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Iron and ferritin deficiency in women with hypothyroidism and chronic lymphocytic thyroiditis — systematic review

Marcin Gierach, Monika Rudewicz, Roman Junik

Department of Endocrinology and Diabetology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Toruń, Poland

Abstract

Iron is one of the essential microelements necessary for maintaining the body's homeostasis. It serves various roles, including being a crucial component in the proper structure of many enzymes and supporting the transport of oxygen and electrons. Its deficiency can lead to anaemia, which is a common clinical condition often associated with thyroid diseases.

Iron deficiency is one of the most common nutritional deficiencies, and its prevalence is strongly associated with socioeconomic status. It is the primary cause of anaemia in 42% of children and 50% of women. Importantly, iron deficiency is placed among the top 5 causes of disability in women.

Thyroid peroxidase (TPO) is an enzyme essential for the production of thyroid hormones, and iron is a key factor in its proper functioning. Therefore, in the case of iron deficiency, the activity of this enzyme is also reduced. Iron is also a factor that is important in epigenetic modification processes, and its deficiency may contribute to genomic changes potentially promoting the development of autoimmune thyroid diseases.

Adequate supplementation in patients with Hashimoto's disease is one of the crucial elements of effective therapy. In addition to iodine, selenium, and magnesium supplementation, attention should be paid to proper iron intake. Iron is an element that is a component of the heme enzyme - thyroid peroxidase, which owes its activity to the binding of haem, and its function is the production of thyroid hormones. Iron can be delivered to the body in haem and non-haem forms. The haem form is found particularly in haemoglobin-rich red meat, but also in eggs, fish, and poultry. On the other hand, non-haem iron can be found in legumes, grains, fruits, and vegetables.

Our study aimed to gather and summarise knowledge from scientific literature regarding iron deficiency anaemia and its association with hypothyroidism in women, as well as the possible mechanisms and pathogenesis of these conditions. The paper also aims to highlight that considering the high risk of iron deficiency, assessing iron status along with ferritin should be an integral part of additional diagnostic measures in cases of hypothyroidism, particularly Hashimoto's disease. **(Endokrynol Pol 2024; 75 (3): 253–261)**

Key words: *iron; ferritin; hypothyroidism*

Introduction and aims

Iron is one of the essential microelements necessary for maintaining the body's homeostasis. It serves various roles, including being a crucial component in the proper structure of many enzymes and supporting the transport of oxygen and electrons [1, 2]. Its deficiency can lead to anaemia, which is a common clinical condition often associated with thyroid diseases. The coexistence of these 2 clinical issues remains ambiguous and requires further research. This problem particularly affects women who are physiologically more predisposed to developing anaemia. Our study will focus on the occurrence of microcytic anaemia [3, 4].

Hypothyroidism is a complex of clinical symptoms resulting from a deficiency of thyroxine, leading to inadequate action of triiodothyronine in the body's cells, which results in, among other things, a general slowing down of metabolic processes. The most characteristic symptoms in adults include fatigue, weight gain, decreased cold tolerance, constipation, dry skin, and changes in voice tone. Occasionally, the clinical course can be asymptomatic for many years [5–7].

The most common cause is Hashimoto's disease, which is chronic lymphocytic thyroiditis of autoimmune origin characterised by the presence of anti-thyroid peroxidase antibodies (anti-TPO) and anti-thyroglobulin antibodies (anti-TG), along with a characteristic ultrasonographic pattern showing a hypoechoic, heterogeneous gland structure. Anti-TPO antibodies are present in approximately 90% of individuals with Hashimoto's disease, while anti-TG antibodies, being less specific and sensitive, are present in 60–80% of patients [8, 9].

Our study aimed to gather and summarise knowledge from scientific literature regarding iron deficiency anaemia and its association with hypothyroidism in

Marcin Gierach, M.D., Ph.D., Department of Endocrinology and Diabetology of Ludwik Rydygier, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel./fax: (+48 052) 585 42 40; e-mail: marcin_gierach@wp.pl

women, as well as the possible mechanisms and pathogenesis of these conditions. The paper also aims to highlight that, considering the high risk of iron deficiency, assessing iron status along with ferritin should be an integral part of additional diagnostic measures in cases of hypothyroidism, particularly Hashimoto's disease [1].

Epidemiology

Autoimmune thyroid diseases (AITD), including Hashimoto's disease, are among the most common autoimmune disorders worldwide. At the same time, Hashimoto's disease is the most frequent cause of hypothyroidism in countries where there is no iodine deficiency, which is necessary for proper thyroid hormone production. AITD occurs 4–10 times more frequently in women than in men. It affects 0.3–1.5/1000 individuals per year (including 3.5–5/1000 individuals per year in females and 0.6–1.0/1000 individuals per year in males).

An important observation is that studies indicate the presence of anti-TPO and anti-TG antibodies in as many as 2–17% of women of reproductive age [1].

The group of women in a euthyroid state is characterised by significantly higher haemoglobin levels compared to women with decreased or elevated thyrotropin hormone (TSH) values [3, 10].

The prevalence of subclinical hypothyroidism increases with age and can affect up to 20% of women over 60 years old. This condition is defined as the coexistence of proper levels of thyroxine and triiodothyronine, with TSH levels exceeding the upper limit of the normal range. In the case of this condition, opinions regarding the frequency of its coexistence with anaemia are contradictory. M'Rabet-Bensalah et al. suggest that the frequency of anaemia occurrence is similar to the frequency in the euthyroid population [11]. On the other hand, Erdogan et al. found that the frequency of coexistence of anaemia in overt and subclinical hypothyroidism does not differ significantly. In the former case, it was reported as 43%, while in the latter, it was 39% [12].

Iron deficiency is one of the most common nutritional deficiencies, and its prevalence is strongly associated with socioeconomic status. It is the primary cause of anaemia in 42% of children and 50% of women. Importantly, iron deficiency is placed among the top 5 causes of disability in women. It is estimated to affect approximately 64% of the population in Asia, 62% in Latin America, 54% in South Asia, 9–50% in Eastern Europe, and 4–18% in the United States and North and Western Europe [1, 13, 14]. The peak incidence of anaemia particularly affects the elderly population and approximately 10% of women of reproductive age [3, 15].

In the face of the above data, an important observation is the frequent coexistence of these 2 clinical conditions. In the case of recurrent or treatment-resistant anaemia, thyroid diseases are among the most common causes, and achieving a euthyroid state is a significant factor positively influencing haematological parameters. It is also worth noting that the characteristics of anaemia in laboratory tests can serve as a clue for initiating thyroid dysfunction diagnostics [16, 17].

