accompanied by a reduction of energy expenditure of 75 ± 150 kcal/day [2]. A moderate increase of TSH activity is not usually associated with changes in thyroxin activity in obesity. The diagnosis of significantly increased TSH activity and decreased T4 activity may suggest the presence of hypothyroidism in obesity. Furthermore, in obesity T3 activity rises above recommended levels. Moderate growth of free triiodothyronine (fT3) and T3 leads to increased energy expenditure in the body [3,64].

It is essential for physicians and nutrition specialists to understand the effects of changes of activity of thyroid hormones in obesity. Using thyroid hormones in the treatment of obesity could be dangerous because of the possibility of numerous complications such as tachycardia, arrhythmia, fatigue, irritability, loss of muscle and bone mass [9,65]. In the treatment of hypothyroidism and Hashimoto's disease, a diet therapy should be applied alongside drug treatment.

Diabetes mellitus type 1 and 2 in autoimmune thyroid disease

ATDs are associated with improper glucose metabolism in the body and therefore could lead to increased risk of developing diabetes mellitus type 1 and type 2 [44]. The risk factors of thyroid autoimmunity include gender, age, duration of diabetes, disorders of thyroid hormone activity and abnormal levels of antibodies in serum [43]. More and more frequently, the coexistence of ATDs and diabetes mellitus is observed among children and young people. 3-8% of children with type 1 diabetes suffer from overt hypothyroidism, whereas SH occurs in 5-10% of patients. Thyroid autoimmunity is especially common in girls with diabetes and may be associated with increased activity of TSH – this might indicate the presence of SH [44].

Gierach et al. [30] evaluated the incidence of hypoglycemia in patients with Hashimoto's thyroiditis. In 27.8% of patients with Hashimoto's thyroiditis the presence of type 1 diabetes was reported. Also in 16.6% of the patients impaired fasting glucose or impaired glucose tolerance were noted. The authors concluded that abnormal glucose metabolism may occur in up to half of patients with Hashimoto's disease.

Hyperthyroidism and high plasma concentrations of thyroxine and triiodothyronine hormones are considered as risk factors for developing diabetes. Up to half of the patients suffer from impaired glucose tolerance and in 2-3% of them overt diabetes mellitus was diagnosed. The main causes of carbohydrate metabolism disturbance in hyperthyroidism are as follows: increased glucose absorption in the gastrointestinal tract, enhanced gluconeogenesis and glycogenolysis processes, increased lipolysis and ketogenesis. This leads to pancreatic beta-cell dysfunction. In patients with hyperthyroidism and diabetes it is necessary to apply the appropriate insulin therapy. Effective treatment and normalization of thyroid gland function may be associated with carbohydrate metabolism [33].

Endocrinopathies can coexist with type 1 diabetes in as many as 10-30% of patients. It is recommended to perform screening tests for the diagnosis of thyroid autoimmunity in diabetics in order to apply the appropriate medical treatment and nutrition therapy [45].

Malabsorption disorders in thyroid dysfunctions

In celiac disease (CD) there occurs damage or complete disappearance of the intestinal villi, which results in permanent gluten intolerance. Adverse effects of gluten lead to the onset of symptoms such as impaired digestion and improper absorption of nutrients. Long-term intensity of the disease results in malnutrition, symptoms of which can include: deficit of weight, anemia and reduced levels of microelements and proteins in blood serum.

CD can be characterized by several autoimmune-type features and can provide a model for studying autoimmune processes [49,55]. CD also increases the risk of the onset of symptoms of other autoimmune diseases and can manifest itself in both children and adults [4]. Numerous reports indicate the coexistence of CD and ATD in pediatric patients [48,83]. Even more alarming is the research conducted by Kaczorowska et al. [42] suggesting that CD is 3.4 to 13 times more common among children with ATD. Larizza et al. [48] found that CD prevalence in children with ATD, aged 1.8 to 17.3, was 7.7% higher. Furthermore, coexistence of iron deficiency with diarrhea in patients with CD was reported.

