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THE ROLE OF INGREDIENTS CONTAINED IN FISH AND FISH PRODUCTS IN HASHIMOTO DISEASE®

Rola składników zawartych w rybach i produktach rybnych w chorobie Hashimoto®

Research financed by Polish Ministry of Science and Higher Education within founds of Institute of Human Nutrition Sciences, Warsaw University of Life Sciences (WULS), for scientific research

Praca finansowana przez Ministerstwo Nauki i Szkolnictwa Wyższego w ramach utrzymania potencjału badawczego Instytutu Nauk o Żywieniu Człowieka, SGGW w Warszawie

Hashimoto disease is one of the most commonly recognized autoimmune and endocrine diseases. The development and the course of the ailment depends on a variety of factors, nutritional among other things. Fish and fish-based products contain nutrients regulating the homeostasis of thyroid hormones and the immune system functions. The paper provides up-to-date knowledge on the mechanisms of effects exerted by nutrients contained in fish on the thyroid functions and thyroid-released hormones, and on the course of inflammation in this gland. Familiarity with these issues is necessary for a proper planning of nutrition in Hashimoto-affected patients.

Key words: fish, thyroid, autoimmunity.

Choroba Hashimoto jest jedną z najczęściej rozpoznawanych chorób autoimmunologicznych i endokrynnych. Rozwój i przebieg schorzenia zależy od wielu czynników, w tym żywieniowych. Ryby i ich przetwory są produktami zawierającymi składniki regulujące homeostazę hormonów tarczycy i funkcjonowanie układu odpornościowego. W artykule scharakteryzowano aktualną wiedzę na temat mechanizmów wpływu składników zawartych w rybach na działanie tarczycy i wydzielanych przez nią hormonów oraz przebieg procesu zapalnego w gruczole. Ich znajomość jest niezbędna do prawidłowego planowania żywienia dla osób z chorobą Hashimoto.

Słowa kluczowe: ryby, tarczyca, autoimmunizacja.

INTRODUCTION

An autoimmune (lymphocytic) thyroid inflammation of Hashimoto type, commonly known as Hashimoto disease or Hashimoto thyroiditis, is a chronic disease derived from the immune system's abnormal stimulation and response. The disease most commonly affects people, predominantly women, aged between 45 and 65 years, however populations all around the world are concerned with the problem [12,23]. The effect of the disease is a progressive destruction of thyroid cells, leading to hypothyroidism that interferes with metabolic processes in almost every cell of the body. Both genetic and environmental factors are considered the triggers or enhancers of the disease. The latter cover nutritional agents such as an excessive iodine supply or an insufficient intake of selenium and vitamin D [15,32]. On the other hand, it is obvious that nutrients influence on the course of inflammation, modulate functions of the thyroid and its hormones, and affect the assimilation of drugs used in hypothyroid patients' pharmacotherapy. Given that, the food components play an essential, however often underestimated, role in the management of Hashimoto disease [30,63]. In this respect, a special role should be attributed to fish, which provide a proven health-improving effects by containing nutrients, bioactive compounds and other components regulating thyroid hormone metabolism and the immune system functions. Therefore, it seems justifiable to characterise their role in the development and treatment assistance of Hashimoto disease.

HASHIMOTO DISEASE CHARACTERISTICS

A mode of development of Hashimoto thyroiditis is not fully clear. Nevertheless, it is known as complex and multifactor-dependent. In the disease, proportions among various cell types of the autoimmune system change over time.

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Their activity is different than in healthy individuals as well. The alterations are manifested in the enhancement of the pro-inflammatory cell activity, more specifically type I T helper lymphocytes (Th1) and cytotoxic lymphocytes (Tc), and in the reduction of the anti-inflammatory cell activity – type II T helper lymphocytes (Th2) and regulatory lymphocytes (Treg). Moreover, the accumulation of B lymphocytes and macrophages in the thyroid parenchyma takes place [45].

The pathogenic process starts from an excessive inflow and thyroid-specific accumulation of the circulatory immunocompetent cells that produce and release greater quantities of proinflammatory compounds, i.e. mainly proinflammatory cytokines, e.g. interferon-gamma (INF-γ), tumour necrosis factor α (TNF-α) and interleukin 12 (IL-12), and anti-thyroid protein antibodies. Thyroid peroxidase (TPO) and thyroglobulin (TG), i.e. thyroid proteins providing a normal synthesis and accumulation of thyroid hormones, are antigens taking part in the autoagression. The effect of anti-TPO and anti-TG autoantibodies on the thyroid gland leads to the destruction of its follicular cells (thyrocytes), which synthesize and release smaller and smaller amounts of hormones into the blood. Besides, an enhancement of oxidative stress, an excessive stimulation of processes based on the programmable cell death (apoptosis) and thyroid fibrosis appear in the thyroid gland. This accelerates the destruction of thyrocytes and leads to hypothyroidism. In Hashimoto disease thyrocytes are exposed to an intensive activation of apoptosis by synergistic impact of proinflammatory cytokines on numerous genes involved in the signalling pathway of the process. On the other hand, those regulatory mechanisms are weakened that would cope with the blockage of an initiated cascade leading to autodestruction, e.g. by the triggering of apoptosis within the intrathyroid lymphocytes, which is inhibited in the Hashimoto thyroiditis [2, 12, 17, 32, 34, 35].