Recent studies have shown that anaemia is more commonly associated with hyperthyroidism than hypothyroidism, but the proportion of these cases is still significant. M'Rabet-Bensalah et al. reported a coexistence of anaemia in 14.6% of cases with hyperthyroidism and 7.7% with hypothyroidism [11].

The phenomenon that, even in patients in a euthyroid state, there is a positive correlation between the levels of free thyroid hormones and the level of erythrocytes, haemoglobin, and haematocrit, has been emphasised in a large cohort study. It also led to the conclusion highlighting a simultaneous negative association between TSH levels, transferrin saturation, and serum iron levels [18–20].

In a group of individuals with subclinical hypothyroidism, a prospective study was conducted by Christ-Crain et al., which demonstrated that achieving a euthyroid state results in an increase in erythropoietin levels, while haemoglobin and haematocrit remain unchanged [21].

The role of thyroid hormones in haematopoiesis

Thyroid hormones are essential for the proper functioning of the human body because they influence the regulation of metabolism. They are involved in modifying the basal metabolism and the metabolism of essential nutrients, including proteins, carbohydrates, and fats. Many systems in the human body rely on these molecules for proper functioning. They are especially vital for the cardiovascular, haematopoietic, reproductive, nervous, digestive, and integumentary systems, and mental health. Therefore, fluctuations in thyroid hormone levels have a negative impact on a patients' daily functioning [8, 23–26]. When discussing their impact on the haematopoietic system, thyroid hormones have a particular influence on erythropoiesis, which they promote by increasing the expression of the erythropoietin gene and its production in the kidneys. They also directly act on red blood cell precursors by enhancing their proliferation. There is an observation that the proliferative activity of the red blood cell

lineage in the bone marrow is reduced in individuals with hypothyroidism, and there is a decreased concentration of erythropoietin in the serum. Additionally, there is accumulation of mucopolysaccharides in the bone marrow observed in this patient group, which constitutes a part of physiological adaptation [16, 27]. Hypothyroidism is associated with a deficiency of triiodothyronine, and its role also involves the induction of erythroid colony growth [3, 28].

A deficiency of thyroid hormones is associated with a decrease in the rate of metabolic processes in the body, which is related to reduced tissue oxygen demand. As a result, physiological adaptations occur, leading to a reduction in erythropoietin secretion and a decrease in the number and proliferative activity of erythroid cells. When the state of euthyroidism is restored, these processes are reversed [16, 29].

Causes of iron deficiency and possible mechanisms leading to the development of anaemia in hypothyroidism

Several mechanisms can lead to the development of microcytic anaemia in hypothyroidism. These may include the following:

— impaired absorption;
— poor nutritional status;
— chronic inflammation due to the activation of pro-inflammatory cytokines;
— heavy menstrual bleeding, which is a common symptom in women with hypothyroidism [16, 29].

Excessive menstrual bleeding in hypothyroidism is caused by multiple factors. TSH consists of alpha and beta subunits. The alpha subunit is shared with follicle-stimulating hormone (FSH) and luteinising hormone (LH) and can partially mimic their actions. This results in decreased secretion of luteinising hormone, leading to reduced progesterone levels, mid-cycle bleeding, and the absence of ovulation. Among the hormonal disturbances observed in hypothyroidism, it is also important to note that the levels of hormone-binding proteins decrease. This leads to an increased concentration of free oestrogen in the blood, which exerts a proliferative effect on the endometrium. Changes in the extracellular matrix surrounding blood vessels and alterations in platelet function contribute to primary haemostatic disorders. In cases of severe hypothyroidism, it can even lead to severe menstrual bleeding, posing a serious risk of life-threatening anaemia [3, 30, 31].

Iron metabolism and thyroid hormone function are closely interconnected. On one hand, thyroid hormones directly act on the bone marrow, stimulating erythropoiesis, and on the kidneys, promoting erythropoietin (EPO) synthesis. On the other hand, iron is an essential element for the production of thyroid hormones as it is a component of thyroid peroxidase. Despite the abovementioned knowledge, the exact pathomechanism and cause of disturbances in iron homeostasis in hypothyroidism are fully understood [16, 32].

Iron deficiency in patients with Hashimoto's disease can also be caused by coexisting conditions that predispose patients to autoimmune disorders. These include impaired iron absorption, autoimmune gastritis, and celiac disease, which contribute to excessive loss of this microelement from the organism [8, 33, 34].

Another mechanism is the chronic inflammatory state maintained by the activity of pro-inflammatory cytokines. Another mechanism is the chronic inflammatory state maintained by the activity of pro-inflammatory cytokines. Hepcidin, belonging to acute-phase proteins, is a liver-derived peptide consisting of 25 amino acids. Its transcription occurs through 2 signalling pathways — the Stat3 pathway and the Smad 1/5/8 pathway. The first pathway is mainly triggered by interleukin 6 (IL-6), while the second pathway originates from bone morphogenetic protein (BMP), and its activation is associated with the binding of BMP receptor to activin B. Hepcidin binds to ferroprotein in enterocytes, liver, and splenic macrophages, and is subsequently degraded. The overall effect of its action is a decrease in blood iron levels, which is caused by retaining this element in macrophages and inhibiting its absorption from the gastrointestinal tract. It can be inferred that overexpression of hepcidin will result in iron deficiency anaemia, while its reduced expression will lead to iron overload states [16, 35].

Knowing the role, mechanism of action, and the fact that this protein is often associated with autoimmune diseases, it can be stated that its increased expression is another reason for the increased risk of iron deficiency anaemia in Hashimoto's disease [16].

It has been observed that in the transition from hypothyroidism to euthyroidism in patients with Hashimoto's disease, the concentration of hepcidin significantly decreases. This is related to the dynamics of iron metabolism changes during the course of the disease and its treatment process [16, 36].