Undiagnosed CD may play an important role in development of other autoimmune diseases. Screening tests should be performed in all patients with ATD. A multi-

-center study carried out by Ansaldi et al. [4] aimed to determine the prevalence of ATD in pediatric patients with CD. ATD was observed in 90 of 343 patients with CD (26.2%). High prevalence of ATD in patients with CD suggests the need for assessment of the thyroid gland state and the introduction of appropriate dietetic treatment in the diagnosis of CD.

Studies carried out on a population of adults with CD indicate that they often suffer from diabetes mellitus and from thyroid dysfunction. Very often the concentration of antibodies in the serum is dependent on the concentration of gliadin derived from gluten. In conclusion, as a result of the combination therapy containing a gluten-free diet and thyroxin treatment, the symptoms of ATD may be alleviated or completely removed [18,69]. To avoid complications associated with malnutrition, nutritionists should adapt the diet to the individual patients.

Malnutrition and nutritional deficiencies

Malnutrition or nutritional deficiencies in the body can be the cause of thyroid disorders. Some mineral components are necessary for synthesis and metabolism of thyroid hormones. Coexisting deficiencies of such minerals as iodine, iron, selenium and zinc may impair the thyroid gland function. Other nutrient deficiencies observed in patients with ATD are: protein deficiency, vitamin deficiencies (A, C, B_6, B_5, B_1) and mineral deficiencies (phosphorus, magnesium, potassium, sodium, chromium) [34,75].

Iron

Iron deficiency is a common nutrient deficiency which causes anemia. It is diagnosed in up to 60% of patients with hypothyroidism, and it is not related to severity or duration of thyroid insufficiency. The main cause of iron deficiency in ATD is usually the existence of CD with coexisting malabsorption disturbances in the gastrointestinal tract [82]. Iron deficiency impairs thyroid hormone synthesis by reducing the activity of heme [89]. One of the key enzymes, called thyroid iodine peroxidase, which contains iron in its molecule, is necessary for thyroid function. In this case, iron deficiency leads to a reduction in the synthesis of thyroid hormones in plasma, increases TSH secretion and enlarges the thyroid. Eftekharii et al. [28] conducted a study of 103 girls with iron deficiencies in order to determine whether iron supplementation would improve the functioning of the thyroid gland. The authors concluded that iron supplements have a beneficial effect on the indicators defining thyroid gland functioning.

Beard et al. [7] conducted dietary iron supplementation in women with symptoms of anemia. Supplementation resulted in partial relief of symptoms of anemia and normalization of thyroid hormone activity. These results demonstrated that synthesis and metabolism of thyroid hormones in the body may be responsible for iron deficiency anemia.

Impaired thyroid function during pregnancy can cause neurodevelopmental disorders of offspring. Deficiencies of iron, which can negatively affect the metabolism of the thyroid gland, are commonly observed in pregnant women. The aim of a study conducted by Zimmermann et al. [87] was to evaluate the effect of iron deficiency in pregnant women on the activity of TSH and T4 hormones. The authors concluded that iron deficiencies in the body of pregnant women may cause fetal development retardation and are correlated with the presence of iodine deficiency.

Iodine

In order to attain normal levels of thyroid hormone synthesis, an adequate supply of iodine is essential. It is recommended to increase the supply of iodine in hypothyroidism due to the fact that it is necessary for the synthesis of T3 and T4. The human body contains approximately 15 to 20 mg of iodine, from which about 80% is accumulated in the thyroid. An adult human organism requires about 150 µg of iodine per day. The need for this microelement is increased in pregnant or breast-feeding women and should be provided in about 220-290 mg/day with the daily diet [40]. Both iodine deficiency and excess may lead to the development of disorders of thyroid gland functioning. The main sources of iodine are milk and dairy products, eggs and marine fish. A natural food product that is a good source of iodine is seaweed – it contains approximately 38571.4 µg of iodine in 60 g of the product [47].

The World Health Organization (WHO) acknowledged that iodine deficiency is one of the factors that directly affects the health of the population. The main symptom of iodine deficiency is the occurrence of goiter and consequently the increased prevalence of thyroid gland dysfunction. Lack of this microelement causes a number of other disorders, among which the most important are: irreversible brain damage in the fetus and infants, delayed psychomotor development in pediatric patients, decreased reproductive function, and the impact on overall intellectual development. Major risk groups include pregnant women, infants, children and adolescents during puberty. In Poland, after the obligatory model of iodine prophylaxis, the supply of iodine in the diet has increased, and health effects associated with iodine deficiency have decreased.