Among factors inducing the autoimmune process in the thyroid the first place is mentioned to be taken by genetic factors associated with histocompatibility antigens, like HLA-DR3 and HLA-DR5, and with the polymorphism of a gene encoding for cytotoxic T cell antigen 4 (CTLA-4) protein and of other genes connected to cytokines and thyroid proteins [12, 34]. Both environmental and internal (e.g. hormones) agents can trigger or enhance the disease development in individuals with genetic predispositions. The former cover the following: tobacco smoking, infections, stress, alcohol, some drugs, chemical contaminations, alimentary allergens, an excessive iodine supply and an insufficient intake of selenium and vitamin D [10, 35]. Furthermore, Hashimoto disease frequently co-exist with other autoimmune diseases, i.e. type I diabetes, celiac disease, unspecific inflammatory conditions of the intestines, pernicious anaemia, rheumatoid arthritis and multiple sclerosis, among other things, with hypofunction of other glands (the adrenal glands, gonads and parathyroid glands) and with chromosomal diseases including Down and Turner syndromes, and it may bring to light in pregnant women [40, 57].

A compromised thyroid function stems mainly from intrinsic morphological changes due to an inflammatory process and a reduction in TPO activity, a key enzyme in the regulation of all stages of thyroid hormone biosynthesis, i.e. the oxidation of iodine ions, the iodination of TG thyrosil residues with the formation of iodothyrosines and their fusion to triiodothyronine (T3) and thyroxine (T4). A consequence of a diminished T3 and T4 synthesis is manifested in a drop in blood hormone levels. Based on a phenomenon of feedback, this, in turn, stimulates the upper levels of the hypothalamic-pituitary-thyroid (HPT) axis, thyroid axis for short, for the synthesis and release of thyreoliberin (TRH) and thyreotropin (TSH). However, this does not reflect in the production of sufficient amounts of thyroid hormones (TH). As a consequence, a gradual TSH blood level increase can be observed, with a concomitant reduced level of free thyroid hormone forms (fT4 and/or fT3) after some time [12, 27, 30, 58]. The levels of TSH, fT4 and fT3 correspond to the thyroid functions, however they cannot serve making Hashimoto disease diagnosis but its consequences manifested in primary hypothyroidism – occult (subclinical) or clinically overt. In fact, the disease is diagnosed based on an elevated anti-TPO and/or anti-TG antibody titre and an abnormal image of the thyroid gland in ultrasound (USG) examination [12, 57, 58].

Because of the fact that thyroid hormones are responsible for baseline metabolization and the regulation of metabolic processes in almost every cell of the human body [18], in the event of their deficiency the rate of metabolization and tissue susceptibility to insulin (insulin resistance) drop, and carbohydrate and lipid changes become disturbed. As a result, type 2 diabetes and cardiovascular diseases may develop [23, 40, 59].

Hashimoto thyroiditis develops slowly and, initially, may not be symptomatic. Laboratory test and imaging examination results may also be normal. Most frequently, complaints in patients only appear after considerable thyroid destruction and its hypoactivity have taken place. The list of complaints usually encompasses the following: weakening, chronic fatigue, sleeping problems, emotional changes, excessive sweating, hand tremors, oedemas of the face, palms and feet, the feeling of cold with body mass gain, constipations and hypermenorhoea in women. Apart from that, skin dryness and roughness, nail fragility and hair loss are reported [12, 35, 57]. In children the first clinical sign of Hashimoto-triggered hypothyroidism is a retarded rate of growth and learning difficulties [4].

Hashimoto disease is incurable and its course can only be retarded. Nevertheless, Hashimoto-induced hypothyroidism is subject to pharmacotherapy. It is based on the administration of a levorotatory thyroxine synthetic analogue (L-thyroxine), usually fasting 30-60 minutes prior to breakfast in the morning. In the case of one of Hashimoto disease varieties, a so-called IgG4-dependent variant, a short-lasting glucocorticosteroid therapy is instituted as well [12, 32, 45].

AIM AND GENERAL DIETARY MANAGEMENT RULES IN HASHIMOTO DISEASE

The aim of dietary management in Hashimoto disease is the retardation of processes leading to thyroid destruction, the elongation of normal thyroid function time-period, and the provision of optimum action of hormones, both still released by the gland and delivered in a drug form. Moreover, it is aimed at retarding metabolic disorder development and resulting diseases [30,51,63]. Normal physiological action of

the thyroid hormones are provided by processes at a variety of levels – from the functions of the thyroid axis, through thyroid hormone blood transport, their uptake by tissues and intracellular transformations, up to triiodothyronine binding with its receptor. Nutritional factors play an essential part at every level of the thyroid hormone metabolization [30].

There is no need to use sophisticated diets, widely propagated in the Internet, among other things. Hashimoto disease diet should not be an elimination diet provided there are no specific medical contraindications. It should be based on feeding rules designated for healthy people and take into consideration individual needs related to age, sex, physiological condition and possible concomitant metabolic disorders and other diseases [17, 30, 47].

In nutritional scheduling it is important that the food products would contain adequate quantities of macro- and micronutrients, as required, and compensate possible deficiencies. Components whose deficiency is popular in Hashimoto-affected patients are aforementioned vitamin D and selenium, but also polyunsaturated fatty acids from n-3 (n-3 PUFA) family, vitamins A, E and C and mineral elements, i.e. iron, zinc and iodine. Due to the use of restrictive diets without any consultation with a dietician, patients are additionally exposed to protein-energy deficiencies [23, 38, 42, 44, 51].