Role of chronic inflammation

Hashimoto's disease, also known as chronic lymphocytic thyroiditis or autoimmune thyroiditis (AIT), is a medical condition characterised by chronic inflammation. Its pathogenesis is particularly associated with the production of autoantibodies against thyroid peroxidase (anti-TPO) and thyroglobulin (anti-TG), as well as infiltration of the thyroid gland by T and B lymphocytes,

especially CD4+ Th1 cells. The inflammatory state that occurs in the thyroid gland contributes to the destruction of thyroid follicles, which become replaced by small lymphocytes. This results in a hypoechoic appearance of the tissue in ultrasound imaging. Due to the chronic inflammatory process, fibrosis and atrophy of the thyroid parenchyma occur. It has been observed that the level of anti-TPO antibodies is associated with the concentration of high sensitivity C-reactive protein (hs-CRP), which may indicate the role of chronic inflammation in thyroid autoimmunity [8, 37, 38]. A study conducted on a group of 91 patients with Hashimoto's disease, including 42 individuals in a hypothyroid state and 49 in a euthyroid state, as well as 50 healthy individuals, showed a higher level of pro-inflammatory cytokines (including IL-6, IL-12, IL-10) and tumour necrosis factor alpha (TNF-α) in people with Hashimoto's disease [39]. A similar study was conducted on a group of women, where it has been observed that in the presence of anti-thyroid antibodies, higher levels of Il-6 are secreted into the bloodstream. This increase indicates endothelial dysfunction, which further contributes to the development of atherosclerosis [40]. A factor that can provide evidence supporting the role of chronic inflammation in the development of Hashimoto's disease is the fact that implementing an anti-inflammatory diet, with a reduced intake of animal-derived products and rich in vitamins, can be helpful in the therapy and prevention of this disorder [8, 41, 42]. In terms of inflammation, iron deficiency can be a factor contributing to its development. There is an observed association between iron deficiency and the formation of anti-TPO antibodies [1].

The role of iron in the functioning of TPO and iron deficiency as a modifying factor in the production of anti-TPO antibodies

Thyroid peroxidase (TPO) is an enzyme essential for the production of thyroid hormones, and iron is a key factor in its proper functioning. Therefore, in the case of iron deficiency, the activity of this enzyme is also reduced [1]. A study was conducted on 7 groups of rats, where 3 groups were given an iron-deficient diet (ID-3 — 3 ppm; ID-7 — 7 ppm; ID-11 — 11 ppm), while the rest received an adequate amount of iron (35 ppm). After 4 weeks, the results were evaluated by measuring haemoglobin, T3, T4, and TPO activity. In the iron-deficient diet group, significantly lower values were observed for the measured parameters, and TPO activity was reduced proportionally to the decreasing iron intake by 33%, 45%, and 56%. This study confirms that iron deficiency decreases TPO activity [43]. A study conducted on humans confirms a decrease in TPO activity by 33–56% in the iron-deficiency group. The extent of the enzyme activity reduction was associated with the level of iron deficiency [44]. In the case of iron deficiency, the binding of T3 to its nuclear receptor is impaired [45, 46]. Additionally, iron deficiency results in decreased activity of 5'-deiodinase and reduced utilisation of T3 from the bloodstream [47]. In addition to the abovementioned role of iron deficiency in TPO function, it is vital to emphasise that this condition also plays a role in anti-TPO antibody production. Iron deficiency is one of the factors that initiates the inflammatory process in the thyroid gland, leading to the production of anti-thyroid antibodies, among other effects. Thyroglobulin (TG), which constitutes about 80% of the total thyroid protein, enters the systemic circulation, exposing it to the immune system. Two major conformational epitopes are located on the thyroid peroxidase molecule surface — these are A and B. Anti-TPO antibodies are directed against them [3]. The action of anti-TPO antibodies leads to atrophy of the thyroid gland through 2 types of cytotoxicity: antibody-dependent cytotoxicity and complement-dependent cytotoxicity. The association between iron deficiency and autoimmune diseases is higher in women than in men. The risk is particularly emphasised in chronic obstructive pulmonary disease, urticaria, chronic liver disease, hypertension, and dyslipidaemia. Additionally, the risk is significantly increased in the 20–40 years age group, where the development of an autoimmune disease within 5 years of iron deficiency diagnosis can occur in up to 65% of individuals [1, 48]. Studies show that overt and subclinical hypothyroidism occurs more frequently in individuals with iron deficiency compared to those without iron metabolism disorders. Furthermore, the severity of this deficiency acts as a modifying factor in the prevalence of autoimmune thyroid diseases [1]. Focusing specifically on the female population, a study conducted on 2581 pregnant women revealed that the level of anti-TPO antibodies was higher in the case of iron deficiency, with no differences in T4 observed among the compared groups. Additionally, in 2021, a meta-analysis was conducted, which demonstrated that iron deficiency in women of reproductive age leads to a twofold increase in the risk of elevated levels of anti-TPO and/or anti-TG antibodies [49].

Iron deficiency as a factor inducing genomic changes that promote the development of autoimmune thyroid diseases (AITDs)

In addition to environmental and genetic factors contributing to the development of autoimmune thyroid diseases, epigenetic changes cannot be overlooked.

External factors can significantly modify gene expression, and the best-known type of these modifications is DNA methylation. Iron is a factor that is important in epigenetic modification processes, and its deficiency may contribute to genomic changes potentially promoting the development of autoimmune thyroid diseases [1]. Iron deficiency can impair DNA synthesis and lead to disturbances in programmed cell death. DNA damage is intensified, nuclear DNA bases are destroyed, and single- or double-strand breaks result in genome instability. Chromosome fragility increases, and the exchange of sister chromatids decreases. Insufficient levels of this element promote oxidative stress, and the mechanisms regulating it become dysregulated [1, 50]. In addition to causing DNA damage and promoting oxidative stress, iron deficiency reduces the availability of deoxyribonucleotides, which are necessary for DNA repair. Iron deficiency results in inadequate functioning of enzymes that contain this element. Consequently, insufficient replication, synthesis, and repair of DNA are observed due to impaired functioning of enzymes such as DNA polymerase, ribonucleotide reductase, DNA glycosylase, DNA endonuclease, DNA primase, and DNA helicase. Iron deficiency is also associated with disturbances in the formation and proper expression of microRNAs, which are involved in iron homeostasis. They are responsible for the post-translational regulation of genes involved in iron uptake, utilisation, and storage [51]. Insufficient iron content in the organism leads to hypoxia and enhances the formation of reactive oxygen species. The hypoxic state contributes to the overexpression of miR-373 and miR-210, which in turn disrupt DNA repair. Iron is also essential for histone modifications, which are disrupted in cases of iron deficiency. The removal of methyl groups from lysine residues, which is regulated by histone demethylase activity, is impaired [52].