Appropriate nutrition during pregnancy determines both women's health and proper development of the fetus. Iodine deficiency during pregnancy and lactation occurs quite often, because only 50% of women consume the recommended daily intake of iodine with the diet [76]. Sendrakowska et al. [70] assessed the activity of thyroid hormone in urine and thyroid volume of pregnant women. Iodine concentration in urine was several

times lower in comparison to the standards. 80% of the respondents were diagnosed with increased volume of the thyroid gland.

For pregnant or breast-feeding women, health experts recommend iodine supplementation in the range of 100 to 150 mg/day in the form of pharmaceutical preparations [31]. The Polish Council for the Control of Iodine Deficiency Disorders recommends a change in eating habits by introducing food that is a rich source of iodine in the daily diet. The program of iodine prophylaxis in Poland includes [77]:

- iodination of salt in the amount of 30 ± 10 mg KJ/1 kg,
- iodination of baby food at 10 mg KJ/100 ml,
- dietary supplementation with iodine in the amount of 100-150 mg/day,
- the increase of daily intake of food products that are a good source of iodine,
- iodine fortification of cow's milk (100-150 mg/l).

Waszkowiak et al. [84] estimated the consumption of milk products to be a potential source of iodine among pregnant women. Present in the diets of pregnant women dairy products were good sources of iodine and covered approximately 15% of recommended dietary allowance on iodine. Significant dietary sources of this microelement were ripened cheese, cottage cheese, milk and yogurt. The authors suggested that dairy products may be an important source of iodine in the diet.

The aim of the study of Smyth et al. [73] was to evaluate the differences that occur during pregnancy in the thyroid volume and in the concentration of iodine excreted in the urine. The results showed a significant increase in the volume of the thyroid, even up to 47%, compared to the values observed in non-pregnant women, and increased urinary excretion of iodine. The authors suggested that thyroid dysfunction (resulting from increased excretion of iodine in urine) may occur in women who consumed moderate amounts of iodine during pregnancy. The parts of the population threatened by the occurrence of symptoms of iodine deficiency are children and adolescents. During development and growth the demand for this component is much higher, because of the intense synthesis of thyroid hormones. Some authors claim that even a slight iodine deficiency in children and adolescents can lead to lower IQ by 15-20% [47,73].

Bioavailability of iodine increases if it is consumed in the form of iodide or if it is connected with proteins. Furthermore, limiting factors of iodine absorption are as follows: sulfur-containing glucosides found in cruciferous plants; hemagglutinin in legumes; polyphenols present in fruits, peanuts or red cabbage; cyanogenic glycosides present in almonds; and nitrates, fluorides, calcium, magnesium, iron, cobalt and manganese that can be found in water. The goitrogenic activity is caused by blocking the iodine binding of tyrosine and by forming thyroxine out of tyrosine.

Selenium

The coexistence of selenium deficiency with thyroid hormone disturbances may occur during long-term parenteral nutrition, phenylketonuria or cystic fibrosis, or may be the result of poor nutrition of children, adults and the elderly [7]. A properly functioning thyroid gland has the ability to maintain high levels of selenium in serum even in conditions of inadequate dietary supply of this component [78]. Considerable selenium deficiencies disturb the metabolism of thyroid hormones by inhibiting the synthesis and activity of deiodinase iodothyronine, which is responsible for the conversion of thyroxin into more active metabolically forms [20]. In a study conducted on rats, both selenium and iodine deficiencies caused a significant increase in weight of the thyroid gland and increased the thyrotropin activity in serum more than the iodine deficiency alone. The coexistence of iodine and selenium deficiency may be a major determinant of thyroid disorders [5]. A diet rich in high selenium products supports the synthesis of thyroid hormones and their metabolism and protects the thyroid gland against excessive exposure to iodine [8].