The significance of food products in the diet therapy of Hashimoto-induced hypothyroidism is originated from the effect of the above-mentioned nutrients on thyroid functions and its hormones released. It deserves noting that dietary substitutes are not able to provide the same physiological effect as nutrients occurring in natural products do. Nonetheless, in order to understand the importance of food products in Hashimoto disease and to skilfully use them in the disease-related dietary management, one should be familiar with the modes of action of nutrients contained in them. To sum up, a final physiological effect will be the resultant of action of all products and their components taken into account in all-day alimentary rations. Health-improving products abundant in components relevant in Hashimoto disease are fish and fish products, among other things, whose relevance is characterised below.

FISH AND FISH PRODUCTS VS. HASHIMOTO DISEASE

A positive effect of fish on human health has been confirmed in many clinical trials. It is mainly attributed to fish-contained polyunsaturated fatty acids, especially from the n-3 family, i.e. eicosanopentaenoic (EPA) and docosahexaenoic (DHA) acids, and to a full-value protein, fat-soluble vitamins, and macro- and microelements such as calcium, phosphorus, selenium, fluorine and iodine [64]. The content of the above-mentioned compounds is differentiated and characteristic of a particular fish species, its age, size, physiological condition, type of ingested food, site of feeding, type of pisciculture and fishing time. Besides, a health-improving effect of fish and fish products is due to their quantities in a daily diet, their quality and an extent of processing [13, 21, 65]. The consumption of fish and fish products in Poland is above twice as low as in other EU countries, amounting to 12.5 kg *per capita* in 2017. A greater fish consumption is interfered with by a rise in their prices, the worsening of fish-slaughter animals and poultry price ratio and a reduction in the import of fresh-water fish like carp and trout [19].

The content of fat in the muscular tissue depends on the species. The highest levels of this macronutrient in salt water fishes (11–13%) were found in Atlantic and Baltic salmon, gilthead Sea bream and Atlantic horse mackerel, whereas the lowest (0.08%) in cod, which accumulates lipids mainly in the liver. The greatest fat content in fresh-water fishes (5-6%) has been reported in fish from *Cyprinidae* family (carp, grass carp, silver carp and goldfish), whereas the smallest (0.1-0.3%) – in predatory species like perch, pike and zander. In the muscular tissue of a number of salt- and fresh-water fish species polyunsaturated fatty acids (PUFA) predominate, and, similar to total fat content, they are more abundant in sea- vs. fresh-water fish meat, 23.5–67.4% and 17.7–50.6%, respectively. A high content of PUFA has been found in cod, zander, silver carp and rainbow trout. Sea fishes contain greater quantities of DHA and EPA compared to fresh-water fishes. The latter, in turn, contain more 18-carbon atom PUFA molecules, linoleic from n-6 family and α-linolenic from n-3 family. Apart from PUFA, fishes contain monounsaturated fatty acids (MUFA), especially abundant in the European eel and carp [21].

Fish rich in EPA and DHA, which should be recommended to patients with Hashimoto disease, is the Atlantic salmon. Other fishes rich in n-3 PUFA are: mackerel, tuna, Atlantic sturgeon, herring, anchovy, pilchard and rainbow trout [29]. There is a very beneficial n-3/n-6 PUFA ratio, amounting to 13–14, in the fat of the Atlantic salmon's and cod's muscular tissue. In the remaining marine fishes the parameter ranges from 5 in herring up to 10 in billfish. An exclusion in the group are so-called lagoon fishes from brackish waters like European Sea bass and gilthead, in whom the proportion between n-3 and n-6 PUFA is comparable to fresh-water fishes, where it is estimated to be 1 on average. Among fresh-water fishes the greatest value was recorded in rainbow trout (4.3), and values within the range of 2–3 were found in the fat of silver carp, bighead carp and grass carp, however below 2 and above 1 – in the fat of fishes from *Cyprinidae* family, i.e. carp, bream, tench and goldfish [21]. A beneficial n-3/n-6 PUFA ratio is also reflected in the fat of pikes and zanders [13].

The effect of **n-3 PUFA** is mainly based on risk reduction in cardiovascular incidents including fatal episodes. This is due to their hypolipaemic, hypotensive and antithrombotic effects. Moreover, n-3 PUFAs provide normal functions of the endothelium, an arterial wall internal layer. Besides, beneficial effects of n-3 PUFAs on the functions of the brain and the eyesight sense organ have been documented. Moreover, they have been found to alleviate rheumatoid disease-related symptoms, prevent from systemic lupus erythematosus, neoplastic diseases, type 2 diabetes and bronchial asthma [64].