Influence of iron deficiency on residual symptoms in AITD

Residual symptoms of hypothyroidism include, among others, reduced quality of life, cognitive impairments, fatigue, and memory problems. These symptoms affect approximately 10-15% of patients and are often present despite proper control of the thyroid hormone levels. One of the most common symptoms in patients with hypothyroidism is commonly referred to as "brain fog" Researchers suggest that oxidative stress, autoimmune conditions, and changes in neurotransmitter levels may contribute to its development [53]. Etteson et al. observed that the phenomenon of "brain fog" may be present in up to 79% of patients with hypothyroidism [54]. Mental health is another aspect that is particularly affected by thyroid dysfunction. Wet et al. observed an association between elevated levels of anti-TPO antibodies and an increased risk of depression and anxiety [55]. Autoimmunisation of the thyroid gland, in addition to its impact on quality of life, significantly increases the risk of depression and anxiety disorders in euthyroid patients with Hashimoto's disease who are undergoing independent levothyroxine substitution [8, 56]. Another modifying factor influencing residual symptoms is the individual's iron status. Deficiency of this microelement has a negative impact on neuroplasticity and the production of neurotransmitters. In a study conducted by Japanese scientists, the abovementioned issue of depression and perceived stress was observed. Analysis of 11,876 cases revealed that iron deficiency significantly exacerbates the experience of low mood, including depression and stress [57, 58]. Iron deficiency significantly weakens the body's tolerance to stress and noticeably increases the activity of the sympathetic nervous system by reducing tissue oxygenation and the consumption of noradrenaline. In Finland, a study was conducted involving 25 women who, despite achieving a euthyroid state, still experienced symptoms of hypothyroidism. At the beginning of the experiment, none of the women had anaemia, but their ferritin levels were < 60 mcg/L. They were given 6–12 months of oral iron supplementation. After this period, the symptoms related to hypothyroidism gradually disappeared, with significant improvement observed when ferritin levels exceeded 100 mcg/L. Symptoms noticeably diminished in 2/3 of the patients at this ferritin level [59]. Iron supplementation in hypothyroidism treatment can help increase the body's resilience to stress, improve immune function, and reduce sympathetic nervous system activity. It enhances the binding of T3 to its nuclear receptor. Additionally, it improves the utilisation of iodine in thyroid hormone production and increases the bioavailability of thyroid hormones by supporting the activity of deiodinases and thyroid peroxidase [1].

The microbiome and iron metabolism changes in hypothyroidism

The intestines are one of the most vital sites responsible for the body's immunity. This is due to the presence of tissues and immune cells that remain in close contact with the gut microbiota [3, 60]. It also serves as an essential element for maintaining the body's homeostasis, and it is through the gut that the immune system defends the body against microorganisms. It also plays a role in maintaining metabolic and nutritional homeostasis [8, 61, 62]. In adults, the composition of gut mi-

crobiota is associated with dietary habits and changes that occur during illnesses, but over a longer period it tends to remain relatively stable [63, 64]. The immune function is not the only role of the microbiota. One of its vital roles is having an influence on thyroid function through the thyroid-gut axis. It also affects the absorption of iron, which can lead to anaemia in patients with thyroid disorders [65, 66]. The development of autoimmune and inflammatory diseases, as indicated by research, is associated with gut dysbiosis, which refers to disturbances in the proper composition of the microbiota, increased intestinal permeability, and bacterial overgrowth [8]. Gut dysbiosis is a commonly occurring phenomenon in Hashimoto's disease. Specific bacterial strains present in dysbiosis of lymphocytic thyroiditis are found to be associated with clinical features of the disease [63, 67]. These processes contribute to the promotion of autoimmune processes occurring in the body [68]. Cross-sectional studies conducted on patients with Hashimoto's disease highlight that their gut microbiota has a different composition and diversity compared to control groups [8, 63, 67, 69]. Studies conducted by Cayres et al. have shown that patients with Hashimoto's disease experience a reduction in the number of Bifidobacterium species, while there is an increase in the number of *Bacteroides* species. Among patients receiving levothyroxine supplementation, the presence of *Lactobacillus* species was less frequent compared to those not undergoing this replacement therapy [8]. These changes are associated with the function of thyroid hormones themselves and fluctuations in their levels [63]. Diet is one of the main factors modulating the composition of gut microbiota, and researchers have observed significant differences in the consumption of specific nutrients and foods. Importantly, patients with hypothyroidism should pay special attention to a diet supporting a healthy gut microbiota composition [70, 71]. The main problem for patients with Hashimoto's disease, which is the variability of thyroid hormone levels, is also a factor that has a significant impact on the composition and quantity of gut microbiota. Importantly, these changes also contribute to an increased risk of bacterial overgrowth. In addition to thyroid dysfunction contributing to changes in gut microbiota, the microbiota itself can lead to significant metabolic changes. This is due to its role in regulating the circulation and deconjugation of thyroid hormones [63]. Proper gut microbiota ensures sufficient acquisition of various nutrients, macronutrients, and micronutrients from the intestines. Therefore, the homeostasis of iron metabolism is also dependent, among other factors, on the state of gut bacterial flora. Gut microbiota can increase the iron bioavailability by lowering the pH through the short-chain fatty acids production. Low pH is necessary for the iron absorption in the proximal part of the duodenum through the divalent metal ion transporter 1. Non-haem iron in its III oxidised form is reduced to the ferrous form II by cytochrome b. Any disruptions in the gut microbiota composition lead to disturbances in this process [72]. On the other hand, completing the issue of inflammation, which is an integral part of autoimmune processes, improving the overall condition of gut microbiota is essential to reduce the activity of inflammatory processes in the body [63].

Changes in complete blood count in hypothyroidism

Anaemia is a common phenomenon associated with hypothyroidism, which can be observed in up to 20–60% of patients [16, 64]. In general, anaemia in this group of patients is most commonly normocytic, while in Hashimoto's disease it is often macrocytic. However, the coexisting iron deficiency in these disorders contributes to the exacerbation of anaemia, and thyroid hormone deficiency further impairs the viability of red blood cells [73]. One of the most common causes of recurrent or treatment-resistant anaemia is thyroid dysfunction. On the other hand, the characteristics of anaemia can be the first symptom suggesting thyroid disease in asymptomatic patients [16]. An important finding is that even subtle changes in thyroid function in euthyroid patients can modify red blood cell parameters [18, 73]. A characteristic indicator that increases in cases of iron deficiency anaemia is red cell distribution width (RDW), which reflects red blood cell anisocytosis. The higher the value, the greater the degree of anisocytosis. A decrease in this parameter indicates iron homeostasis improvement and, consequently, more efficient erythropoiesis [16]. Its increase has been observed in patients with hypothyroidism in the course of Hashimoto's disease [73, 74]; however, its gradual reduction occurs with the restoration of euthyroid state. Additionally, an increase in the RDW index may suggest the presence of thyroid inflammation in Hashimoto's disease, even in patients in a euthyroid state [75]. Changes in the RDW coefficient variation (RDW-CV) index can be an early indicator of disturbances in iron homeostasis. This parameter is positively correlated with TSH levels in the healthy population, which makes it a potential indirect marker of hypothyroidism in women, particularly in cases where iron deficiency anaemia has been ruled out [16].