Zinc

Zinc is an essential element for the proper synthesis and metabolism of thyroid hormones. Occurrence of zinc deficiency can reduce thyroid activity and resting metabolic rate (RMR). The aim of a study conducted by Maxwell and Volpe [51] was to evaluate the effect of zinc supplementation on the zinc and ferritin concentration in plasma and on T3 and T4 activity in serum. The authors confirmed the beneficial effect of zinc supplementation on the activity of thyroid hormones in serum, especially on RMR and T3 hormone activity.

Morley et al. [53] fed rats with food poor in zinc. They observed the effects of zinc deficiency on the hypothalamic-pituitary-thyroid axis. Zinc deficiency reduced the activity of T3 hormone in blood of animals more than the reduction in the energy supply. It was concluded that zinc deficiency may reduce the synthesis of T3 hormone.

Furthermore, zinc deficiency is frequently observed in patients with Down syndrome who have problems with proper functioning of the thyroid gland. Bucci et al. [15] assessed the prevalence of zinc deficiency in SH. After 6 months of zinc supplementation the functioning of the thyroid gland had improved. The authors suggested introducing to ATD therapy zinc supplementation as an effective method of therapy in children with zinc deficiency.

Protein-calorie malnutrition

Protein-calorie malnutrition (PCM) is frequently observed in patients with ATD. The occurrence of PCM contributes significantly to intensity of iodine deficiency and disturbances in thyroid weight. Furthermore, the

increased incidence of goiter leads to the occurrence of malnutrition. The impact of PCM on the thyroid weight and thyroid hormone activities in children was confirmed [14]. A significant correlation between the weight of the thyroid gland and thyroid weight to body surface area ratio was found. Much lower activity of thyroid hormones, in comparison to the recommended value, was found in the group of children with marasmus and kwashiorkor. In fact, higher activity of TSH was noted in the group of tested children in comparison to the control group. In addition, the average thyroid weight was higher in the study group than in the control group.

A prolonged state of protein-energy deficiency can lead to weakened activity of TSH and T3 hormones. During the occurrence of PCM in Senegalese children, a reduction in activity of T3 hormone in serum (25.3%), in comparison to the recommended value, was observed. After a suitable nutritional therapy was introduced, T3 hormone activity returned to normal values and proper values of biochemical indicators were also recorded [57].

Furthermore, a significant association was observed between TSH activity and nutritional status assessed by BMI. Patients with PCM may have higher activity of TSH in comparison to a well-nourished person. Increased TSH activity in patients with PCM is probably a response to the stimulation of the pituitary gland to secrete the peptide hormone TSH by thyrotropin-releasing hormone (TRH) despite normal activity of T3 and T4. Such changes result from adaptation to the energy and protein deficit in the body. The corresponding energy values of the diet and protein intake help to restore the normal function of the thyroid gland [36].

Vitamins

A variety of factors influence thyroid function disturbances, one of them being vitamin deficiencies. Numerous deficiencies of vitamins such as antioxidant vitamins, vitamin B complex and vitamin D are observed in patients with ATD [75].

The authors of several studies have pointed out the important role of increased oxidative stress in the pathogenesis of ATD [1,24,59]. Deficiencies of antioxidant vitamins cause the development of oxidative stress and disrupt homeostasis, which can lead to structural and functional cell damage [68]. Reactive oxygen species (ROS), known as free radicals, can cause damage to thyroid gland function. Intensified oxidative metabolism leads to increased mitochondrial functions of free radical production, which in turn leads to lipid peroxidation of cell membranes. Ademoglu et al. [1] discovered increased concentrations of lipid peroxides in plasma in patients with hyperthyroidism. Simultaneously, an association between low vitamin E and ascorbic acid concentration was found.

Occurrence of vitamin A deficiencies in ATD may be associated with a reduced uptake of iodine by the thyroid gland and the restricted synthesis and secretion of thyroid hormones. A diet low in vitamin A affects the functioning of the pituitary-thyroid axis. It was proven that a diet low in vitamin A and iodine can be the cause of higher incidence of hypothyroidism compared with a diet low in iodine only [10]. The authors of other studies have reported increased secretion of TSH and increased size of the thyroid gland in children with severe deficiency of iodine and vitamin A [88]. Vitamin A supplementation can reduce the impact on the activity of TSH and thus reduce the risk of goiter appearance and its consequences. A deficiency of B-group vitamins, especially B_{12}, can lead to neurological disorders, and also to psychiatric and metabolic abnormalities in the functioning of the hematopoietic system and gastrointestinal tract. An increased incidence of vitamin B deficiency was noted in patients with ATD [54,58].