Special attention should be paid to a regulatory effect of n-3 PUFAs on the immune system and their anti-inflammatory and antioxidative properties. This fact can be used in dietary management with Hashimoto patients in order to alleviate thyroid inflammation and retard the gland's autodestruction. The n-3 PUFAs exert an impact on the functions of macrophages, neutrophils, B and T lymphocytes and other immunocompetent cells like dendritic

cells, natural killers (NK), basophils, eosinophils and mast cells. Additionally, they change proportions among various T lymphocyte subpopulations [14]. The n-3 acids affect the immune system cells by the modification of mediator synthesis, e.g. eicosanoids, cytokines and nitrogen oxide (NO), which are responsible for intercellular communication. The immunomodulatory effect of n-3 PUFA is mainly based on an inhibition of excessive immune system response by reducing the expression and synthesis of agents involved in the pathophysiology of an inflammatory condition, i.e. interleukin 1 (IL-1), TNF-α, fibrinogen and C-reactive protein (CRP), and by enhancing monocyte-mediated synthesis of anti-inflammatory cytokines, i.e. interleukin 4, interleukin 10 (IL-4 and IL-10) and transforming growth factor beta (TGF-β) [8, 53]. Apart from that, EPA and DHA derivatives, produced in our bodies, like resolvins, maresins and protectins, take an active part in eliminating the inflammatory process at the site of its development, mainly by inducing anti-inflammatory factors [8, 43].

Many studies have also revealed a beneficial effect of n-3 PUFA on thyroid functions by enhancing the activity of Na^+-I^- symporter (NIS) and TPO, thereby improving iodine uptake by the thyroid and the gland's synthetic and secretory potentials. Apart from that, these acids increase an enzymatic activity of type 1 and 2 deiodinases (D1 and D2, respectively), which are responsible for T4 transformation, a prohormone, into a metabolically active T3 in the liver and in the peripheral tissues. They also condition a normal binding of T3 to its nuclear receptor [30].

Another element linking the action of fatty acids with Hashimoto disease is their competitiveness together with TH for binding with plasma transporting proteins. When the blood level of free fatty acids becomes increased, the elevation of free forms of thyroid hormones may take place. Those hormones provoke a feedback inhibition of TRH and TSH, thereby stimulating the thyroid gland. In human studies it has been documented that PUFAs decrease T4 binding with thyroxine-binding globulin (TBG). In other studies plasma fT4 level has positively correlated with the blood level of arachidonic acid from the n-6 family. In contrast, it has not correlated with either EPA or DHA levels [50].

Eicosapentaenoic acid exerts a protective effect on thyrocytes. This was confirmed by study results, in which the administration of ethyl ester EPA in animals subjected to the effect of methimazole, an anti-thyroid drug, prevented from thyroid destruction and diminution of blood T3 and T4 levels [36]. This mechanism may be mediated by one of the nuclear receptors, i.e. a *peroxisome proliferator-activated receptor gamma* (PPAR-γ). This is due to the fact that n-3 PUFAs and their derivatives synthesized in the body, e.g. prostaglandins, are PPAR-γ natural ligands. Most probably, this is the pathway by means of which n-3 PUFAs regulate the differentiation of thyroid cells and protect from the development of autoimmune thyroid diseases [50]. Using n-3 PUFA-deficient and saturated-acid-rich diets results in a decrease in the following: HPT axis activity, thyroid gland synthetic capacity, hepatic conversion of T4 to T3 and T3 binding with the nuclear receptor [30].

Apart from n-3 PUFA, an immunomodulatory effect is also exerted by **vitamin D**, which can be found in fish and fish products. Fatty fishes, like herring, rainbow trout, salmon, sardine, mackerel and carp, are its most abundant source. These fish species contain from 5 up to approximately 20 μg of vitamin D per 100 g of their eatable parts [29]. Vitamin D presents a series of beneficial functions. It regulates the homeostasis of calcium, phosphates and bone metabolization. It also influences on smooth muscle cells of the blood vessels and the cardiac muscle. It regulates insulin secretion by pancreatic B cells and conditions normal development of the nervous system. Moreover, it is a strong stimulator of the immune system [3,33]. Vitamin D deficiency is a common phenomenon both in Poland and abroad. A mean amount of vitamin D supplied with diet of a European is only 2.5-4 μg daily [8]. Not only is it associated with a greater incidence of rickets and osteoporosis, but also with disturbances regarding insulin secretion and carbohydrate metabolization, cardiovascular and autoimmune diseases including Hashimoto. A negative correlation between 25(OH)D blood level *vs.* anti-TPO and anti-TG antibody titres has been reported [3, 33].

The effect of vitamin D on the immune system stems from the presence of vitamin D receptors (VDR) in the cells of T and B lymphocytes, monocytes, macrophages and dendritic cells. Vitamin D reduces the activity of Th1 and Th2 cells. In contrast, it enhances the activity of Th2 and Treg cells. Hence, there is a transition in the cytokine production from Th1 towards Th2. As a result, the secretion of proinflammatory cytokines, e.g. INF-γ, is diminished, while the secretion of anti-inflammatory cytokines, e.g. IL4 and IL-10, becomes augmented. The effect of vitamin D on various subpopulations of T lymphocytes indicates that it plays an essential role in an inflammatory process fading. This protects from tissue damage caused by inflammatory cells. Additionally, vitamin D demonstrates an impact on B lymphocytes by stimulating their apoptosis and inhibiting their proliferation. This is reflected in a drop in immunoglobulin secretion. Moreover, it activates the proliferation of monocytes and their differentiation into macrophages, which present more effective phagocytic abilities. Vitamin D also weakens the maturation of dendritic cells and their capacity to present antigens, which proves its immunosuppressive properties. The maintenance of normal vitamin D blood level may therefore reduce the risk of Hashimoto disease and affect its course [25, 33, 41].