In a prospective observational study conducted at a tertiary endocrinology centre, patients with newly diagnosed hypothyroidism due to Hashimoto's disease were observed. In the next phase of the study, their

results were compared before and after restoration of euthyroid state. The results revealed a significantly lower median hepcidin concentration after treatment [7.7 (6.2–13.0) ng/mL] compared to the pre-treatment period [17.4 (7.6–20.4) ng/mL]. There was a positive correlation between hepcidin concentration and fT3 levels at the time of diagnosis. Overall, no significant changes in iron and ferritin levels were observed, but among the female participants, a positive correlation was found between ferritin concentration before and after treatment. Additionally, despite the levels of RDW-CV and mean corpuscular volume (MCV), and mean corpuscular haemoglobin (MCH) being within the normal range in both study periods, statistically significant differences were noted between hypothyroidism and euthyroidism. Importantly, in the course of hypothyroidism, there is a decrease in plasma volume, which may lead to an underestimation of haemoglobin concentration and subsequent failure to diagnose anaemia. It is also related to the fact that upon returning to a euthyroid state, there is no significant change in haemoglobin concentration due to plasma volume increase. An important conclusion drawn from this study is that effective L-thyroxine supplementation leading to the restoration of a euthyroid state is associated with a reduction in hepcidin concentration, closely related to maintaining iron homeostasis. The RDW-CV index improves, and the association between hepcidin concentration, free triiodothyronine (fT3), and ferritin becomes apparent [16]. Improvement in thyroid hormone levels has been observed in women with thyroid dysfunction and anaemia who have undergone iron supplementation [8]. On the other hand, one of the retrospective studies conducted on 180 women highlights that haemoglobin levels, MCV, ferritin levels, haematocrit, and iron status were significantly reduced in subjects with elevated TSH levels and anti-TPO and anti-TG antibodies. There is a significant positive correlation between the levels of free thyroid hormones and ferritin, while a negative correlation exists between ferritin levels and TSH [3].

Iron supplementation in Hashimoto's disease

Adequate supplementation in patients with Hashimoto's disease is one of the crucial elements of effective therapy. In addition to iodine, selenium, and magnesium supplementation, attention should be paid to proper iron intake. Iron is an element that is a component of the haem enzyme — thyroid peroxidase, which owes its activity to the binding of haem, and its function is the production of thyroid hormones [8]. Iron can be delivered to the body in haem and non-haem forms. The haem form is found particularly in haemoglobin-rich red meat, but also in eggs, fish, and poultry. On the other hand, non-haem iron can be found in legumes, grains, fruits, and vegetables [76]. Thyroid diseases, especially autoimmune ones, including Hashimoto's disease, often coexist with other autoimmune disorders that disrupt iron metabolism. These include autoimmune gastritis, which contributes to iron absorption impairment, and celiac disease, which further exacerbates the loss of this element from the organism [8, 77]. On the other hand, iron deficiency contributes to the increased production of autoantibodies against TPO and TG, which is particularly evident in women of reproductive age [8]. Studies have shown that iron supplementation in women with coexisting anaemia and thyroid disorders contributed to regulating thyroid hormone levels [78, 79]. It is emphasised that in the presence of significantly elevated levels of TSH, anti-TPO, and anti-TG, there is a significant decrease in haemoglobin, haematocrit, iron, ferritin, and MCV levels [8]. Studies lead to the conclusion that patients with autoimmune thyroid diseases are more susceptible to developing iron deficiency anaemia. Individualised iron supplementation is a crucial element in the therapy of thyroid disorders because there is evidence suggesting a negative correlation between the concentration of anti-TPO autoantibodies and the levels of ferritin and iron. This confirms an increased risk of iron deficiency, among other factors, in Hashimoto's disease [8]. Just as proper supplementation of thyroid hormones in the form of L-thyroxine normalises haematological parameters, iron substitution in subclinical hypothyroidism further enhances the effectiveness of levothyroxine treatment. Importantly, in patients with anaemia, L-thyroxine therapy is less well tolerated. Therefore, a recommended approach is to initiate iron supplementation as the first step, followed by the addition of levothyroxine.

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References

1. Szklarz M, Gontarz-Nowak K, Matuszewski W, et al. Iron: Not Just a Passive Bystander in AITD. Nutrients. 2022; 14(21), doi: 10.3390/nu14214682, indexed in Pubmed: 36364944.