ATDs are characterized by decreased parathyroid hormone activity that is responsible for the increased production of the active form of vitamin D. Studies observed reduced activity of parathyroid hormone in the serum of patients with hyperthyroidism. In contrast, increased activity of parathyroid hormone was noted in the serum of patients with hypothyroidism in comparison to healthy subjects. The authors suggested that abnormal levels of vitamin D in serum may be the cause of dysfunction in the intestinal absorption of calcium in patients with ATD [12]. Vitamin D concentration in serum should be constantly monitored. It is recommended to dose vitamin D and/or calcium supplements to patients with ATD who have a deficiency of vitamin D.

Diet therapy

In patients with ATD, apart from the pharmacological treatment, the therapy should be supported by changing eating habits. The appropriate diet helps in alleviating the symptoms of the disease, maintaining a healthy weight and preventing malnutrition. In the state of thyroid hormone deficiency the rate of metabolism in the body slows down; most of the energy supplied by food is stored in the adipose tissue, which contributes to the occurrence of overweight and obesity – that is why it is recommended to introduce the therapy of a balanced weight loss diet. If hypothyroidism occurs together with other diseases, it is recommended to introduce a diet that would be appropriate for the disease entity. Before the introduction of the diet therapy it is essential to normalize the thyroid hormone concentrations, because their deficiency could retard the metabolism. Reducing energy intake should not be included in the treatment of patients with hypothyroidism who have normal body weight.

Treatment of hypothyroidism is based mainly on hormone therapy. Synthetic thyroid hormone analogs should be taken in the morning on an empty stomach, about 30 minutes before eating a meal, and washed down with a glass of water. It has been observed that iron can inhibit

the absorption of levothyroxine. Other factors impeding levothyroxine absorption from the gastrointestinal tract are a high-fiber diet, a vegetarian diet, aluminum preparations and CD.

Goitrogenic substances have a negative impact on thyroid gland functions. Goitrogens are anti-nutritional substances, which are found in various kinds of food products. These compounds interfere with iodine metabolism and inhibit thyroid hormone synthesis. Especially sensitive to them are patients who suffer from iodine deficiency. Both iodine uptake and its storage by the thyroid gland can be disturbed by thiocyanates, isothiocyanates, nitrites, thio-oxazolidone compounds and cyanogenic compounds found mainly in the crucifer plants. Goitergenic activity is exhibited by the cyanogenic glycosides included in potatoes and corn, and by n-propyl disulfides present in onions and garlic, which inhibit iodine uptake and interfere with the metabolism of thyroglobulin.

Products that present goitrogenic properties reduce their activity by up to 30% during cooking. Goitrogenic substances should not be consumed with high-iodine products because it reduces the bioavailability of iodine. Recommendations indicate that patients with hypothyroidism should reduce the intake of foods that are a rich source of goitrogens. However, there is no need to completely eliminate these products from the daily diet, because they contain other essential microelements and vitamins.

Soybeans have a high nutritional value because of the presence of easily digestible protein, the presence of polyunsaturated fatty acids (PUFA) and oligo- and polysaccharides. Furthermore, soy is a rich source of saponins and isoflavones. Researchers consider that soy may also have destructive properties and adversely affect the excretory system in the body [25,26]. In a study conducted in a group of children who showed signs of congenital hypothyroidism (CH) and consumed soy blend, thyroid disorders and impaired absorption of levothyroxine from the gastrointestinal tract were observed [17,19,39]. Fort et al. [29] reported a relationship between soy consumption during infancy and ATD development. The frequency of feeding by milk supplements containing soy was significantly higher in children with ATDs (31%) than in their siblings (12%) and in the control group (13%). A negative impact has also been observed in healthy adults [38]. The first group of respondents consumed 30 g of soya beans for 30 days whereas the second group consumed 30 g of soya beans for 3 months. There was no negative impact of soybean consumption on thyroid function in the first group of patients. However, in the second group, goiter development and symptoms indicating the possible development of hypothyroidism were observed. All of the respondents suffered from constipation, general weakness, fatigue and somnolence. The observed symptoms subsided after eliminating soy from the diet.