Vitamin D deficiency leads to an imbalance among T lymphocyte subpopulations, an enhancement of the inflammatory process in the thyroid and the elevation of anti-thyroid antibodies in the blood. Furthermore, an increase in TSH release by the pituitary gland and a decrease in the thyroid hormone blood levels occur. Yet, not all study results have confirmed the relationship between vitamin D blood level and anti-TPO antibody titre and/or TSH level. It is worth noting that vitamin D deficiency in the body may be either a cause or an effect of Hashimoto disease and other autoimmune diseases [26, 60].

Fatty fish, like herring, salmon, trout and mackerel, not only contain vitamin D but also considerable amounts of **vitamin A**. It is irreplaceable in the regulation of the following: vision process, cell division and differentiation, development, growth, reproduction and normal functions of the immune system. Vitamin A plays an important role in the maturation and differentiation of the immune system cells, e.g. lymphocytes, monocytes and neutrophils. To add more,

it affects lymphocyte T subpopulation and macrophagous phagocytic activity. Vitamin A deficit compromises the immune system functions by reducing macrophagous phagocytosis and disturbing Th1 to Th2 normal proportions to Th1's advantage [8].

The relevance of vitamin A in Hashimoto disease is also originated from its anti-inflammatory and antioxidative effects. This is important due to the fact that in the course of the disease a pronounced oxidative stress takes place in the thyroid gland. Both thyrocytes and immunocompetent cells are sensitive to the phenomenon. Therefore, normal supply of vitamin A can retard an auto-destructive process in the thyroid cells and exert a beneficial effect on TH synthesis [30, 56].

Moreover, vitamin A influences on HTP axis activity and the peripheral metabolization of thyroid hormones. In the event of hypovitaminosis A, a reduced iodine uptake by the thyroid and a lowered synthesis and secretion of thyroid hormones appear. This is accompanied by TSH level increase and thyroid hypertrophy, thereby the development of goitre. A synthesis of thyroid hormone transporting proteins, the level of T4 into T3 transformation in target tissues, TH uptake by the cells and T3 binding with the nuclear receptor become reduced, as well [56, 66].

Also, **carotenoids** belong to valuable compounds contained in fish. They can either play a role of provitamin A – mainly β-carotene, or not – astaxanthin, fucoxanthin, lutein, zeaksanthin and cantaxanthin [1]. All these substances display stronger antioxidative properties than vitamin A, which are based on the quenching of singleton oxygen and removing free radicals. Antioxidative properties of carotenoids also determine their anti-inflammatory potential. Furthermore, they regulate the functions of the immune system cells by taking synergistic actions with B and T lymphocytes, macrophages and other white blood cells. Astaxanthin gives red pigmentation to salmons, trouts and red breams. Importantly, it is a stronger antioxidant than other carotenoids and, definitely, more potent than α-tocopherol [1, 8, 16]. In clinical studies it has been demonstrated that astaxanthin reduces the level of oxidative stress and inflammation markers. Fucoxanthin is involved in the protection of cells against the oxidative stress, too. The significance of both these compounds in Hashimoto disease may also stem from the fact of their participation in the prevention of the development of Hashimoto-induced disorders and diseases. The two carotenoids directly or indirectly reduce the risk of cardiovascular diseases and improve plasma lipid profile. Furthermore, fucoxanthin decreases tissue insulin-resistance and glycaemia. It leads to the enhancement of thermogenesis and prevents from adipose tissue accumulation, especially within the abdominal cavity [1, 65].

A full-value piscine **protein** is a macronutrient whose activity may be used in the Hashimoto's diet therapy. Its quality is comparable to the quality of slaughter animals' and poultry's protein, and its digestibility exceeds 95%. Protein content in fish ranges from 13 up to 24%, from which the majority (95–97%) is the full-value protein of a beneficial amino acid content, outstripping a model protein content [19]. Fresh fishes, like halibut, sardine and tuna, feature the greatest protein content [29]. A considerable protein content (17–21%) and nutritional quality is also displayed by fishes originating from national cultures, like zander, pike, rainbow trout, perch and most species from the *Cyprinidae* family [54]. A good source of tyrosine and phenylalanine are the following: zander, roach, bream, perch, herring and salmon [49].

Protein significance in Hashimoto thyroiditis is derived from the amino acid participation in the synthesis of thyroid hormones and proteins relevant in the regulation of this process, i.e. TPO and TG. Tyrosine is a direct substrate for TH molecule synthesis, which is an iodinated derivative of the amino acid. Another amino acid indirectly participating in the thyroid hormone synthesis is phenylalanine, which is subject to conversion into tyrosine in the body [30].

An insufficient protein supply in a diet leads to HPT axis inhibition at all its levels and an impairment of its negative feedback mechanism. This is reflected in a reduced TSH release by the pituitary and its diminished stimulatory effect on TH secretion. Protein deficit also induces a stronger binding of T3 by transporting proteins in the blood, which results in fT3 level drop [46]. Besides, the protein role in Hashimoto disease is due to its participation in the regulation of food-induced thermogenesis and the acceleration of satiety feeling. Metabolic changes of proteins require a greater load of energy than of the remaining macronutrients, which makes proteins the least efficient energetic substrate. This conditions the acceleration of metabolization, which is important for hypothyroid patients, in whom the metabolization rate is slowed down [61]. Furthermore, eating the full-value protein inhibits hair loss, a phenomenon frequently observed in Hashimoto thyroiditis patients [63].