2. Kumar A, Sharma E, Marley A, et al. Iron deficiency anaemia: pathophysiology, assessment, practical management. BMJ Open Gastroenterol. 2022; 9(1), doi: 10.1136/bmjgast-2021-000759, indexed in Pubmed: 34996762.
3. Szczepanek-Parulska E, Hernik A, Ruchała M. Anemia in thyroid diseases. Pol Arch Intern Med. 2017; 127(5): 352–360, doi: 10.20452/pamw.3985, indexed in Pubmed: 28400547.
4. Alqahtani SA. Prevalence and Characteristics of Thyroid Abnormalities and Its Association with Anemia in ASIR Region of Saudi Arabia: A Cross-Sectional Study. Clin Pract. 2021; 11(3): 494–504, doi: 10.3390/clinpract11030065, indexed in Pubmed: 34449542.
5. Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. Lancet. 2017; 390(10101): 1550–1562, doi: 10.1016/S0140-6736(17)30703-1, indexed in Pubmed: 28336049.
6. Taweesomboonyat C, Oearsakul T, Haskard-Zolnierek K, et al. TRUST Study Group. Provider variability in the initial diagnosis and treatment of congenital hypothyroidism. J Pediatr Endocrinol Metab. 2017; 30(5): 583–586, doi: 10.1515/jpem-2016-0326, indexed in Pubmed: 28328531.
7. Jansen HI, Boelen A, Heijboer AC, et al. Hypothyroidism: The difficulty in attributing symptoms to their underlying cause. Front Endocrinol (Lausanne). 2023; 14: 1130661, doi: 10.3389/fendo.2023.1130661, indexed in Pubmed: 36814580.
8. Mikulska AA, Karaźniewicz-Łada M, Filipowicz D, et al. Metabolic Characteristics of Hashimoto's Thyroiditis Patients and the Role of Microelements and Diet in the Disease Management-An Overview. Int J Mol Sci. 2022; 23(12), doi: 10.3390/ijms23126580, indexed in Pubmed: 35743024.
9. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev. 2014; 13(4-5): 391–397, doi: 10.1016/j.autrev.2014.01.007, indexed in Pubmed: 24434360.
10. Lippi G, Montagnana M, Salvagno GL, et al. Should women with abnormal serum thyroid stimulating hormone undergo screening for anemia? Arch Pathol Lab Med. 2008; 132(3): 321–322, doi: 10.5858/2008-132-321-SWWAST, indexed in Pubmed: 18318574.
11. M'Rabet-Bensalah K, Aubert CE, Coslovsky M, et al. Thyroid dysfunction and anaemia in a large population-based study. Clin Endocrinol (Oxf). 2016; 84(4): 627–631, doi: 10.1111/cen.12994, indexed in Pubmed: 26662849.
12. Erdogan M, Kösenli A, Ganidagli S, et al. Characteristics of anemia in subclinical and overt hypothyroid patients. Endocr J. 2012; 59(3): 213–220, doi: 10.1507/endocrj.ej11-0096, indexed in Pubmed: 22200582.
13. Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019; 2019(1): 315–322, doi: 10.1182/hematology.2019000034, indexed in Pubmed: 31808874.
14. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. J Intern Med. 2020; 287(2): 153–170, doi: 10.1111/joim.13004, indexed in Pubmed: 31665543.
15. Taylor S, Rampton D. Treatment of iron deficiency anemia: practical considerations. Pol Arch Med Wewn. 2015; 125(6): 452–460, doi: 10.20452/pamw.2888, indexed in Pubmed: 25922941.
16. Hernik A, Szczepanek-Parulska E, Filipowicz D, et al. The hepcidin concentration decreases in hypothyroid patients with Hashimoto's thyroiditis following restoration of euthyroidism. Sci Rep. 2019; 9(1): 16222, doi: 10.1038/s41598-019-52715-3, indexed in Pubmed: 31700042.
17. Wopereis DM, Du Puy RS, van Heemst D, et al. Thyroid Studies Collaboration. The Relation Between Thyroid Function and Anemia: A Pooled Analysis of Individual Participant Data. J Clin Endocrinol Metab. 2018; 103(10): 3658–3667, doi: 10.1210/jc.2018-00481, indexed in Pubmed: 30113667.
18. Bremner AP, Feddema P, Joske DJ, et al. Significant association between thyroid hormones and erythrocyte indices in euthyroid subjects. Clin Endocrinol (Oxf). 2012; 76(2): 304–311, doi: 10.1111/j.1365-2265.2011.04228.x, indexed in Pubmed: 21913954.
19. Garofalo V, Condorelli RA, Cannarella R, et al. Relationship between Iron Deficiency and Thyroid Function: A Systematic Review and Meta-Analysis. Nutrients. 2023; 15(22), doi: 10.3390/nu15224790, indexed in Pubmed: 38004184.
20. Wang F, Zhang Y, Yuan Z, et al. The association between iron status and thyroid hormone levels during pregnancy. J Trace Elem Med Biol. 2022; 74: 127047, doi: 10.1016/j.jtemb.2022.127047, indexed in Pubmed: 35930951.
21. Christ-Crain M, Meier C, Huber P, et al. Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. Hormones (Athens). 2003; 2(4): 237–242, doi: 10.14310/horm.2002.11105, indexed in Pubmed: 17003028.
22. Ellegård L, Krantz E, Trimpou P, et al. Health-related quality of life in hypothyroidism-A population-based study, the WHO MONICA Project. Clin Endocrinol (Oxf). 2021; 95(1): 197–208, doi: 10.1111/cen.14448, indexed in Pubmed: 33665871.
23. Barreiro Arcos ML. Role of thyroid hormones-induced oxidative stress on cardiovascular physiology. Biochim Biophys Acta Gen Subj. 2022; 1866(12): 130239, doi: 10.1016/j.bbagen.2022.130239, indexed in Pubmed: 36064072.