Nutritional therapy in Hashimoto's disease should be based on the principles of diet therapy in hypothyroidism. The dietary energy value in overweight or obese patients should not be drastically reduced, as this may cause a decrease of metabolism. Nutrient supply of anti-inflammatory activity should also be taken into consideration because such supplements as PUFA omega-3 and antioxidant vitamins could alleviate the symptoms of the disease [56,75].

A balanced diet in hyperthyroidism is a factor supporting pharmacological treatment. One of the primary goals of such therapy is to maintain a proper weight. The excessive metabolic processes are responsible for excessive loss of body weight. Depending on the course of the disease, the treatment is different and the diet energy intake could increase even by several tens of percent. Furthermore, due to severe protein catabolism it is recommended to increase the protein intake of the diet [32]. Hyperthyroidism is also associated with loss of fat tissue. This is a result of increased lipolysis which leads to the increased concentration of free fatty acids and glycerol in the blood serum; reduced cholesterol concentration can also be observed. Too low fat intake causes dysfunctions of the immune system and disturbance of fat-soluble vitamin absorption [72]. It is also important to provide an appropriate amount of vitamins which influence the course of the disease and nutritional status. Antioxidant vitamins reduce oxidative stress, which negatively affects thyroid gland functioning. In patients with Graves' disease, who are treated pharmacologically, antioxidant supplementation may have positive effects on reduction of the clinical symptoms of the disease [75].

Conclusion

The thyroid is one of the endocrine glands which affects functions of other organs and is responsible for homeostasis in the body. For this reason, thyroid dysfunction is a serious medical problem requiring careful diagnosis and comprehensive treatment. The excessive secretion of thyroid hormones leads to hyperthyroidism, and conversely, insufficient thyroid hormone activity results in hypothyroidism. It has been proven that the main cause of hyperthyroidism is Graves' disease, whereas Hashimoto's disease is responsible for hypothyroidism [50,62].

A proper diet not only supports the pharmacological treatment but also improves the nutritional status of the body. It also prevents the development of other diseases, such as obesity, diabetes, CD and osteoporosis [46,65,66,80]. Typical for ATD is the presence of antibodies resulting from a disturbed immune system [2]. Nutrition therapy is based on the delivery of the appropriate amount of anti-inflammatory ingredients, the proper intake of vitamins D and B, and minerals such as selenium and zinc.

Proper nutrition in hypothyroidism is primarily based on the treatment of overweight and obesity. It is recommended to increase the protein intake, the intake of such minerals as selenium, zinc, copper and iron, as well as vitamins A, C and D. Moreover, food (cruciferous

vegetables and legumes, peanuts, corn, sweet potatoes) may have adverse effects on thyroid gland functioning due to the goitrogenic substances [56].

Excessive activity of the thyroid hormones can be diabetogenic; therefore, preventive treatment of diabetes development in patients with hyperthyroidism should be applied [44]. In addition, autoimmune diseases are often associated in particular with the occurrence of other diseases resulting from autoimmunity and including diabetes and CD. In CD, gluten proteins provoke the immune response. The introduction of a gluten-free diet reduces degenerative changes in the small intestine, and improves absorption of nutrients and drugs [18].

The problem of nutritional therapy in ATD and comorbidities requires precise research to be conducted. Difficulties in finding suitable medical reports about nutrition in ATD are reported by physicians and dietitians.

Table 1. Recommended Dietary Allowance (RDA) of iodine in women [40,77,86]

Country / organization	Pregnant women [µg/day]	Women aged 19-75 [µg/day]
Poland	220	150
WHO/UNICEF/ICCIDD	250	150
United States	220	91-96

*WHO – World Health Organization; UNICEF – United Nations International Children's Emergency Fund; ICCIDD – International Council for the Control of Iodine Deficiency Disorders

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