Proteins of a number of fishes, like mackerel, scad, silver hake, tuna, salmon, herring, carp, tilapia, silver carp, grass carp, fish species from the Siluriformes order, yellowstripe scad, sardinella, capelin, southern blue whiting, coho, round scad, Conger eel, yellowfin sole, flounder, Pacific hake and Atlantic cod are also the source of bio-peptides, released into the alimentary tract as a response to proteolytic enzymes. The bio-peptides can exert antioxidative and cardioprotective effects [7].

Apart from unsaturated fat, protein, vitamin D, vitamin A and carotenoids, the health-improving properties of the fish, mainly marine fish, is reflected in the presence of iodine and selenium in them. The best source of iodine are cod, mackerel, pollock and salmon. In turn, the best source of selenium are herring, cod, tuna, sardines, carp and eel [29, 39, 48].

Apart from tyrosine, **iodine** is the second substrate for HT synthesis. A deficit of this microelement is the cause of goitre development and the thyroid gland's hypoactivity. An excessive stimulation of HPT axis in response to a drop in thyroid hormone level makes its contribution. As a consequence, blood TSH elevation occurs. In turn, an increased level of thyreotropin in the event of iodine deficiency leads to an excessive production of hydrogen peroxide and other reactive oxygen species (ROS) in the thyroid. Hydrogen peroxide has a cytotoxic effect on the thyroid, which initiates or deepens its fibrosis and destruction [15, 39].

On the other hand, an excessive iodine supply is considered a risk factor of Hashimoto disease due to its detrimental effect on the immune system cells, enhancement of apoptotic changes in thyrocytes and inhibition of thyroid hormone

production [22]. Nonetheless, the amount of iodine delivered to the body with fish does not bring any risk of the iodine excessive supply.

Thyroid contains not only large quantities of iodine but also of **selenium**, which source are fish and fish products. Selenium plays a pivotal part in maintaining the homeostasis of the whole body. This pertains to the thyroid and the immune system, in particular. A daily consumption of this trace element in Poland is 20–59 μg. Selenium deficiency has been reported in many countries. It may refer to as many as milliard people all around the world [55].

Selenium action is based on the maintaining of thyroid hormone homeostasis at the level of HPT axis, liver and other target tissues. Its direct or indirect participation in TH synthesis regulation in the thyroid and other organs is conditioned by its presence in the active centre of deiodinases and antioxidative enzymes. In the former case selenium regulates thyroid hormone transformations mainly in target tissues, however also in the thyroid and the glands of higher HPT axis levels – the hypothalamus and the pituitary. In turn, antioxidative enzymes, i.e. glutathione peroxidases 1, 3 and 4 (GPx1, GPx3 and GPx4) and isoform 1 of thioredoxin reductase (TrxR1) protect from the oxidative stress, whose intensification is inseparably associated with thyroid hormone synthesis. GPx3 level is a factor deciding on the thyroid concentration of hydrogen peroxide – a TPO cofactor. Given that, selenium is a micro-component protecting the thyroid against toxic effects of hydrogen peroxide. This is directly reflected in TH synthesis level. Moreover, this prevents from an excessive thyroid stimulation [15, 39, 60].

Furthermore, selenium is a component of selenoproteins (SELENOs), which regulate the immune system functions. This is based on the inhibition of proinflammatory cytokines and on the enhancement of Th2 and Treg cell activity. In turn, Th2 and Treg cells reduce the oversensitivity and over-reactivity of the body's own antigens, thereby protecting the thyroid gland from autoagression that might lead to self-destruction [52].

Selenium deficit in a diet causes a reduced activity and impairment of selenoenzyme functions, which disturbs hepatic conversion of T4 into T3, potentiates thyroid oxidative stress, the apoptosis of thyrocytes and thyroid tissue fibrosis. Mechanisms leading to thyroid damage are not only mediated by oxidative stress but also by a high TSH level. This may initiate the development of Hashimoto disease or accelerate its progression and intensify symptoms. In the event of selenium deficit, iodine metabolization also becomes compromised, which leads to TH synthesis disturbance. The thyroid destruction has a more rapid and more intense course if selenium deficiency co-exists with iodine deficit. On the other hand, a normal supply of selenium may compensate the consequences of the iodine excess and prevent from destructive and inflammatory lesions [31, 55].

Selenium modulates the immune system functions not only by its protection against the oxidative stress and the regulation of SELENOs synthesis and activity, but also by its effect on B lymphocyte-mediated antibody production and on the activation of T lymphocytes and macrophages. Additionally, the beneficial impact of selenium in Hashimoto disease can also be accounted for by its potential for reducing the expression levels of HLA-DR antigens on the surface of thyrocytes, for diminishing anti-thyroid antibody levels and for inhibiting proinflammatory cytokine synthesis and other proinflammatory mediators, like prostaglandins and leukotrienes [55].

Selenium demonstrates a beneficial effect on the body only in a narrow range and its overconsumption leads to the appearance of undesirable effects. A consequence of selenium excess is reflected in thyroid hormone synthesis disturbance and the enhancement of thyroid oxidative stress and inflammation. Daily consumption of selenium exceeding 400–700 μg may have a toxic effect [55]. Fortunately, eating recommended amounts of fish will not contribute to an excessive supply of this micro-nutrient with diet.