24. Ahmed SS, Mohammed AA. Effects of thyroid dysfunction on hematological parameters: Case controlled study. Ann Med Surg (Lond). 2020; 57: 52–55, doi: 10.1016/j.amsu.2020.07.008, indexed in Pubmed: 32714526.
25. Silva JF, Ocarino NM, Serakides R. Thyroid hormones and female reproduction. Biol Reprod. 2018; 99(5): 907–921, doi: 10.1093/biolre/ioy115, indexed in Pubmed: 29767691.
26. Sun Y, Kan X, Zheng R, et al. Hashimoto's thyroiditis, vitiligo, anemia, pituitary hyperplasia, and lupus nephritis-A case report of autoimmune polyglandular syndrome type III C + D and literature review. Front Pediatr. 2023; 11: 1062505, doi: 10.3389/fped.2023.1062505, indexed in Pubmed: 37063678.
27. Savage RA, Sipple C. Marrow myxedema. Gelatinous transformation of marrow ground substance in a patient with severe hypothyroidism. Arch Pathol Lab Med. 1987; 111(4): 375–377.
28. Malgor LA, Valsecia ME, Verges EG, et al. Enhancement of erythroid colony growth by triiodothyronine in cell cultures from bone marrow of normal and anemic rats with chronic renal failure. Acta Physiol Pharmacol Ther Latinoam. 1995; 45(2): 79–86, indexed in Pubmed: 8580525.
29. Banday T, Bhat S, Bhat S, et al. To study prevalence of incipient iron deficiency in primary hypothyroidism. Int J Res Med Sci. 2014; 2(2): 472, doi: 10.5455/2320-6012.ijrms20140518.
30. Saei Ghare Naz M, Rostami Dovom M, Ramezani Tehrani F. The Menstrual Disturbances in Endocrine Disorders: A Narrative Review. Int J Endocrinol Metab. 2020; 18(4): e106694, doi: 10.5812/ijem.106694, indexed in Pubmed: 33613678.
31. Dreisler E, Frandsen CS, Ulrich L. Perimenopausal abnormal uterine bleeding. Maturitas. 2024; 184: 107944, doi: 10.1016/j.maturitas.2024.107944, indexed in Pubmed: 38412750.
32. Hess SY, Zimmermann MB, Arnold M, et al. Iron deficiency anemia reduces thyroid peroxidase activity in rats. J Nutr. 2002; 132(7): 1951–1955, doi: 10.1093/jn/132.7.1951, indexed in Pubmed: 12097675.
33. Boutzios G, Koukoulioti E, Goules AV, et al. Hashimoto Thyroiditis, Anti-Parietal Cell Antibodies: Associations With Autoimmune Diseases and Malignancies. Front Endocrinol (Lausanne). 2022; 13: 860880, doi: 10.3389/fendo.2022.860880, indexed in Pubmed: 35528009.
34. Starchl C, Scherkl M, Amrein K. Celiac Disease and the Thyroid: Highlighting the Roles of Vitamin D and Iron. Nutrients. 2021; 13(6), doi: 10.3390/nu13061755, indexed in Pubmed: 34064075.
35. Ruchala P, Nemeth E. The pathophysiology and pharmacology of hepcidin. Trends Pharmacol Sci. 2014; 35(3): 155–161, doi: 10.1016/j.tips.2014.01.004, indexed in Pubmed: 24552640.
36. Nekrasova TA, Strongin LG, Ledentsova OV. [Hematological disturbances in subclinical hypothyroidism and their dynamics during substitution therapy]. Klin Med Mosk. 2013; 91(9): 29–33.
37. Jin B, Wang S, Fan Z. Pathogenesis Markers of Hashimoto's Disease-A Mini Review. Front Biosci (Landmark Ed). 2022; 27(10): 297, doi: 10.31083/j.fbl2710297, indexed in Pubmed: 36336870.
38. Ajjan RA, Weetman AP. The Pathogenesis of Hashimoto's Thyroiditis: Further Developments in our Understanding. Horm Metab Res. 2015; 47(10): 702–710, doi: 10.1055/s-0035-1548832, indexed in Pubmed: 26361257.
39. Lei Yi, Yang J, Li H, et al. Changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with autoimmune thyroid disease. J Clin Lab Anal. 2019; 33(7): e22929, doi: 10.1002/jcla.22929, indexed in Pubmed: 31350776.
40. Siemińska L, Wojciechowska C, Walczak K, et al. Associations between metabolic syndrome, serum thyrotropin, and thyroid antibodies status in postmenopausal women, and the role of interleukin-6. Endokrynol Pol. 2015; 66(5): 394–403, doi: 10.5603/EP.2015.0049, indexed in Pubmed: 26457493.
41. Matana A, Torlak V, Brdar D, et al. Dietary Factors Associated with Plasma Thyroid Peroxidase and Thyroglobulin Antibodies. Nutrients. 2017; 9(11), doi: 10.3390/nu9111186, indexed in Pubmed: 29143786.
42. Tonstad S, Nathan E, Oda K, et al. Vegan diets and hypothyroidism. Nutrients. 2013; 5(11): 4642–4652, doi: 10.3390/nu5114642, indexed in Pubmed: 24264226.
43. Fayadat L, Niccoli-Sire P, Lanet J, et al. Role of heme in intracellular trafficking of thyroperoxidase and involvement of H2O2 generated at the apical surface of thyroid cells in autocatalytic covalent heme binding. J Biol Chem. 1999; 274(15): 10533–10538, doi: 10.1074/jbc.274.15.10533, indexed in Pubmed: 10187846.
44. Beard J, Tobin B, Green W. Evidence for thyroid hormone deficiency in iron-deficient anemic rats. J Nutr. 1989; 119(5): 772–778, doi: 10.1093/jn/119.5.772, indexed in Pubmed: 2498473.
45. Smith S, Finley J, Johnson L, et al. Indices of in vivo and in vitro thyroid hormone metabolism in iron-deficient rats. Nutr Res. 1994; 14(5): 729–739, doi: 10.1016/s0271-5317(05)80208-8.
46. Szklarz M, Gontarz-Nowak K, Matuszewski W, et al. "Ferrocrinology" — Iron Is an Important Factor Involved in Gluco- and Lipocrinology. Nutrients. 2022; 14(21), doi: 10.3390/nu14214693, indexed in Pubmed: 36364955.