Some fishes, such as herring, eel and smoked sprat are a good source of **zinc** [19]. A correlation of this micronutrient with Hashimoto disease stems from its anti-inflammatory and antioxidative properties. Zinc regulates the functions of the higher levels of HPT axis, TH synthesis and extrathyroid metabolization by means of D2 activity increase. It is the component of nuclear receptors specific for the activation of T3. Zinc deficiency is one of subclinical causes of the hypothyroidism. Moreover, such a condition impairs the secretion of TRH and TSH, the conversion of T4 into T3 and T3 binding with its nuclear receptor. Zinc plasma level in Hashimoto disease-affected patients is usually smaller compared to healthy individuals. It demonstrates a negative correlation with the level of anti-thyroid antibodies [11, 23, 24, 39].

EPA and DHA, vitamin D and vitamin A, carotenoids, iodine, selenium and zinc are the components of fish and fish products that exert a beneficial effect on thyroid functions and its hormones secreted. Moreover, they retard the gland's autodestruction. Due to that, fish-containing meals – of mainly marine, but also of fresh-water fish – should be scheduled in the nutrition of Hashimoto disease patients in the amount of two portions per week, including a fatty fish as one of them [20]. It is recommended to eat fresh and frozen fish. In the case of tinned fish, consumers should first choose fish in its own sauce or tomato sauce. On the other hand, in the case of fish in oil, consumers should remove the oil. The best ways of preparing fish are stewing, baking, steam-boiling and grilling with the use of an electric grill. Contrary to that, it is contraindicated to fry fish, especially in deep fat, and to coat it in bread crumbs and egg [64].

Concerns arise when it comes to the content of harmful compounds in fish and fish products, namely heavy metals (mercury, lead, cadmium, arsenic), dioxins and polychlorinated biphenyls (PCBs), which can contribute to their supply reduction in a diet of Hashimoto disease-affected patients. Fishes taking their places on the top of food-chain, e.g. pike, shark, tuna and swordfish, may accumulate the greatest quantities of mercury. Its absorption in the form of methylmercury rises along with the temperatures of seas and oceans. The least amounts of harmful substances are contained in fishes from the Pacific Ocean, the Atlantic Ocean and the North Sea [28].

Methylmercury and other heavy metals, as so-called endocrine disruptors, impair thyroid hormone metabolization at a variety of levels. Methylmercury inhibits the beneficial

effect of selenium on the thyroid and the transformations of thyroid hormones because of the fact that it is a specific and irreversible inhibitor of selenoenzymes. A considerable affinity of methylmercury to selenium makes it easily forms stable and insoluble complexes with this chemical element. Moreover, it links to the active centre of enzymes, thereby inhibiting their synthesis and activity. Selenium bound with mercury is not absorbable by the human body. This is an inactive connection but, at the same time, non-toxic. Furthermore, selenoenzymes affect methylmercury metabolization, by means of which reduce its toxicity [37]. Also, mercury impairs the immune system functions by demonstrating an immunotoxic effect on T and B lymphocytes, by disturbing the secretion of cytokines and by inhibiting the activity of T lymphocyte subpopulation, which ends up with autoimmune disorders [28].

Besides mercury, an excess of cadmium and lead contributes to structural and functional changes in the thyroid gland. Both those heavy metals tend to easily accumulate in the thyroid and other organs essential in TH metabolization, in the liver and in the kidneys, among other things. Furthermore, they impair the synthesis and secretion of TRH, TSH and TH, the conversion of T4 into T3, change lymphocytic functions and initiate the autoimmune process. In addition, cadmium induces functional changes in TG and the elevation of apoptosis and oxidative stress markers, whereas lead interferes with glucose metabolization [5, 6, 62].

Due to documented adverse effects of harmful substances present in fish and fish products on the thyroid and TH homeostasis, it is recommended to eat fishes with a short lifespan and situated as low in the food-chain as possible. Patients with Hashimoto disease, children, pregnant or breast-feeding women should not be advised to consume predatory fish species such as shark, swordfish, cero and golden tile. Instead, they should choose from fishes containing inconsiderable amounts of mercury and large amounts of n-3 PUFA and selenium, e.g. sardines, mackerel, anchovy and salmon [20,37]. Such an approach guarantees the achievement of expected medicinal effects, particularly with regard to a diet-assisted prophylaxis and Hashimoto disease diet therapy. Indeed, scientific evidence indicates the advantage of health-improving benefits resulting from fish consumption over risks connected to the avoidance of the fish-based food [9].

SUMMARY AND CONCLUSIONS

Components contained in fish and fish products exert a complex and multidirectional effect on all the levels of HPT-target tissue axis and on the course of inflammation in the thyroid. That action is predominantly of a beneficial nature, although some components consumed in excess or regarded as endocrine disruptors may compromise the synthesis of thyroid hormones and enhance pro-oxidative and proinflammatory processes in the thyroid gland. Due to the presence of harmful substances, the use of some fishes in the Hashimoto disease dietary management is limited. A summary of the relationship between fish components and Hashimoto disease has been illustrated in table (tab.1).

Table 1. Fish ingredients and Hashimoto thyroiditis
Tabela 1. Składniki ryb a choroba Hashimoto

Fish ingredients	Thyroid and TH action					Preventing thyroid destruction			
	A	B	C	D	E	F	G	H	I
Protein (amino acids)	V	V	V						V
Protein (biopeptides)						V			V
n-3 PUFA	V	V	V	V	V	V	V	V	V
Vitamin D		V					V	V	V
Vitamin A	V	V	V	V	V	V*	V	V	
Iodine	V	V						X**	
Selenium	V	V		V	V	V*	V*	V	V
Zinc	V	V		V	V	V	V		
Carotenoids		V			V	V	V	V	V
Mercury	X	X		X		X	X	X	X
Lead	X	X		X				X	X
Cadmium	X	X		X		X		X	X

A – thyroid hormone synthesis
B – regulation of thyroid hormone synthesis within the hypothalamic-pituitary-thyroid axis
C – thyroid hormone transport
D – conversion of thyroxine to triiodothyronine
E – receptor binding of triiodothyronine
F – antioxidant effect
G – anti-inflammatory effect
H – immunomodulatory effect
I – prevention of metabolic disorders and diseases caused by hypothyroidism

V – beneficial effect; X – adverse effect; * – pro-oxidative and/or pro-inflammatory effect at excess; ** - with excess

Source: Own study

Źródło: Opracowanie własne

TH synthesis and secretion and the mechanisms regulating these processes within the thyroid axis are stimulated by the following compounds contained in fish: n-3 PUFA, full-value protein, iodine, selenium and zinc. In order to retard the thyroid autodestruction, immunomodulatory, anti-inflammatory and antioxidative effects of n-3 PUFA, vitamin D, vitamin A, carotenoids, selenium and zinc should be taken into account in scheduling nutrition programmes for Hashimoto disease-affected patients. Normal uptake of thyroid hormones by the cells, either naturally produced in the thyroid or administered as synthetic drugs, thyroid hormone activation and functions at the cellular level are to the greatest extent conditioned by selenium, zinc, vitamin A and n-3 PUFA. Thyroid degradation may be accelerated as a response to an insufficient consumption of n-3 PUFA, protein, vitamin D, vitamin A, iodine, selenium and zinc [30]. The consumption of recommended fish rations does not bring the risk of excessive supply of the aforementioned micronutrients and harmful chemical compounds, which might impair the thyroid hormone homeostasis and the immune system functions. Yet, it is advised to include other sources of the discussed substances in a daily diet including dietary supplements.

Moreover, nutrients present in fish play a crucial role in preventing or retarding the development of disorders and diseases resulting from the hypothyroidism, i.e. obesity, metabolic syndrome, type 2 diabetes and cardiovascular diseases.

From a review of the literature made it is clear that fish is products, which – apart from well-known and widely described health-improving features – demonstrate the influence on the thyroid gland and mechanisms regulating the homeostasis of thyroid hormones. Furthermore, fish can contribute to reducing the risk of Hashimoto disease and to alleviating its course.

PODSUMOWANIE I WNIOSKI

Składniki obecne w rybach i przetworach rybnych wywierają złożony i wielokierunkowy wpływ na wszystkie piętra osi HPT-tkanki docelowe oraz na przebieg procesu zapalnego w tarczycy. Działanie to ma głównie charakter korzystny, ale niektóre składniki spożywane w nadmiarze lub zaliczane do dysruptorów endokrynnych mogą upośledzać syntezę hormonów tarczycy oraz nasilać procesy prooksydacyjne i prozapalne w gruczole. Ze względu na obecność substancji szkodliwych, wykorzystanie niektórych ryb w postępowaniu dietetycznym w chorobie Hashimoto jest ograniczone.

Syntezę i wydzielenie TH oraz mechanizmy regulujące te procesy w obrębie osi tarczycowej pobudzają występujące w rybach: n-3 PUFA, pełnowartościowe białko, jod, selen, i cynk. W celu spowolnienia autodestrukcji tarczycy w planowaniu żywienia osób z chorobą Hashimoto należy uwzględnić immunomodulacyjne, przeciwzapalne i antyoksydacyjne działanie n-3 PUFA, witaminy D i A, cynku, selenu i karotenoidów. Prawidłowy wychwyt przez komórki i aktywację hormonów tarczycy (zarówno powstających w tarczycy, jak i dostarczanych w postaci leku) i ich działanie na poziomie komórkowym w największym stopniu warunkują selen, cynk, witamina A i n-3 PUFA. Niszczenie tarczycy może ulec przyspieszeniu w sytuacji niedostatecznego spożycia n-3 PUFA, białka, witamin D i A, jodu, selenu i cynku [30]. Spożywanie zalecanej porcji ryb nie stanowi ryzyka nadmiernej podaży wymienionych mikroskładników, co mogłoby zaburzać homeostazę hormonów tarczycy i funkcjonowanie układu odpornościowego. Należy jednak uwzględnić inne ich źródła w całodziennej racji pokarmowej, w tym suplementy diety.

Składniki obecne w rybach mają również istotne znaczenie w zapobieganiu lub opóźnianiu rozwoju zaburzeń i schorzeń będących konsekwencją niedoczynności tarczycy tj. otyłość, zespół metaboliczny, cukrzyca typu 2 i choroby sercowo-naczyniowe.

Z dokonanego przeglądu piśmiennictwa wynika, że ryby są produktami, które poza dobrze znanymi i opisanymi właściwościami prozdrowotnymi wykazują wpływ na tarczycę i mechanizmy regulujące homeostazę hormonów tarczycy oraz mogą przyczynić się do zmniejszenia ryzyka choroby Hashimoto i złagodzenia jej przebiegu.

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