47. Dillman E, Gale C, Green W, et al. Hypothermia in iron deficiency due to altered triiodothyronine metabolism. Am J Physiol. 1980; 239(5): R377–R381, doi: 10.1152/ajpregu.1980.239.5.R377, indexed in Pubmed: 7435650.
48. Chang R, Chu KA, Lin MC, et al. Newly diagnosed iron deficiency anemia and subsequent autoimmune disease: a matched cohort study in Taiwan. Curr Med Res Opin. 2020; 36(6): 985–992, doi: 10.1080/03007995.2020.1748585, indexed in Pubmed: 32223346.
49. Luo J, Wang X, Yuan Li, et al. Iron Deficiency, a Risk Factor of Thyroid Disorders in Reproductive-Age and Pregnant Women: A Systematic Review and Meta-Analysis. Front Endocrinol (Lausanne). 2021; 12: 629831, doi: 10.3389/fendo.2021.629831, indexed in Pubmed: 33716980.
50. Inoue H, Kobayashi KI, Ndong M, et al. Activation of Nrf2/Keap1 signaling and autophagy induction against oxidative stress in heart in iron deficiency. Biosci Biotechnol Biochem. 2015; 79(8): 1366–1368, doi: 10.1080/09168451.2015.1018125, indexed in Pubmed: 25754743.
51. Davis M, Clarke S. Influence of microRNA on the maintenance of human iron metabolism. Nutrients. 2013; 5(7): 2611–2628, doi: 10.3390/nu5072611, indexed in Pubmed: 23846788.
52. Barks AK, Liu SX, Georgieff MK, et al. Early-Life Iron Deficiency Anemia Programs the Hippocampal Epigenomic Landscape. Nutrients. 2021; 13(11), doi: 10.3390/nu13113857, indexed in Pubmed: 34836113.
53. Jurado-Flores M, Warda F, Mooradian A. Pathophysiology and Clinical Features of Neuropsychiatric Manifestations of Thyroid Disease. J Endocr Soc. 2022; 6(2): bvab194, doi: 10.1210/jendso/bvab194, indexed in Pubmed: 35059548.
54. Ettleson MD, Raine A, Batistuzzo A, et al. Brain Fog in Hypothyroidism: Understanding the Patient's Perspective. Endocr Pract. 2022; 28(3): 257–264, doi: 10.1016/j.eprac.2021.12.003, indexed in Pubmed: 34890786.
55. Watt T, Hegedüs L, Bjorner JB, et al. Is Thyroid Autoimmunity per se a Determinant of Quality of Life in Patients with Autoimmune Hypothyroidism? Eur Thyroid J. 2012; 1(3): 186–192, doi: 10.1159/000342623, indexed in Pubmed: 24783018.
56. Yalcin MM, Altinova AE, Cavnar B, et al. Is thyroid autoimmunity itself associated with psychological well-being in euthyroid Hashimoto's thyroiditis? Endocr J. 2017; 64(4): 425–429, doi: 10.1507/endocrj.EJ16-0418, indexed in Pubmed: 28260699.
57. Hidese S, Saito K, Asano S, et al. Association between iron-deficiency anemia and depression: A web-based Japanese investigation. Psychiatry Clin Neurosci. 2018; 72(7): 513–521, doi: 10.1111/pcn.12656, indexed in Pubmed: 29603506.
58. Vulser H, Wiernik E, Hoertel N, et al. Association between depression and anemia in otherwise healthy adults. Acta Psychiatr Scand. 2016; 134(2): 150–160, doi: 10.1111/acps.12595, indexed in Pubmed: 27238642.
59. Soppi E. Iron deficiency is the main cause of symptom persistence in patients treated for hypothyroidism. Thyroid. 2015; 25: A74.
60. Wastyk HC, Fragiadakis GK, Perelman D, et al. Gut-microbiota-targeted diets modulate human immune status. Cell. 2021; 184(16): 4137–4153.e14, doi: 10.1016/j.cell.2021.06.019, indexed in Pubmed: 34256014.
61. Wang J, Zhu N, Su X, et al. Gut-Microbiota-Derived Metabolites Maintain Gut and Systemic Immune Homeostasis. Cells. 2023; 12(5), doi: 10.3390/cells12050793, indexed in Pubmed: 36899929.
62. Ishaq HM, Mohammad IS, Guo H, et al. Molecular estimation of alteration in intestinal microbial composition in Hashimoto's thyroiditis patients. Biomed Pharmacother. 2017; 95: 865–874, doi: 10.1016/j.biopha.2017.08.101, indexed in Pubmed: 28903182.
63. Ihnatowicz P, Drywień M, Wątor P, et al. The importance of nutritional factors and dietary management of Hashimoto's thyroiditis. Ann Agric Environ Med. 2020; 27(2): 184–193, doi: 10.26444/aaem/112331, indexed in Pubmed: 32588591.
64. Antonijević N, Nesović M, Trbojević B, et al. [Anemia in hypothyroidism]. Med Pregl. 1999; 52(3-5): 136–140, indexed in Pubmed: 10518398.
65. Knezevic J, Starchl C, Tmava Berisha A, et al. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? Nutrients. 2020; 12(6), doi: 10.3390/nu12061769, indexed in Pubmed: 32545596.
66. Su X, Zhao Y, Li Y, et al. Gut dysbiosis is associated with primary hypothyroidism with interaction on gut-thyroid axis. Clin Sci (Lond). 2020; 134(12): 1521–1535, doi: 10.1042/CS20200475, indexed in Pubmed: 32519746.
67. Zhao F, Feng J, Li J, et al. Alterations of the Gut Microbiota in Hashimoto's Thyroiditis Patients. Thyroid. 2018; 28(2): 175–186, doi: 10.1089/thy.2017.0395, indexed in Pubmed: 29320965.
68. Virili C, Fallahi P, Antonelli A, et al. Gut microbiota and Hashimoto's thyroiditis. Rev Endocr Metab Disord. 2018; 19(4): 293–300, doi: 10.1007/s11154-018-9467-y, indexed in Pubmed: 30294759.
69. Liu J, Qin X, Lin B, et al. Analysis of gut microbiota diversity in Hashimoto's thyroiditis patients. BMC Microbiol. 2022; 22(1): 318, doi: 10.1186/s12866-022-02739-z, indexed in Pubmed: 36564707.
70. Liu S, An Y, Cao B, et al. The Composition of Gut Microbiota in Patients Bearing Hashimoto's Thyroiditis with Euthyroidism and Hypothyroidism. Int J Endocrinol. 2020; 2020: 5036959, doi: 10.1155/2020/5036959, indexed in Pubmed: 33224194.
71. Cayres LC, de Salis LV, Rodrigues GS, et al. Detection of Alterations in the Gut Microbiota and Intestinal Permeability in Patients With Hashimoto Thyroiditis. Front Immunol. 2021; 12: 579140, doi: 10.3389/fimmu.2021.579140, indexed in Pubmed: 33746942.
72. Knezevic J, Starchl C, Tmava Berisha A, et al. Thyroid-Gut-Axis: How Does the Microbiota Influence Thyroid Function? Nutrients. 2020; 12(6), doi: 10.3390/nu12061769, indexed in Pubmed: 32545596.
73. Szczepanek-Parulska E, Adamska M, Korda O, et al. Changes in complete blood count parameters influenced by endocrine disorders. Endokrynol Pol. 2021; 72(3): 261–270, doi: 10.5603/EP.a2021.0059, indexed in Pubmed: 34292577.
74. Montagnana M, Lippi G, Targher G, et al. The red blood cell distribution width is associated with serum levels of thyroid stimulating hormone in the general population. Int J Lab Hematol. 2009; 31(5): 581–582, doi: 10.1111/j.1751-553X.2008.01082.x.
75. Aktas G, Sit M, Dikbas O, et al. Could red cell distribution width be a marker in Hashimoto's thyroiditis? Exp Clin Endocrinol Diabetes. 2014; 122(10): 572–574, doi: 10.1055/s-0034-1383564.
76. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. J Res Med Sci. 2014; 19(2): 164–174, indexed in Pubmed: 24778671.
77. Hu S, Rayman MP. Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. Thyroid. 2017; 27(5): 597–610, doi: 10.1089/thy.2016.0635, indexed in Pubmed: 28290237.
78. Rayman MP. Multiple nutritional factors and thyroid disease, with particular reference to autoimmune thyroid disease. Proc Nutr Soc. 2019; 78(1): 34–44, doi: 10.1017/S0029665118001192, indexed in Pubmed: 30208979.
79. Hu S, Rayman MP. Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. Thyroid. 2017; 27(5): 597–610, doi: 10.1089/thy.2016.0635, indexed in Pubmed: 28290237.